CANCER DIAGNOSIS & PROGNOSIS
4: 605-610 (2024) doi: 10.21873/cdp.10370

Association of Oncotype-DX HER2 Single Gene Score With HER2 Expression Assessed by Immunohistochemistry in HER2-low Breast Cancer

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Abstract. *Background/Aim: "HER2-low" is an emerging subtype of breast cancer, with a documented role in predicting response to treatment with novel antibody-drug conjugates. It is defined based on immunohistochemistry, but increasing evidence is challenging this approach as appropriate for identifying the HER2-low subgroup, due to both interobserver variability and limitations of the method itself. Patients and Methods: We retrospectively analyzed data from 430 patients from our departmental databases who had been subjected to an Oncotype-DX score and assessed the correlation of the Oncotype-DX HER2 single-gene score with the HER2 expression on immunohistochemistry. The Oncotype-DX Recurrence Score was also evaluated in the HER2-0 versus HER2-low subgroups. Results: The HER2 single-gene score was found to accurately correlate with the HER2 result on immunohistochemistry, with a statistically significant difference both between HER2-0 and HER2 +1 tumors ($p<0.0001$), as well as between HER2 +1 and +2 tumors ($p<0.0001$). There was no statistically significant difference in the recurrence score between the HER2-0 and the HER2-low subgroups. Conclusion: Oncotype-DX single-gene scores for HER2 are a potential surrogate marker for assessing the precise HER2 status, with better reproducibility and less interobserver variance compared to immunohistochemistry. The use of rt-PCR emerges as an alternative method of assessment of the HER2-low subgroup.*

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Key Words: Breast cancer, oncotype-DX, HER2-low, Rt-PCR, immunohistochemistry.

Breast cancer has traditionally been classified into subtypes according to the expression of Hormone Receptors (HR) and HER2 assessed *via* immunohistochemistry (IHC). Regarding HER2, the classification used until recently was a dichotomy between HER2-positive (defined as HER2 +3 or HER2 +2 with positive *in situ hybridization* – ISH) and HER2-negative tumors (defined as HER2 +2 with negative ISH and HER +1 or 0). HER2-low is an emerging subtype of breast cancer, where a "low" expression of HER2 is present (defined as IHC +1 or +2 with negative ISH). The emergence of HER2 low as a distinct subgroup in clinical practice gained prominence following the results of the landmark Destiny-Breast 04 clinical trial, which showed impressive responses as well as a survival benefit in patients with low HER2 expression with the antibody-drug conjugate trastuzumab deruxtecan (1). However, even though the predictive value of low HER2 expression has been documented, defining the biology of the HER2-low subgroup has proven to be much more complicated. Low expression of HER2 was not shown to have prognostic significance in one of the largest cohorts examined to date of 5235 patients (2). Similar results have been reported in smaller patient cohorts in different studies (3-5). On the contrary, conflicting results have also been reported, with several studies noting a prognostic value of low HER2 expression (6-8). Therefore, both the identity of HER2low as a distinct biologic subgroup and its prognostic significance remain unclear at the moment.

No definitive explanation for these conflicting results has yet been conclusively provided. Several theories have been proposed, including the use of different patient populations in different studies, the different endpoints in each study, as well as the need to also incorporate the assessment of Hormone Receptor expression in HER2 low tumors (3, 6, 9). However, the key factor to take into account is that all of these studies are retrospective studies, examining a marker which at the time of documentation was not clinically significant. Since the discovery of trastuzumab, and the other HER2-targeted treatments that have since followed including pertuzumab, trastuzumab-emtasine, tucatinib and others, the clinical significance of HER2 expression was solely focused on the distinction between a positive and a negative result, because a positive result was predictive of response to HER2-targeted treatment. Therefore, pathologists were not trained in precisely identifying which tumors were HER2 0 and HER2 +1, since the result would be bereft of clinical significance. All the current literature on HER2 low tumors includes the retrospective documentation of HER2 expression assessed as "low" by different pathologists in different centers, at a time when there was no standardized method of assessing low HER2 expression, and no clear clinical incentive to precisely assess it. In fact, it is entirely likely that immunohistochemistry as a method itself is inherently flawed in assessing low HER2 expression, since it is not designed for the HER2-low dynamic range (10). Emerging data are showing significant discordance between HER2 low readings by different pathologists (11). The only way to achieve homogeneity of results would be to either use prospective studies with central assessment of low HER2 expression, which are currently being designed and will not provide results for several years, or to use an entirely different method of assessment.

