UNIVERSA MEDICINA

pISSN: 1907-3062 / eISSN: 2407-2230

Univ Med 2025;44:43-49

DOI: https://doi.org/10.18051/UnivMed.2025.v44.43-49

ORIGINAL ARTICLE

Discordance of HER2 between primary tumors and lymph node metastatic lesions in invasive breast cancer

Noviana Nugrohowati [1,2]*, Sumadi Lukman Anwar[2], Juwaryani[2], and Firda Ridhayani[3]

[1]Department of Anatomical Pathology, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2]Academic Hospital Universitas Gadjah Mada, Yogyakarta, Indonesia
[3]Department of Pharmacology and Therapeutics, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

*** Correspondence Author:**
dr.noviana.n@ugm.ac.id

Date of first submission, October 10, 2024
Date of final revised submission, February 18, 2025
Date of acceptance, February 24, 2025

Cite this article as: Nugrohowati N, Anwar SL, Juwaryani, Ridhayani F. Discordance of HER2 between primary tumors and lymph node metastatic lesions in invasive breast cancer. Univ Med 2025;44:43-49

ABSTRACT

BACKGROUND
Breast cancer therapy is mostly influenced by the type and molecular subtype, especially in the case of human epidermal growth factor receptor 2 (HER2) status, where HER2-positive patients will receive anti-HER2 therapy. HER2 status is obtained from HER2 immunohistochemistry examination which can be performed on primary breast tumors or lymph node metastatic lesions. This study aimed to determine the concordance of HER2 status between primary tumors and lymph node metastatic lesions in invasive breast cancer.

METHODS
A cross-sectional study was conducted involving 30 invasive breast cancer patients. HER2 immunohistochemistry examination was carried out on both the primary tumor and lymph node metastatic lesions. The Cohen κ coefficient was used to analyse the data.

RESULTS
The concordance rate for HER2 was 86.67%. Thirteen cases were concordantly HER2-negative in primary breast cancer (BC) and nodal metastases, and 13 cases were HER2-positive in both primary and metastatic tumors. Changes in HER2 status between primary BC and corresponding synchronous metastases were observed in four (4.72%) cases. One of the discordant cases was HER2-negative in the primary tumor and HER2-positive in the metastases, while three cases were HER2-positive in the primary breast cancer and HER2-negative in the metastases.

CONCLUSION
There is a discordance of HER2 status between the primary tumor and lymph node metastases in invasive breast cancer patients. It is necessary to evaluate the HER2 status of the primary tumor and metastases simultaneously. Such an evaluation is recommended for better prognosis and survival.

Keywords : Breast cancer, HER2 status, lymph node metastatic lesions, primary tumor

INTRODUCTION

Breast cancer (BC) remains one of the most common and deadly malignancies among women.[1] According to the 2020 Global Cancer Observatory (GLOBOCAN) report, breast cancer accounts for 2,261,419 cases around the world. Meanwhile, the number of cases in Indonesia in 2020 reached 65,858 (16.6%), with 22,430 deaths (9.6%).[2,3] According to Riskesdas, two of the most prevalent malignancies in Indonesia are cervical cancer and breast cancer. The province of Yogyakarta has a substantially greater cancer rate than the national average, at 4.1 per 1,000 individuals.[4]

Breast cancer treatment continues to develop considerably, particularly in connection with antibody therapy. The current approach to breast cancer treatment utilizing an antibody regimen comprises monoclonal antibodies, which bind specifically to cancer cells and provoke an immune response and apoptosis in those cells. The Food and Drug Administration (FDA) has approved many monoclonal antibodies for cancer treatment, including epidermal growth factor receptor (cetuximab and panitumumab) and vascular endothelial growth factor (VEGF).[5]

Approximately 30% of breast cancer patients were projected to have overexpression of human epidermal growth factor 2 (HER2), which is linked to malignant tumors that have a poor prognosis. Trastuzumab (herceptin), an anti-HER2/neu monoclonal antibody, has received authorization for use in the United States since 1998. Trastuzumab binds to the extracellular domain of the HER2 protein. Clinical trials have shown that trastuzumab may elevate disease-free survival rates in metastatic breast cancer patients. Trastuzumab is effective not solely in metastatic breast cancer, but also in the early stages of breast cancers that express the HER2 protein.[5,6]

