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RESEARCH ARTICLE

PATTERN OF HER-2 EXPRESSION WITH SPECIAL REFERENCE TO LOW HER-2 EXPRESSION IN IHC SAMPLES OF BREAST CANCER PATIENTS AT TERTIARY CANCER HOSPITAL HCG AHMEDABAD

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Abstract

Background: Breast cancer is the 2nd most common cancer worldwide and number one cancer in women. As per American Society of Clinical Oncology 2018 guidelines, HER2 classification is binary HER2 positive and HER2 negative. DESTINY-Breast04 trial (2022), the FDA expanded the approval of the HER2 antibody-drug conjugate (T-Dxd) from metastatic breast cancer patients with HER2 protein over-expression/amplification, to also include metastatic patients with HER2 IHC 1+ or 2+ & ISH negative results. This clinical trial adopted a new terminology, "HER2 Low," which successfully prolonged both progression-free survival (PFS) and overall survival (OS).

Material and Method: A descriptive and retrospective analysis was performed, including all patients diagnosed with Invasive breast cancer in HCG cancer Centre, Ahmedabad- Triesta Laboratory between 1st July 2022 to 31st June 2023. Total of 395 patients of both genders were studied. All those individuals who were diagnosed with Invasive breast carcinoma according to WHO and CAP guideline by H&E, IHC and FISH test were included in our study and those with missing data were excluded from our study.

Result: This was a descriptive and retrospective study where 395 cases were diagnosed as breast cancer. HER2 low pattern was found commonly in 4th and 6th decades of life. In our study, out of 395 cases, 34.9% (n = 138) were HER2-negative, 39.5% (n = 156) were HER2-low, and 25.6% (n = 101) were HER2-positive. Among 156 HER2-low cases, 15.4% (24/156) cases were hormone negative, and 84.6% (132/156) cases were hormone positive.

Conclusion: We observed that approximately 40 % of the cases were recategorized to be HER2 low which were classified HER2 negative according to old guidelines. Approximately 84% cases of HER2 low group were hormone positive. With the development of novel ADCs and other targeted agents, the treatment strategies for HER2-low breast cancer are expanding, and hence detecting low expression levels of HER2 is important.

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Introduction:-

Breast cancer being the most common cancer in India, accounts for 28.2% of all female cancers, with an estimated 216,108 cases by 2022.[1] In breast ER, PgR and HER2 are the most used markers for predicting prognosis and response. HER2/NEU an oncogene, in which, the protein product functions as a growth factor receptor.[2] The HER-2/NEU oncogene encodes for transmembrane tyrosine kinase receptor, it's primary sequence is similar to the epidermal growth factor receptor(EGFR/ERBB1).[3] Amplification of the HER-2 gene or overexpression of the HER-2/NEU protein has been identified in 15% to 20% of breast cancers candidates. The potential use of HER-2 status in the prediction of response to therapy is evaluated in this study.[4]

As per American Society of Clinical Oncology 2018 guidelines, HER2 classification is of two types. One is positive (defined as IHC 3+ or IHC 2+ &/ ISH+), and negative (defined as IHC 0, IHC 1+, or IHC 2+ &/ ISH−).[5]

Based on results of the DESTINY-Breast04 trial (2022), the Food and Drug Administration (FDA, USA) expanded the approval of the HER2 antibody-drug conjugate, trastuzumab deruxtecan (T-Dxd) from metastatic breast cancer patients with HER2 protein over-expression/amplification, to also include metastatic patients with HER2 IHC 1+ or 2+ & ISH negative results. This clinical trial adopted a new terminology, "HER2 Low," for the HER2 IHC 1+ or 2+ & ISH negative breast cancer cases. The antibody-drug conjugate (ADC) trastuzumab-deruxtecan (T-DXd) successfully prolonged both progression-free survival (PFS) and overall survival (OS) among patients having HER2-low unresectable and metastatic breast cancer, as compared with standard single-age chemotherapy.[6]

