# Evaluating Low HER2 Status in Invasive Breast Carcinoma via HER2 Immunohistochemistry, a Cohort of 112 Patients

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Disclosures: None

## INTRODUCTION

- HER2-nonamplified tumors were not considered eligible for any anti-HER2 targeted therapies until recent trials demonstrated clinically significant benefits to patients with primary and metastatic breast cancers and HER2-low expression using novel anti-HER2 antibody-drug conjugates.
- HER2-low is currently defined as invasive breast carcinoma with HER2 immunohistochemistry (IHC) score of 1+, or 2+ with a negative in-situ hybridization (ISH) assay, according to current scoring criteria [1].
- Recently, HER2-low expression in invasive breast cancer was proposed as a separate diagnostic category.
- Herein, we assess the viability of recategorizing HER2-low IHC scores using a modified system for reporting low HER2 expression in invasive breast carcinomas and hypothesize further distinguishing HER2(1+) from HER2(0) will provide granularity into HER2-low vs. HER2-negative tumors.

## METHODS

- 114 invasive breast tumors (112 patients, three patients with two tumors each) were identified from the pathology database of Mayo Clinic, Jacksonville, FL, between January 2019 and August 2022, that were interpreted as either HER2(0) or HER2(1+) on the final pathology report.
- Two blinded breast pathologists (BP) independently reviewed the hematoxylin and eosin (H&E) stained and HER2 IHC stained slides.
- HER2 IHC slides were rescored using 10× eyepiece with 20× objective (200× magnification) and 20× eyepiece with 20× objective (400× magnification). Discordant cases between the two BPs were re-scored together. Fluorescent in-situ hybridization (FISH) testing was performed to all cases.
- The most recent 2018 ASCO/CAP HER2 scoring criteria was used in this study [1]. HER2-negative category was subdivided into two categories for purposes of the study: HER2(absent) and HER2(very low), according to a reference study (Table 2) [2].

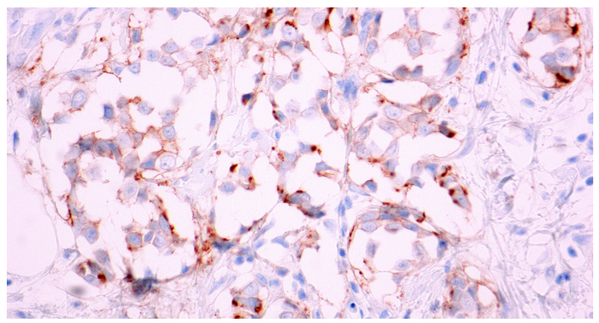

Figure 1: Edge artifact, at 40x magnification

Table 1: Patient demographics in all HER2 rescored subcategories

| | HER2 (absent) | HER2 (very low) | HER2 (1+) | HER2 (2+) |
|---|---|---|---|---|
| **Number of slides (n)** | 15 | 35 | 63 | 1 |
| **Age(mean)** | 65.93 | 63.71 | 67.50 | 76 |
| **Status (alive/deceased) (n)** | 14/1 | 35/0 | 61/2 | 1/0 |
| **Core biopsy/ Excision (n)** | 13/2 | 34/1 | 54/9 | 1/0 |
| **Type of tumor** | | | | |
| Ductal | 10 | 22 | 42 | 1 |
| Lobular | 3 | 10 | 15 | - |
| Poorly differentiated | 2 | 1 | 2 | - |
| Ductal + lobular | - | 1 | 4 | - |
| Ductal + metaplastic | - | 1 | - | - |
| **Tumor Size (mean, mm)** | 7.85 | 7.73 | 8.81 | 4 |
| **Tumor Grade (n)** | | | | |
| Grade 1 | 1 | 11 | 17 | 1 |
| Grade 2 | 6 | 13 | 37 | - |
| Grade 3 | 8 | 11 | 9 | - |
| **Hormonal Status (n)** | | | | |
| ER+/ PR+ | 6 | 25 | 56 | 1 |
| ER+/PR- | 3 | 3 | 4 | - |
| ER-/PR+ | 1 | 3 | 2 | - |
| ER-/PR- | 5 | 4 | 1 | - |