Patients with clinical breast cancer undergo surgery and anatomical pathology screenings to determine histopathological staging according to the 8th edition of the American Joint Committee on Cancer (AJCC), followed by HER2 immunohistochemical investigations of both the primary tumor and lymph node metastatic lesions.[7]

The assessment of hormone receptors (HRs) and HER2 is necessary to select patients who are candidates for hormonal and anti-HER2 therapy (trastuzumab). However, it remains unclear whether the molecular status should be assessed only in primary tumors to predict the status in metastatic lesions. Development of resistance to therapy is still frequent and often leads to cancer recurrence. Does therapeutic failure or drug resistance develop in patients who have received anti-HER2 or hormonal therapy because of discordant molecular status of estrogen receptor (ER), progesterone receptor (PR), and HER2 at metastatic sites? Therefore, it is very important to determine whether the biological parameters in metastatic lymph nodes are similar to their status in the primary breast cancer.

A study on lymphatic metastatic lesions and corresponding primary lesions of 107 cases of invasive breast cancer, showed that there was only a moderate concordance of estrogen receptor, progesterone receptor, and HER2 status between primary tumors and metastatic lymph nodes.[8] The population in Indonesia differs from those in other countries, making it essential to conduct research in Indonesia to further develop studies and practices in the healthcare field in the future. In this connection, our study aimed to describe the concordance of HER2 status between primary tumors and lymph node metastatic lesions among patients with invasive breast cancer.

METHODS

Research design

This cross-sectional study was conducted at Universitas Gadjah Mada for 7 months, from April to October 2023.

Study subjects

The population was patients with clinical breast cancer who were registered as patients at the Academic Hospital of Universitas Gadjah Mada and underwent both surgery and histopathological examination from January 2016 to October 2023. This research was conducted using the total sample size, which involves selecting all subjects that meet the inclusion criteria of the Academic Hospital of Universitas Gadjah Mada. In total, this study included 30 participants who fulfilled the inclusion criteria, namely being a registered patient at the Academic Hospital of Universitas Gadjah Mada with breast cancer diagnosis who had mastectomy or lumpectomy with axillary dissection, histopathologically tested surgical specimens, and complete medical records. This study did not

include patients with suspected breast cancer with a benign histopathological diagnosis, patients without lymph node involvement, or lymph nodes without tumor, and patients who had received chemotherapy prior to surgery.

Immunohistochemistry

HER2 status according to the results of HER2 immunohistochemical (IHC) examination on formalin-fixed paraffin-embedded (FFPE) sections was defined based on the following criteria: i) HER2 (0)/ negative HER2 if the stain was negative on the whole of the tumor cell's nuclear membrane;(ii) HER2 (+1) if the stain was positive but the circular pattern on the tumor cell's nuclear membrane was not intact. This result was considered to be HER2 negative;(iii) HER2 (+2) if the stain was positive with high intensity and had a perfect circular pattern in <10% tumor cell's nuclear membrane. This result was considered equivocal and the examination proceeded to in situ hybridization; and (iv) HER2 (+3) if the stain was positive with high intensity and had a perfect circular pattern in ≥10% tumor cell's nuclear membrane. This result was considered to be HER2 positive. Overall, specimens were considered positive for HER2 in cases in which the IHC was 3+, or the IHC was 2+ and HER2 was amplified via fluorescence in situ hybridization (FISH).

Laboratory analysis

In this study, the HER2 immunohistochemistry analysis procedure was done using an antigen retrieval reagent (Citrate buffer pH 6.0).[9] This procedure required several materials, including phosphate buffered saline (PBS), endogenous peroxidase blocker (3% H_2O_2 in methanol), blocking buffer, HER2/neu primary antibody, secondary antibody (biotin conjugate), Strep avidin horseradish peroxidase (SA-HRP), diaminobenzidine (DAB) chromogen, and .Mayer's hematoxylin counterstain. The assay proceeded using automatic immunohistochemistry analysis tools, specifically the Ventana GX series.

Statistical analysis

The agreement of HER2 status between primary tumors and matched metastatic lymph nodes was expressed both by concordance and the Cohen κ coefficient. The relation between the Cohen kappa value and the level of agreement was suggested by McHugh[10] , with κ values of 0.00-0.20 indicating slight agreement, 0.21-0.40 indicating fair agreement, 0.41-0.60 indicating moderate agreement, 0.61-0.80 indicating substantial agreement, and 0.81-1.00 indicating almost perfect agreement. Calculations were done with SPSS 20.0 (IBM Inc., Chicago, IL, U.S.A.).