HER2 low, is defined as a score of 1+ on immunohistochemical (IHC) analysis or as an IHC score of 2+ and negative results on in situ hybridization (ISH).[7] These "HER2-low" tumors constitute a heterogeneous population including both hormone receptor–positive and negative breast cancers that vary in prognosis and sensitivity to systemic treatments.[8]

The American Society of Clinical Oncology guidelines recommend HER2 testing by immunohistochemistry (IHC) assay or by in situ hybridization.[5]

This observational study aims to identify the pattern and number of cases of each HER-2 category in our patients by IHC, FISH and to identify number of HER-2 low cases. Breast cancers (BCs) that are traditionally categorized as HER2-negative [IHC-1+, or 2+/in situ hybridization (ISH) negative] express low levels of HER2 and are currently categorized as HER2 low. Until recently, patients with HER2-low tumors were not eligible for treatment with HER2-directed agents. T-DXd is now the first HER2-directed agent approved to treat HER2-low tumors and improve patient's outcome.

Aim and Objectives:-

Aim:-

To know number of cases of each HER-2 category in our patient by IHC, FISH and to identify number of HER-2 low cases.

Objectives:-

To assess the prevalence of HER2-low in breast cancer.

Material and Method:-

A descriptive and retrospective analysis was performed, including all patients diagnosed with Invasive breast cancer in HCG cancer Centre, Ahmedabad and Triesta Laboratory between 1st July 2022 to 31st June 2023. The above study commenced after obtaining institutional ethical clearance and written consent from the authority.

Total of 395 patients of both genders were studied. All those individuals who were diagnosed with Invasive breast carcinoma according to WHO and CAP guideline by H&E, IHC and FISH test were included in our study and those with missing data were excluded from our study.

Cases from pathology database were evaluated. Her 2 code was entered and based on that, reports were retrieved using unique ID and MRN numbers. Slides were retrieved from the archive and studied.

We used VENTANA 4B5 which has been approved by the US Food and Drug Administration (FDA) for the detection of HER2 status on VENTANA platform Benchmark.

Results of HER2 testing by immunohistochemistry (IHC) were as- Negative (Score 0) - no staining observed or membrane stating that is incomplete and is faint or barely perceptible within ≤10% of tumor cells. Negative (Score 1+)- incomplete membrane staining that is faint or barely perceptible and within >10% of tumor cells. Equivocal (Score 2+)- weak to moderate complete membrane staining in >10% of tumor cells. Complete membrane staining that is intense but within ≤10% of tumor cells and Positive (Score 3+)- complete membrane staining that is intense and >10% of tumor cells. Breast cancers with HER2 IHC score 1+ or HER2 IHC score 2+ and a negative ISH result are eligible for clinically appropriate HER2-targeted therapy and may be reported as "HER2 Low".[9]

The data was entered in excel worksheet and analysis was performed using SPSS 23. Descriptive statistics were carried out. Results on continuous measurements are presented on mean ± SD and results on categorical measurements, presented in number(%). Statistical significance between two categorical variables were performed using a chi-square test. Significance was assessed at 5% level.