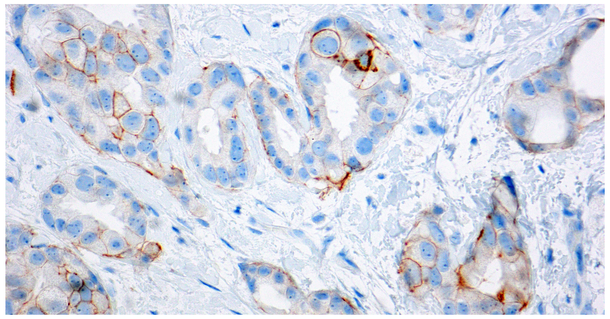

Figure 2: Incomplete faint/ barely perceptible membranous staining in up to 10% of tumor cells, suggesting a HER2(very low) tumor, at 40x magnification

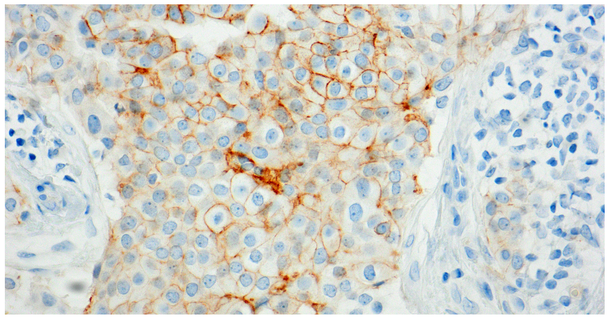

Figure 3: Incomplete faint/barely perceptible membranous staining in >10% of tumor cells, suggesting a HER2(1+) tumor, at 20 x magnification

Table 2: Comparison of current criteria and study criteria in HER2 immunohistochemistry

| **HER2 IHC Score** | | | |
|---|---|---|---|
| **Current 2018 ASCO/CAP Criteria** | 0 | | 1+ |
| | No staining or incomplete faint/barely perceptible membranous staining in up to 10% of tumor cells | | Incomplete faint/barely perceptible membranous staining in >10% of tumor cells |
| **Criteria that were used in this study** | Absent | Very Low | 1+ |
| | No staining observed | Incomplete faint/barely perceptible membranous staining in up to 10% of tumor cells | Incomplete faint/barely perceptible membranous staining in >10% of tumor cells |

Table 3: Recategorization of invasive breast cancer with negative and low (1+) HER2 protein expression into HER2(absent), HER2(very low), and HER2 low (1+) in 112 patients

| HER2 IHC Score Categories, Initial | Initial Scores per report, n and % | HER2 IHC Score Categories, Rescoring | First rescoring BP1, n and % | First rescoring BP2, n and % | Second Rescoring (BP1 and BP2), n and % |
|---|---|---|---|---|---|
| **HER2(0)** | 38 (33.3%) | HER2 (absent) | 17 (14.9%) | 20 (17.5%) | 15 (13.2%) |
| | | HER2 (very low) | 31 (27.2%) | 33 (28.9%) | 35 (30.7%) |
| **HER2(1+)** | 76 (66.7%) | HER2 (1+) | 64 (56.2%) | 61 (53.5%) | 63 (55.3%) |
| | | HER2 (2+) | 2 (1.8%) | NA | 1 (0.9%) |

## RESULTS

- Results are summarized in Table 1 and Table 3.
- Comparison of first round of rescoring between two BPs showed substantial agreement with Cohen's kappa value of 0.67. Both comparison of first round of rescoring by BP1 and first round of rescoring by BP2 to second rescoring showed perfect agreement with Cohen's kappa value of 0.83. The comparison of initial scores and the second rescoring showed fair agreement with Cohen's kappa value of 0.35.
- Follow-up FISH studies of the cohort showed one amplified tumor.

## DISCUSSION

- HER2-low as a subcategory within HER2-non-amplified tumors is still not well-studied and remains to be investigated, with promising therapeutic options.
- HER2-nonamplified tumors require further substratification. Finer granularity into HER2 IHC scoring needs to be considered with suggested subgroups of HER(absent), HER2(very low) and HER2(1+)
- Accurate scoring of HER2 IHC necessitates evaluation at high magnifications such as 200× and 400× magnifications.
- Artifacts (edge artifact etc.) and the type of staining (cytoplasmic, membranous, granular-like etc.) should be taken into consideration when interpreting HER2-low tumors.

## CONCLUSIONS

- Many studies are investigating low-HER2 breast cancer, their clinicopathologic features, genetic profiles and their response to novel chemotherapeutics, which demonstrate promising results in treatment of these patients.
- Clinical approach, guidelines and pathologic evaluation of HER2 might need revision, as well as new developments in HER2 testing, especially for the lower end of HER2 spectrum.

## REFERENCES

1. Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med. 2018;142(11):1364-1382.
2. Boyraz B, Ly A. Discerning subsets of breast cancer with very low and absent HER2 protein expression. Hum Pathol. 2022;127:50-55