Ethical clearance

The study was approved by the Ethics Committee, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Indonesia (No. KE/FK/0903/EC/2023) published on May 31, 2023.

RESULTS

The study included 30 cases of invasive breast cancer diagnosed in the period of January 2016 to October 2023. All patients were females with a mean age of 55.03 ± 10.61 years. The youngest age was 31 years and the oldest age was 91 years. Nearly a third of these invasive breast cancer patients were ≤ 50 years of age. The tumor size was dominated by sizes of 2 – 5 cm in 43.3% of cases, followed by > 5 cm in 40.0%. By histopathological assessment, more than half or 25 (83.3%) out of 30 cases were classified as grade III carcinomas. Patient and tumor characteristics in this study are presented in Table 1.

Table 1. Patient and tumor characteristics in 30 cases of invasive breast cancer

Characteristics	n (%)
Age (years)	55.03 ± 10.61
≤ 50	9 (30.0)
> 50	21 (70.0)
Tumor size (cm)	
< 2	5 (16.7)
2 - 5	13 (43.3)
> 5	12 (40.0)
Histological grade	
Grade I	0 (0.0)
Grade II	5 (16.7)
Grade III	25 (83.3)

Note : data presented as mean ± SD, and n (%)

The final study included 30 paired specimens from invasive breast cancer patients. Primary tumors were categorized into 14 (46.67%) HER2-negative results (5 HER2-zero (35.71%) and 9 HER2-low (64.29%)) and more than a half (53.33%) showed HER2-positive results. This study reported 26 (86.67%) incidences of HER2 concordance in primary tumors with metastatic

lymph nodes (Table 2). The Kappa value of consistency was 0.735 for HER2 expression in primary tumor and metastatic lymph nodes, suggesting a substantial agreement and a high degree of consistency in its expression (Table 3).

This result was divided into two categories: 13 patients with HER2 positive status in both the primary tumor and metastatic lymph node, and 13 patients with HER2 negative status in both the primary tumor and metastatic lymph node. Four patients (13.33%) showed differences in HER2 status between the primary tumor and lymph node metastases. In three cases (10%), the HER2 result was positive in the primary tumor and negative in the metastatic lymph node, whereas in one case (3.33%), the HER2 result was negative in the primary tumor and positive in the lymph node.

Table 2. HER2 characteristics between primary tumor and lymph node metastates

HER2 Result				Conclusion
Primary tumor		Lymph node		
3+	Positive	3+	Positive	Concordance
1+	Negative	0	Negative	Concordance
1+	Negative	1+	Negative	Concordance
1+	Negative	1+	Negative	Concordance
3+	Positive	0	Negative	Discordance
3+	Positive	3+	Positive	Concordance
3+	Positive	3+	Positive	Concordance
3+	Positive	3+	Positive	Concordance
1+	Negative	1+	Negative	Concordance
3+	Positive	3+	Positive	Concordance
1+	Negative	3+	Positive	Discordance
3+	Positive	3+	Positive	Concordance
3+	Positive	3+	Positive	Concordance
3+	Positive	3+	Positive	Concordance
3+	Positive	3+	Positive	Concordance
3+	Positive	1+	Negative	Discordance
0	Negative	0	Negative	Concordance
0	Negative	1+	Negative	Concordance
3+	Positive	3+	Positive	Concordance
1+	Negative	1+	Negative	Concordance
3+	Positive	3+	Positive	Concordance
0	Negative	0	Negative	Concordance
1+	Negative	1+	Negative	Concordance
3+	Positive	1+	Negative	Discordance
1+	Negative	1+	Negative	Concordance
3+	Positive	3+	Positive	Concordance
1+	Negative	0	Negative	Concordance
0	Negative	1+	Negative	Concordance
3+	Positive	3+	Positive	Concordance
0	Negative	0	Negative	Concordance

Table 3. Concordance of HER2 in metastatic lymph nodes and primary sites of invasive breast cancer

	HER2 Status (Primary/Metastatic Lymph Nodes)			
	+/+	+/-	-/+	-/-
n	13	3	1	13

Concordance: 26/30 (86.67%) Kappa coefficient (0.735)