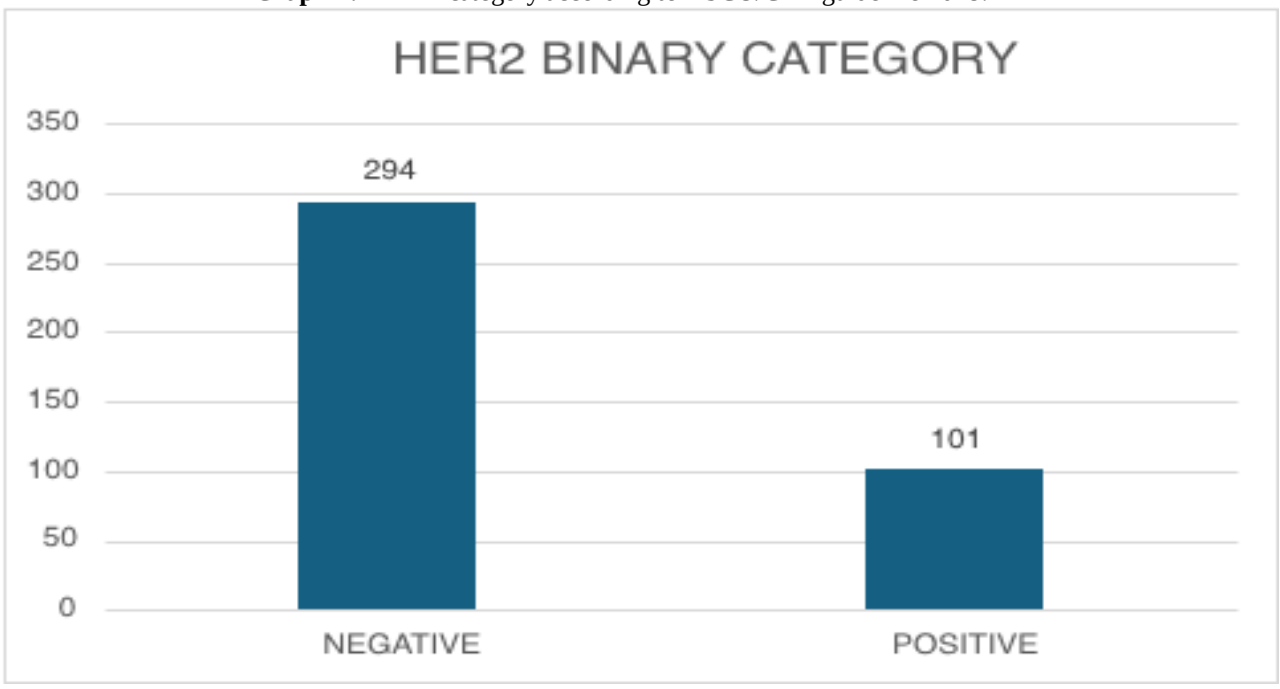
Result:-

This was a descriptive and retrospective study where 395 cases were diagnosed as breast cancer. The aim was to study the number of HER2 low among breast cancer patients. The maximum subjects were from the age group of 41–50 years (28.2%) followed by 61-70 years (26.9%). Other subjects were from the age group of 21-30years (0.6%) followed by 81-90 years (1.28%). Hence, the HER2 low pattern was found commonly in 4th and 6th decades of life.

We observed among 395 study group cases, 388 cases were females out of which 153 cases were HER2 low and 7 cases were males out of which 3 cases were HER2 low category.

CATEGORY	NUMBER OF PATIENTS
HER2 NEGATIVE	294
HER2 POSITIVE	101
TOTAL	395

Graph 1:- HER2 category according to ASCO/CAP guideline 2018.