For this purpose, we examined Oncotype-DX single gene scores. Oncotype-DX is a multigene assay, using reverse-transcription polymerase chain reaction (RT-PCR) to assess 21 genes and provide a recurrence score (RS) for HR-positive patients with early breast cancer, quantifying both the likelihood of recurrence and the relative benefit of chemotherapy in these patients (12-14). All Oncotype-DX reports include quantitative results for the HER2 gene. In contrast to immunohistochemistry results, all Oncotype-DX tests are centrally performed, and there is no heterogeneity between reports. We therefore looked to assess the HER2 single gene score in the Oncotype-DX test in relation to low HER2 expression in immunohistochemistry.

Patients and Methods

Patients. For this retrospective study, we collected data from patients treated in our department between November 2006 and November 2023. Patients were included provided they a) had a histologically confirmed diagnosis of breast cancer, b) had HR-positive, HER2-negative tumors for which the exact HER2 status as determined by IHC was recorded (0, +1, +2/ISH negative), c) had completed their initial surgical treatment, and d) had been subjected to an Oncotype-DX test for which the full report was available, including single gene scores. In patients with multiple (multifocal, multicentral or bilateral) tumors, the HER2 status from every tumor that was sent for Oncotype-DX was matched with the corresponding HER2 single gene score for analysis. Patients that had multiple tumors were excluded if any of the tumors were HR-negative and/or HER2-positive (as no Oncotype-DX was performed in such patients). Patients with a previous breast cancer diagnosis that were under or within a year after completing adjuvant hormonal therapy were not eligible for Oncotype-DX as well.

Histology/IHC. All histologic diagnoses and testing were performed in the same laboratory, which is accredited according to EN ISO 15189:2021 and regularly participates in EQA IHC HER2 schemes run by UKNEQAS and NordiQC. HER2 protein expression by IHC was assessed according to the ASCO/CAP Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer guidelines following their 2008-2013 and 2018 revisions (15).

Endpoints and statistical analysis. The primary endpoint of the study was the assessment of the HER2 single gene score as reported in the Oncotype-DX test with the exact HER2 expression as reported by IHC in the pathology specimen (HER2-0 *versus* HER2 +1, HER2 +1 *versus* HER2 +2). The Oncotype-DX recurrence score was also evaluated in the HER2-0 *versus* HER2-low subgroups. These comparisons were made using the Student's *t*-test for parametric variables or Mann-Whitney *U*-test for non-parametric variables, and one-way ANOVA or Krystal-Wallis test respectively for the comparison of more than two samples. According to the methodological features of an observational non-interventional study, all analyses were descriptive, and the results presented should be interpreted as such. All statistical analyses were performed using GraphPad Prism 10.1.1. The collection of data for this retrospective study was registered and approved by the Euromedica General Clinic Ethics Committee with the registration number 1589/27-12-2023.

Results

We retrospectively collected data from the medical records of patients treated at our unit between 2006 and 2023. A total of 430 patients were included in the study for a total of 465 Oncotype-DX biopsy results. Their median age was 51 years. All patients had a diagnosis of invasive breast cancer; for 388 biopsies this was invasive ductal carcinoma (IDC) and for 77 invasive lobular carcinoma (ILC). 348 patients had N0 disease, 78 had N1 disease, and for 4 patients the N status was unknown (Nx). The exact HER2 status on IHC was recorded for all biopsy samples, as following: 173 samples were HER2-0, 222 samples were HER2 +1, and 70 samples were HER2 +2 (ISH-negative) (Table I). The Oncotype-DX single gene score for HER2 was then recorded in relation to the HER2 status for 464 Oncotype-DX samples (one single gene score was unavailable for a HER2 +2 tumor).

Table I. *Study patient characteristics*.

Variable	Total number
Study patients	430
N stage	
N0	348
T1N0	251
T2N0	94
T3N0	2
TxN0	1
N1	78
T0N1	1
T1N1	58
T2N1	18
T3N1	1
Nx	4
T1Nx	3
TxNx	1
Biopsy samples	465
HER2	
HER2-0	173
HER2+1	222
HER2+2	70
Histological subtype	
IDC	388
ILC	77

HER2: Human epidermal growth factor receptor-2; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma.

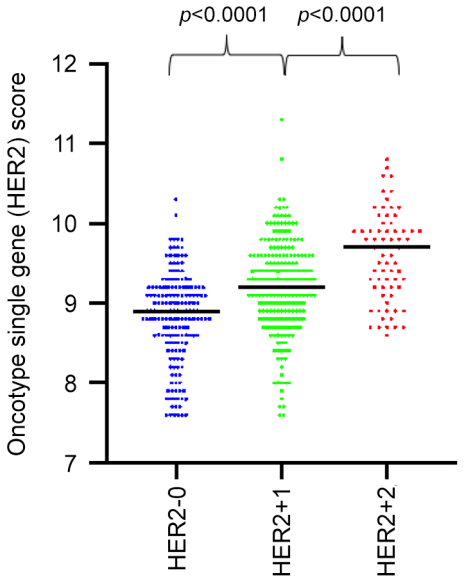

Figure 1. *Oncotype single gene HER2 score in relation to HER2 expression on immunohistochemistry. One-way ANOVA test followed by Bonferroni correction was used to assess statistical significance. HER2: Human epidermal growth factor receptor-2.*