DISCUSSION

This study reported 26 (86.67%) incidences of HER2 concordance in primary tumors with metastatic lymph nodes, suggesting a high degree of consistency in its expression (Kappa 0.735). This result was divided into two categories: 13 patients with HER2 positive in both the primary tumor and metastatic lymph node, and 13 patients with HER2 negative in both the primary tumor and metastatic lymph node. These results are aligned with a previous study conducted in China that reported 90 cases (84.11%) of HER2 results on concordance between the primary tumor and lymph node. HER2 differences between primary tumor and metastatic lymph node occurred among 17 (15.89%) cases.[8] Earlier studies observed a high degree of consistency in HER2 expression between primary tumors and metastases.[8,11,12] However, other findings indicate that the HER2 status of the primary tumor differs from that at the site of metastasis.[8,11,13] The reasons for differences of HER2 status in metastases compared to primary tumors have not been determined.[11] Discrepancies between primary tumors and lymph node metastases can occur for a variety of reasons, including differences in technical assessment or pre-analysis, the use of different histological tissue fixation times and techniques, or biologic changes during tumor progression. Furthermore, in patients with chemotherapy histories, the polyploidization in tumor cells may be misconstrued as HER2 amplification, potentially leading to false-positive results.[14,15] To circumvent this result, patients with chemotherapy history before the surgery were included in the exclusion criteria.

Four patients (13.33%) showed changes in HER2 status between the primary tumor and lymph node metastases, meaning that the HER2 expression profile tends to vary over time with the development of metastases. In one case (3.33%), the HER2 result was negative in the primary tumor and positive in the lymph node. This patient may benefit from targeted anti-HER2 treatment. HER2 targeted treatment could still benefit around 10% of patients with HER2-negative primary breast cancer and HER2-positive metastases, according to the latest research.[16,17]

Although simultaneous determination of HER2 and hormone receptors in breast cancer and associated metastatic lymph nodes is not mandatory at this time, the finding that lymph node metastases in breast cancer may have a different status when compared with markers of the primary tumor is important. This may greatly influence therapeutic management and may impact patient prognosis, given that loss of HER2 amplification in lymph nodes has been shown to worsen post-recurrence outcomes and overall survival in breast cancer patients.[18,19] On the other hand, an increase in HER2 expression in metastatic lymph nodes of breast cancer allows the possibility of targeted treatment.[11,20,21] Therefore, simultaneous evaluation of the HER2 status of the primary tumor and metastatic sites is recommended for patient treatment, such that the patient's prognosis and survival may improve.[8,22]

The limitations of this study include the small sample size, as it only involved the population of the Yogyakarta area, meaning that the results may not be generalizable to the entire population of Indonesia. The findings of this study can provide valuable insights in the decision-making process for the use of anti-HER2 therapy in breast cancer patients. The researchers hope that future studies can be conducted on a larger scale, encompassing a broader population across Indonesia, to offer a more comprehensive overview, especially since similar data is currently unavailable in this country.

CONCLUSION

We conclude that there is a discordance of HER2 status between the primary tumor and lymph node metastases in invasive breast cancer patients. It is necessary to simultaneously evaluate the HER2 status of the primary tumor and the metastases. This way is recommended for better prognosis and survival.

Conflict of Interest

All authors have no conflicts to disclose. No existing or potential conflict of interest relevant to this article was reported.

Acknowledgement

The authors would like to thank the Academic Hospital of Universitas Gadjah Mada for the contribution in this study.

Author Contributions

NN: conceiving and developing the idea of research and article, study design, study supervision, data collection and processing,

analysis and interpretation, literature review, writing the article. SLA: conceiving and developing the idea of research and article, study design, analysis and interpretation, writing the article. JJ: data collection and processing, analysis and interpretation, writing the article. FR: conceiving and developing the idea of research and article, data analysis, literature review, writing the article. All authors have read and approved the final manuscript.

Funding

No funding was received for conducting this study.

Data Availability Statement

The dataset analyzed during the current study is available from the corresponding author upon reasonable request.