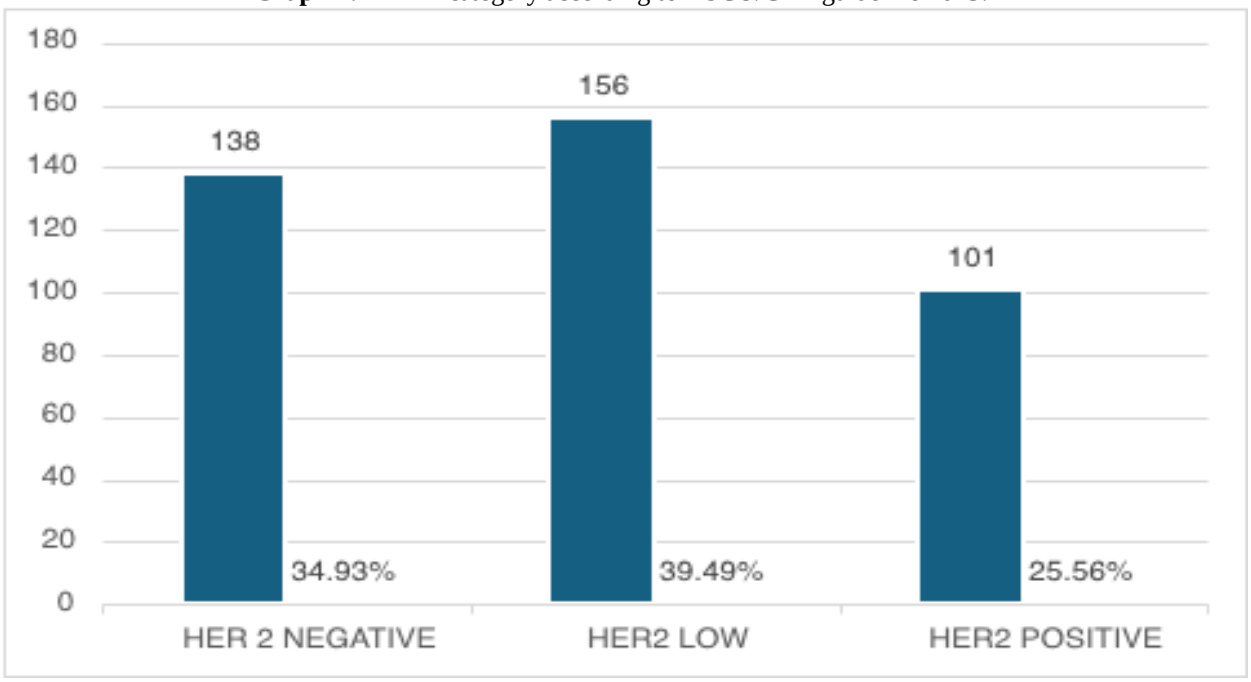


A total of 395 breast cancer patients' data was studied, which were classified as positive (defined as IHC 3+ or IHC 2+ &/ ISH+) and negative (defined as IHC 0, IHC 1+, or IHC 2+ &/ ISH−) patients. Based on the above-mentioned

classification, Graph 1 represents 294 (74.4%) cases were HER2 negative and 101 (25.6%) cases were HER2 positive.

CATEGORY	NUMBER OF PATIENTS	PECENTAGE
HER2 NEGATIVE	138	34.93%
HER2 LOW	156	39.49%
HER2 POSITIVE	101	25.56%
TOTAL	395	100%

Graph 2:- HER2 category according to ASCO/CAP guideline 2023.



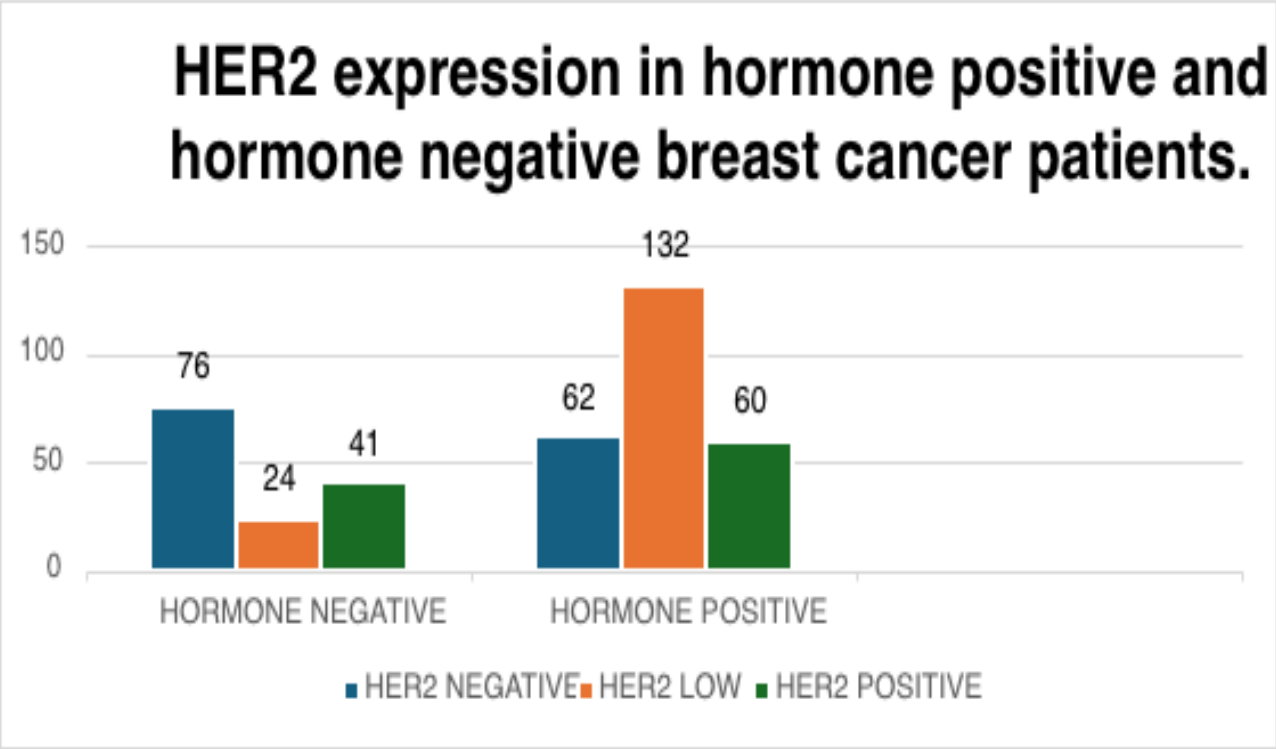
The category "HER2 Low," defined as HER2 IHC 1+ or 2+ & ISH negative breast cancer cases was adopted. Based on this categorization, patients were recategorized as HER2 negative, HER2 low and HER2 positive.