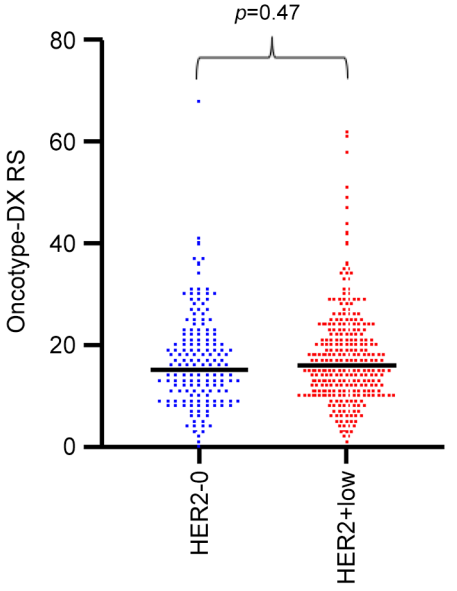

Figure 2. *Oncotype RS in the HER2-0 and HER2-low subgroups. t-test was used to assess statistical significance. RS: Recurrence score; HER2: human epidermal growth factor receptor-2.*

The HER2 single gene score was found to accurately correlate with the exact HER2 status on IHC (Figure 1). The mean single gene score was 8.814 (min=7.600, max=10.30) for HER2-0 tumors, 9.209 (min=7.600, max=11.30) for HER2 +1 tumors, and 9.588 (min=8.600, max=10.80) for HER2 +2 ISH-negative tumors. There was a statistically significant difference between HER2-0 and HER2 +1 tumors (p<0.0001), as well as between HER2 +1 and +2 tumors (p<0.0001).

The Oncotype-DX Recurrence Score (RS) was also evaluated in the HER2-0 *versus* HER2-low (+1, +2 ISH-negative) subgroups. There was no statistically significant difference in the RS score between the two (p=0.47) (Figure 2). No statistically significant difference was observed either when this evaluation was performed in separate histological groups (IDC and ILC) (data not shown).

Discussion

The aim of this study was to examine the association between the Oncotype-DX single gene score for HER2 and the level of HER2 expression on immunohistochemistry in HER2-low HR-positive early breast cancer. To our knowledge, this is the first published study looking at this correlation.

This study was designed in light of the novel HER2-low subgroup in breast cancer, and the emerging uncertainty around it. Since the landmark review study by Tarantino *et al*. proposed HER2-low as a distinct subgroup in 2020 (16),

there has been an abundance of data published on the subject. However, the only proven clinical role of the HER2-low distinction has so far been the ability to identify patients with pretreated metastatic breast cancer who respond to and benefit from trastuzumab deruxtecan (1), which has led to FDA and EMA approvals for this indication. There is no consensus regarding the prognostic role of the HER2-low distinction, with conflicting results in the published literature. A pooled analysis of 2310 patients in four neoadjuvant clinical trials showed higher survival rates in HER2-low tumors compared to HER2 0 tumors, with the differences being more pronounced in the HR-positive subgroup (6). A registry analysis of 5907 patients with early breast cancer showed lower Disease-Free Survival and breast cancer-specific survival in patients with HR-positive HER2 +2/ISH-negative tumors (7). On the contrary, a registry analysis of 5235 patients with early breast cancer showed no difference in DFS or OS between the HER2 0 and HER2-low groups (2). Another registry analysis of 4918 patients with early breast cancer showed no difference in prognosis between the HER2 0 and HER2-low groups (4). No prognostic differences were seen also in smaller studies examining different patient cohorts, including patients with metastatic breast cancer treated with CDK4/6 inhibitors (17). There is also no consensus on the biological and molecular background of the HER2-low subgroup (18).