Declaration of Use of AI in Scientific Writing

Nothing to declare

REFERENCES

1. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—an updated review. Cancers (Basel). 2021;13:4287. doi:10.3390/cancers13174287.
2. Union for International Cancer Control Globocan. GLOBOCAN 2020: new global cancer Data. UICC; 2020.
3. International Agency for Research on Cancer World Health Organization. Global Cancer Observatory. Indonesia. Lyon, France: International Agency for Research on Cancer; 2020.
4. Badan Penelitian dan Pengembangan Kesehatan -. Laporan Provinsi DI Yogyakarta Riskesdas 2018. [Report of the Special Region of Yogyakarta Basic Health Research 2018.] Jakarta: Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan; 2019. Indonesian.
5. Early Breast Cancer Trialists' Collaborative group (EBCTCG). Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials. Lancet Oncol 2021;22:1139-50. doi: 10.1016/S1470-2045(21)00288-6.
6. Kreutzfeldt J, Rozeboom B, Dey N, De P. The trastuzumab era: current and upcoming targeted HER2+ breast cancer therapies. Am J Cancer Res 2020;10:1045-67.
7. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67:93-9. doi: 10.3322/caac.21388.
8. Li MH, Hou CL, Wang C, Sun AJ. HER-2, ER, PR status concordance in primary breast cancer and corresponding metastatic lesion in lymph node in Chinese women. Pathol Res Pract 2016;212:252-7. doi: 10.1016/j.prp.2015.11.019.
9. Sutthipongsupa T, Wongchansom K, Wuttipanich P, Charoenpitakchai M. A comparison study of molecular classification of primary invasive breast carcinoma and corresponding metastatic carcinoma in axillary lymph nodes by immunohistochemistry. Asian Arch Pathol 2020;2:20-32.
10. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb) 2012;22:276-82.
11. Ieni A, Barresi V, Caltabiano R, et al. Discordance rate of HER2 status in primary breast carcinomas versus synchronous axillary lymph node metastases: a multicenter retrospective investigation. Onco Targets Ther 2014;7:1267-72. doi: 10.2147/OTT.S65294.
12. Cai M, Li M, Lv H, et al. HER2-low breast cancer: evolution of HER2 expression from primary tumor to distant metastases. BMC Cancer 2023;23:656. doi: 10.1186/s12885-023-11134-4.
13. Almstedt K, Krauthauser L, Kappenberg F, et al. Discordance of HER2-Low between primary tumors and matched distant metastases in breast cancer. Cancers (Basel) 2023;15:1413. doi: 10.3390/cancers15051413.
14. Valent A, Penault-Llorca F, Cayre A, Kroemer G. Change in HER2 (ERBB2) gene status after taxane-based chemotherapy for breast cancer: polyploidization can lead to diagnostic pitfalls with potential impact for clinical management. Cancer Genet 2013;206:37-41. doi: 10.1016/j.cancergen.2012.12.001.
15. Ahn S, Woo JW, Lee K, Park SY. HER2 status in breast cancer: changes in guidelines and complicating factors for interpretation. J Pathol Transl Med 2020;54:34-44. doi: 10.4132/jptm.2019.11.03.
16. Ulaner GA, Hyman DM, Ross DS, et al. Detection of HER2-positive metastases in patients with HER2-negative primary breast cancer using 89Zr-trastuzumab PET/CT. J Nucl Med 2016;57:1523-8. doi: 10.2967/jnumed.115.172031.
17. Mercogliano MF, Bruni S, Mauro FL, Schillaci R. Emerging targeted therapies for HER2-positive breast cancer. Cancers (Basel) 2023;15:1987. doi:10.3390/cancers15071987.
18. Widiana IK, Irawan H. Clinical and subtypes of breast cancer in Indonesia. Asian Pac J Cancer Care 2020;5:281-5. doi: 10.31557/apjcc.2020.5.4.281-285

19. Mogica JP, Tang H, Liang Y, et al. Prognostic impact of reduced HER2 protein expression in post-neoadjuvant therapy resection specimens: a single institution experience and review of the literature. Breast 2023;72:103586. doi: 10.1016/ j.breast.2023.103586.
20. Canadian Cancer Society. Targeted therapy drugs for HER2-positive breast cancer. Toronto, Canada: Canadian Cancer Society;2025.
21. Swain SM, Shastry M, Hamilton E. Targeting HER2-positive breast cancer: advances and future directions. Nat Rev Drug Discov 2023;22:101. doi: 10.1038/s41573-022-00579-0.
22. Peralta-Castillo G, Maffuz-Aziz A, Sierra-Murguía M, Rodriguez-Cuevas S. Neutrophil-lymphocyte index as prognostic factor for overall survival and disease-free survival in breast cancer patients. Revista de Senología y Patología Mamaria J Senol Breast Dis 2020;33:137-44. doi: 10.1016/j.senol.2020.06.004.