In our study, out of 395 cases, 34.9% (n = 138) were HER2-negative, 39.5% (n = 156) were HER2-low, and 25.6% (n = 101) were HER2-positive. 39.5% of cases from HER2-low category were HER2 negative by 2018 ASCO/CAP HER2 guidelines.

From 156 patients classified as HER2-low category, 41% (64/156) had a HER2 IHC score of 1+, and 59% (92/156) had a HER2 IHC score of 2+.

Among the 105 HER2 IHC 2+ category, 92 (87.6%) cases were ISH negative, and 13 cases (12.4%) were ISH positive.

Graph 3:- HER2 expression in hormone positive and hormone negative breast cancer cases.



Out of 138 HER2 negative cases, 76 were hormone negative and 62 were hormone positive. Among 156 HER2-low cases, 15.4% (24/156) cases were hormone negative, and 84.6% (132/156) cases were hormone positive. Among 101 HER2 positive cases, 41 cases were hormone negative, and 60 cases were hormone positive.

CATEGORY	ER-/PR-	ER+/PR-	ER-/PR+	ER+/PR+	TOTAL
HER2 NEGATIVE	62	10	2	64	138
HER2 LOW	23	21	0	112	156
HER2 POSITIVE	41	22	3	35	101

In the study subjects ER-/PR+group constitutes 1-10% cells positive.

Discussion:-

The Destiny breast 04 trial reports high efficiency for novel HER2-targeted therapy with ADC in low-HER2 expressing breast cancers garnished increasing attention for the addition of a "HER2-low" category for breast cancer.[10] The trial found that trastuzumab deruxtecan (T-DXd) ADC component doubled progression-free survival (PFS) for patients with HER2-low breast cancer and significantly improved overall survival (OS) regardless of hormone receptor status, when compared with standard chemotherapy.

Dr. Shanu Modi stated that previously HER2 status has been defined as positive and negative, but we know that a large proportion of cancers within the HER2-negative also express low levels of HER2, which are referred to as HER2-low breast cancers. This low level of HER2 may still be targetable by trastuzumab deruxtecan (T-DXd) ADC component. Currently available HER2-targeted therapies unfortunately have not been effective for patients with HER2-low breast cancer.

IHC scores for HER2 expression were determined through an investigational IHC assay, the VENTANA HER2 (4B5) assay benchmark XT system, and an algorithm adapted from the American Society of Clinical Oncology College guidelines(2018).

Dr. Modi and colleagues found that for patients with HER2-low and hormone receptor-positive who received T-DXd versus standard chemotherapy, PFS nearly doubled (10.1 months versus 5.4 months) and significantly improved OS (23.9 months versus 17.5 months).