The main issue leading to these discrepancies is the method used to identify the HER2-low subgroup. The current standard-of-care for HER2 assessment is immunohistochemistry, following the ASCO/CAP guidelines (15). However, emerging evidence is pointing to IHC being an outdated method for the assessment of low expression of HER2. IHC was developed to primarily separate HER2-positive from HER2-negative tumors based on HER2 expression, and may not be an ideal method for detecting HER2-low tumors (18). An IHC score of 0 may simply reflect a limitation of the technique used to identify it rather than true absence of HER2 expression (16, 19). ISH has also been shown to be unstable in assessing the lower levels of HER2 expression (20). Furthermore, while clear guidelines exist for assessment of HER2-positivity, no consensus guidelines are yet in place for assessment of low HER2 expression. The most recent update by ASCO/CAP in 2023 specifically did not support the use of a HER2-low interpretive category (21). This invariably creates an area of significant confusion among pathologists, which inevitably leads to discrepancies. In a retrospective study, only 15% of tumors locally scored as HER2 0 by IHC were confirmed to be HER2 0 on central assessment, and 85% were reassigned as +1 or +2 (22). Discrepancies were also found between core biopsy and surgery samples (23), as well as primary and metastatic tumors (24). This issue is particularly problematic when taking into account the fact that almost all the literature available for HER2-low breast cancer is the result of retrospective analyses of reports by different pathologists who were not trained to detect low HER2 expression, which at the time of reporting was not clinically significant.

For this purpose, we aimed to examine an alternative method of assessment of low HER2 expression that could potentially bypass these limitations. We identified Oncotype-DX as a standardized test with central assessment routinely performed in clinical practice. The clinical use of the Oncotype-DX test is to identify the risk of recurrence of early, HR-positive breast cancer, and the relative benefit of chemotherapy for each individual patient. This is accomplished through the calculation of a Recurrence Score, which is based on the expression of a panel of 21 genes from the patient's tumor, including HER2. The Oncotype-DX result includes, apart from the recurrence score, quantitative single-gene scores for ER, PR, and HER2. We therefore examined the association between the single-gene score for HER2 and the exact level of HER2 expression in tumors designated as HER2-low by a single pathology laboratory with international accreditations.

In our study of 430 patients, a statistically significant association was seen between the single-gene score, which is derived from mRNA expression *via* rt-PCR, and the precise HER2 expression level, as defined by IHC (0, +1, +2) (Figure 1). These findings provide evidence for the use of a centralized test for assessment of the HER2-low subgroup, in lieu of IHC which is not standardized, and has significant heterogeneity between pathologists, retrospectively as well as prospectively (in patients not treated in clinical trials). The single gene scores for Oncotype-DX are standardized, centrally performed, and can be easily retrieved retrospectively. This provides a platform for further research using the HER2 single gene score as a method of evaluation of HER2-low cancers.

Furthermore, a novel approach is examined, regarding the use of rt-PCR as an alternative, entirely different method of assessment of the HER2-low subgroup. This approach could potentially completely eschew IHC and all its documented pitfalls. The Destiny-Breast 04 clinical trial used IHC to define HER2-low tumors (1). However, recent data are pointing to the fact that even tumors with lower levels of HER2 expression on IHC (HER2-ultra low) could potentially derive benefit from the use of Antibody-Drug Conjugates like trastuzumab deruxtecan (25). On the basis of this, the newer clinical trials testing the efficacy of trastuzumab deruxtecan, such as Destiny-Breast 06, have begun to include even HER2-ultra low tumors. This distinction continues to be based on IHC, however, and may still be insufficient to accurately predict response to treatment. The use of rt-PCR instead of IHC could provide a more reliable method of assessment of responders to newer agents. This hypothesis could be tested prospectively, but also retrospectively, for example by analyzing the tumor samples from the landmark clinical trials by rt-PCR and correlating the results to patient response to treatment.

A potential limitation of our study is its retrospective nature, as well as the small sample size. However, almost all of the currently available data on HER2-low breast cancer are derived from retrospective studies. In addition, the amount of interobserver variability in this study is minimal, since all IHC tests were performed in a single internationally accredited pathology laboratory and reviewed by the Head of pathology, and the Oncotype-DX results are centralized.

Conclusion

In conclusion, this study provides proof of concept for the use of Oncotype-DX HER2 single-gene scores as a centralized method of assessment of the HER2-low subgroup, as well as evidence for the incorporation of rt-PCR as a novel method of assessment of HER2-low tumors, both of which can be retrospectively evaluated in existing patient samples, and can form the basis for more accurate identification of this subgroup which would have a significant impact on clinical practice.

Conflicts of Interest

GD and TZ declare no relevant conflict of interest. LK has received honoraria and consultancy fees from Ipsen, BMS, Janssen, MSD and Amgen. IN has received honoraria from Roche. KP has received honoraria and consultancy fees from MSD, Gilead, AstraZeneca, Novartis, Eli Lilly, Roche and GSK.

Authors' Contributions

Manuscript preparation: GD, KP. Concept and design: GD, KP. Collection of data: LK, IN, KP. Statistical analysis: GD, KP. Pathology review: TZ. Manuscript reviewing and corrections: All Authors.

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Received March 24, 2024
Revised June 15, 2024
Accepted June 17, 2024