Approximately 60% of HER2-negative metastatic breast cancers express low levels of HER2, yet these patients have always been considered as HER2-negative breast cancers. In these patients, choice of treatment was decided by the hormone receptor status. With resistance to initial therapies, patients with HER2-low breast cancers have limited late-line targeted options and ultimately are offered palliative single agent chemotherapy. The results with T-Dxd show potential to significantly improve treatment outcomes for this large population of patients.

HER2-low tumors represent a high proportion of breast cancer cases, estimated at around 45–55%. [11]

After the new definition of "HER2-low" in breast cancer was introduced, the Cancer Genome Atlas and a clinical trial dataset reported HER2-low breast cancer incidences of 31% and 51%, respectively.[12],[13]

In this study, we re-evaluated 395 patients diagnosed with invasive breast cancer previously diagnosed as HER2-negative, the prevalence of HER2-low was 39.49%. Our HER2-low prevalence findings were similar to those of other studies in patients with HER2 low –31%[14], HER2 low - 31.3%[15], HER2 low – 35.2%[16] , HER2 low- 59.9%[17] and HER2 low- 67.2%[18]. Together, these data suggest that HER2 low prevalence range is 31% to 67.2%. Under the current definition, identification of HER2-low breast cancer predominantly relies on the HER2 status tested by a semi-quantitative IHC assay, Dr. Rimm and his team found there was a discordance of 41% in distinguishing HER2 0 from HER2 1 or higher, but a discordance of 11% between HER2 3 vs not 3. They only get it right about 60% of the time.[19]

We used VENTANA 4B5 antibody clone for HER 2 IHC staining. Scott et al. demonstrated that the VENTANA 4B5 antibody clone identified a higher proportion of HER2-low cases than HercepTest (27.4% vs 9.2%) in their study.[20]

In our study, the HER2 low pattern was found commonly in 4^{h} and 6^{th} decades of life. Similar observation was also found in ajay at al study. (17)

ER and PR expressing tumors account for 70% of all breast cancers and are known as hormone receptor (HR) positive breast cancers. Around 15% of breast cancers overexpress HER2, the remaining 15% do not overexpress HR or HER2; this subtype is known as the triple-negative breast cancer (TNBC).[21]The HER2-positive subtype is more aggressive and fast-growing. Within this, two subgroups can be distinguished: luminal HER2 (E+, PR+, HER2+ and Ki-67:15–30%) and HER2-enriched (HER2+, E-, PR-, Ki-67>30%).[22]

The rate of HER2-low identified among patients with HR-positive disease in our study is 84.6% (132/156) while, with HR- negative is 15.4% (24/156). The higher proportion of HER2-low breast with HR-positive breast cancer found in Ajay et al study was 80% vs 29.69% (17) while higher rate of HER2 low with HR-negative was observed at 71.1% vs 52.8% in Viale et al study (18). Like our study, findings observed in previous studies that HER2-low cases were more common in patients with HR-positive as compared to HR-negative disease, like 33.6% vs 15% in Huina at al study (14) ,33.6%vs 23%in Hye sung at al. (15), and 39.8% vs 22.5% in Simon et al study. (16)

Patients with hormone receptor–positive, HER2-negative metastatic breast cancer, combinations of endocrine therapy and cyclin dependent kinase 4 and 6 (CDK4/6) inhibitors are effective for a median age of approximately 2 years, after which resistance often occurs.[23],[24]

Real-world data suggest a progression-free survival as low as 4 months with systemic therapies given after CDK4/6 inhibitors and chemotherapy in the context of metastatic disease.[25]

For patients with hormone receptor–negative, HER2-negative metastatic disease, few targeted agents are available, particularly for those without pathogenic BRCA mutations or tumors without programmed death ligand 1 expression.[26]

Trastuzumab, a monoclonal antibody to HER2, accrues significant clinical benefit in the metastatic and adjuvant settings.[27]

Trastuzumab deruxtecan, an antibody–drug conjugate consisting of a humanized anti-HER2 monoclonal antibody linked to a topoisomerase I inhibitor act through a tetrapeptide-based cleavable linker, has been approved for the treatment of patients with metastatic HER2-positive breast cancer which also effectively target tumor cells that express low levels of HER2. (6)

Approximately 60–70% of HER2+ breast cancer co-express hormone receptors (HRs). HR/HER2 co-expression modulates response to both anti-HER2–directed and hormonal therapy due to "crosstalk" between the estrogen receptor (ER) and HER2 pathways. Combined HER2/ER blockade may be an effective treatment strategy for patients with HR+/HER2+ breast cancer in the appropriate clinical setting(s).[28]

Conclusion:-

We observed that approximately 40 % of the cases were recategorized to be HER2 low which were classified HER2 negative according to old guidelines. Approximately 84% cases of HER2 low group were hormone positive. With the development of novel ADCs and other targeted agents, the treatment strategies for HER2-low breast cancer are expanding, and hence detecting low expression levels of HER2 is important.

Limitations

The study has a few limitations, such as retrospective design of the study, short time frame i.e. 1-year, single institution nature of the study, lack of clinical data of the study subjects.

References:-

1. Sathishkumar K, Sankarapillai J, Mathew A, Nair RA, Gangane N, Khuraijam S, Barmon D, Pandya S, Majumdar G, Deshmane V, Zomawia E, Bhutia TW, Jerang K, George PS, Maliye S, Laishram R, Das G, Shah A, Debbarma S, Koyande S, Pachuau L, Sherpa A, Jongkey G, Chaturvedi M, Das P, Santhappan S, Mathur P. Breast cancer survival in India across 11 geographic areas under the National Cancer Registry Programme. Cancer. 2024 May 15;130(10):1816-1825. doi: 10.1002/cncr.35188. Epub 2024 Jan 6. PMID: 38183671.
2. Longacre TA, Greenson JK, Hornick JL, Reuter VE.Mills and Sternberg's diagnostic surgical pathology.7th edition. wolters kluwer health; 2022.
3. Gutierrez C, Schiff R. HER2: biology, detection, and clinical implications. Arch Pathol Lab Med. 2011 Jan;135(1):55-62. doi: 10.5858/2010-0454-RAR.1. PMID: 21204711; PMCID: PMC3242418.
4. Ross JS, Fletcher JA. The HER-2/NEU oncogene in breast cancer: prognostic factor, predictive factor, and target for therapy. Stem Cells. 1998;16(6):413-28. doi: 10.1002/stem.160413. PMID: 9831867.
5. Wolff AC, Hammond ME, 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. J Clin Oncol. 2018;36:2105–22.
6. Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, Tsurutani J, Ueno NT, Prat A, Chae YS, Lee KS, Niikura N, Park YH, Xu B, Wang X, Gil-Gil M, Li W, Pierga JY, Im SA, Moore HCF, Rugo HS, Yerushalmi R, Zagouri F, Gombos A, Kim SB, Liu Q, Luo T, Saura C, Schmid P, Sun T, Gambhire D, Yung L, Wang Y, Singh J, Vitazka P, Meinhardt G, Harbeck N, Cameron DA; DESTINY-Breast04 Trial Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20. doi: 10.1056/NEJMoa2203690. Epub 2022 Jun 5. PMID: 35665782; PMCID: PMC10561652.
7. Schettini F, Chic N, Brasó-Maristany F, et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. NPJ Breast Cancer 2021;7:1
8. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-low breast cancer: pathological and clinical landscape. J Clin Oncol 2020;38:1951-62.
9. https://www.cap.org/protocols and guidelines/cap guidelines/current cap-guidelines/recommendations for human epidermal growth factor 2 testing in breast-cancer-2023 guideline update.
10. Modi, S. et al. Antitumor activity and safety of trastuzumab deruxtecan in patients with HER2-low-expressing advanced breast cancer: results from a phase Ib study. J. Clin. Oncol. **38**, 1887–1896 (2020).
11. Dieci MV, Miglietta F, Griguolo G, Guarneri V. Biomarkers for HER2-positive metastatic breast cancer: Beyond hormone receptors. Cancer Treat Rev. 2020 Aug;88:102064. doi: 10.1016/j.ctrv.2020.102064. Epub 2020 Jun 24. PMID: 32622272.

12. Agostinetto, E. et al. HER2-low breast cancer: molecular characteristics and prognosis. Cancers **13**, 2824 (2021).
13. Denkert, C. et al. Clinical and molecular characteristics of HER2-low-positive breast cancer: pooled analysis of individual patient data from four prospective, neoadjuvant clinical trials. Lancet Oncol. **22**, 1151–1161 (2021).
14. Zhang, H., Katerji, H., Turner, B.M. et al. HER2-low breast cancers: incidence, HER2 staining patterns, clinicopathologic features, MammaPrint and BluePrint genomic profiles. Mod Pathol **35**, 1075–1082 (2022).
15. Won, H.S., Ahn, J., Kim, Y. et al. Clinical significance of HER2-low expression in early breast cancer: a nationwide study from the Korean Breast Cancer Society. Breast Cancer Res **24**, 22 (2022).
16. Gampenrieder SP , Rinnerthaler G, Petzer A, et al. Landscape of HER2-low metastatic breast cancer (MBC): results from the AGMT-MBC-Registry [abstract]. In: Proceedings of the 2019 San Antonio Breast Cancer Symposium; 2019; San Antonio, TX. Philadelphia, PA: AACR; 2020. Abstract nr P3-08-29.
17. Ajay Gogia et al., Prevalence of low HER2 expression in breast cancer patients: An Indian experience. JCO **41**, e12543-e12543(2023).
18. Viale G, Basik M, Niikura N, Tokunaga E, Brucker S, Penault-Llorca F, Hayashi N, Sohn J, Teixeira de Sousa R, Brufsky AM, O'Brien CS, Schmitt F, Higgins G, Varghese D, James GD, Moh A, Livingston A, de Giorgio-Miller V. Retrospective study to estimate the prevalence and describe the clinicopathological characteristics, treatments received, and outcomes of HER2-low breast cancer. ESMO Open. 2023 Aug;8(4):101615. doi: 10.1016/j.esmoop.2023.101615. Epub 2023 Aug 8. PMID: 37562195; PMCID: PMC10515285.
19. Rimm D: HER2 low: A pathologist's perspective. 2022 San Antonio Breast Cancer Symposium. Special Session. Presented December 7, 2022.
20. Scott, M., Vandenberghe, M., Scorer, P., Boothman, A. M. & Barker, C. Prevalence of HER2 low in breast cancer subtypes using the VENTANA anti-HER2/NEU (4B5) assay. American Society of Clinical Oncology annual meeting 2021 Abstract. J. Clin. Oncol. **39** (Suppl 15;abstr 1021) (2021).
21. DeSantis C.E., Ma J., Gaudet M.M., et al. Breast cancer statistics, 2019. CA A Cancer J Clin. 2019;69(6):438–451.
22. Krishnamurti U, Silverman JF. HER2 in breast cancer: a review and update. Adv Anat Pathol. 2014;21(2):100–107.
23. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/ TRIO-18): a randomised phase 2 study. Lancet Oncol 2015;16:25-35.
24. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375:1925-36.
25. Mo H, Renna CE, Moore HCF, et al. Real-world outcomes of everolimus and exemestane for the treatment of metastatic hormone receptor-positive breast cancer in patients previously treated with CDK4/6 inhibitors. Clin Breast Cancer 2022;22:143-8.
26. Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. Nat Rev Dis Primers 2019;5:66.
27. Gajria D, Chandarlapaty S. HER2-amplified breast cancer: mechanisms of trastuzumab resistance and novel targeted therapies. Expert Rev Anticancer Ther. 2011 Feb;11(2):263-75. doi: 10.1586/era.10.226. PMID: 21342044; PMCID: PMC3092522.
28. Pegram, M., Jackisch, C. & Johnston, S.R.D. Estrogen/HER2 receptor crosstalk in breast cancer: combination therapies to improve outcomes for patients with hormone receptor-positive/HER2-positive breast cancer. npj Breast Cancer **9**, 45 (2023).