Nigerian Medical Journal
NIGERIA MEDICAL ASSOCIATION
Print ISSN 0300-1652, E-ISSN 2229-774X

Original Article

Comparative Evaluation of HER2 Overexpression in Breast Carcinoma Using Cell Blocks and Corresponding Formalin-Fixed Paraffin-Embedded Tissue Blocks: A Prospective Study

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Abstract

Background: Breast cancer is one of the most common cancers among women in Nigeria. Human epidermal growth factor receptor 2 (HER2) is an important prognostic and predictive biomarker that guides targeted therapy. The tumour grade is an important prognostic factor and is also important in the treatment of patients. In a resource-limited setting, cell block cytology may serve as an alternative for initial biomarker assessment and also as an initial diagnostic tool for planning definitive management. The study aims to compare HER2 overexpression of breast carcinoma using cell blocks and corresponding paraffin wax-embedded (FFPE) tissue blocks and to evaluate the concordance between both methods.

Methodology: This was a one-year prospective study involving 83 cases of breast carcinoma patients with both cell block and corresponding FFPE tissue specimens. HER2 immunohistochemistry was performed using the ASCO/CAP 2018 guideline. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with 95% confidence intervals (CI). Concordance was assessed using Cohen's kappa statistic. McNemar's test was used for paired comparisons.

Results: The mean age of the study participants was 43.1 ±13.1 years, with a peak age group of 40-49 years. IHC HER2 overexpression was done on both cell blocks and histological blocks. In cell blocks, HER2 expression showed 15 cases (18.1%), 65 cases (78.3%), 3 cases (3.6%) were positive, negative, and equivocal, respectively while from histologic tissues, 15 cases (18.1%), 63 cases (75.9%), 5 cases (6.0%) were also positive, negative and equivocal respectively. The overall concordance rate between the two methods was 93.5%, with concordance rates of 100% for HER2-positive cases, 96.9% for HER2-negative cases, and 60% for equivocal cases. Sensitivity and specificity of cell block HER2 assessment were 96.9% (95% CI: 82.9-99.9) and 100% (95% CI: 94.3-100.0), respectively. The PPV of HER2 assessment on cell block was 100.0% (95% CI: 78.2-100.0), and the NPV was 97.1% (95% CI: 89.9-99.6). The kappa coefficient for agreement was 0.935, indicating excellent agreement. McNemar's test showed no statistically significant difference (p = 0.480). Equivocal (2+) cases were included without FISH confirmation. Most of the cases were invasive ductal carcinoma (NST), accounting for 97.6% (81 cases).

Conclusion: Cell block cytology demonstrates strong concordance with FFPE tissue for HER2 assessment and may serve as a reliable alternative for initial triaging in resource-limited settings, particularly where tissue is not readily feasible. However, confirmatory testing on tissue biopsy remains essential, particularly for equivocal cases.

Keywords: Breast carcinoma, HER-2 overexpression, Cell block, Histological tissue block, Immunohistochemistry.

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How to Cite: Sofoluwe GA, Yunusa R, Hamza A, Gana SL, Muazu J, Atanda AT, *et al.* Comparative Evaluation of HER2 Overexpression in Breast Carcinoma Using Cell Blocks and Corresponding Formalin-Fixed Paraffin-Embedded Tissue Blocks: A Prospective Study. Niger Med J 2026; 67 (2): 2994-3007. https://doi.org/10.71480/nmj.v67i2.1269

Quick Response Code:

Introduction

Breast cancer is the most common cancer in women, accounting for more than 1 in 10 new cancer diagnoses per year, and ranks fifth among all cancer-related causes of death globally.[1,2] However, breast cancer ranks first for incidence in the great majority of nations (159 out of 185), and for fatality in 110. Compared to developing countries, incidence rates are 88% higher in developed nations (55.9 and 29.7 per 100,000, respectively). Breast cancer incidence rates are rapidly increasing in developing nations of South America, Africa, and Asia, as well as in formerly low-incidence Asian nations (Japan and the Republic of Korea).[3,4] In Kano, Northwestern Nigeria, breast cancer was rated as the most common cancer, accounting for 14.1% of all diagnosed malignancies.[5]

Human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase receptor involved in cell proliferation and survival. HER2 overexpression occurs in approximately 15-20% of breast cancers and is associated with aggressive tumour behavior, poor prognosis, and response to targeted therapies such as trastuzumab. Accurate assessment of HER2 status is therefore critical in guiding therapeutic decisions.

In low-and middle-income countries (LMICs), access to standard histopathological processing and molecular confirmation techniques such as Fluorescence In-Situ Hybridization (FISH) is often limited due to cost and infrastructure constraints. As a result, alternative approaches such as cell block cytology are increasingly being explored for early diagnosis and biomarker assessment.

This study aims to evaluate the concordance of HER2 expression between cell block preparations and corresponding FFPE tissue blocks and to assess the potential role of cell blocks as a diagnostic adjunct in resource-limited settings.

Methodology

This was a one-year prospective study of breast carcinoma cases diagnosed in Kano. The study was conducted on clinically evaluated and suspected breast cancer patients.

Inclusion Criteria

1. All patients are clinically suspected to have breast cancer.
2. All newly diagnosed breast carcinoma cases were confirmed using Cell Block (CB) and Formalin Fixed Paraffin Embedded (FFPE) Tissue block, irrespective of their age, sex, and clinical conditions.

Exclusion Criteria

1. All cases were negative for malignant epithelial cells by initial cytology.
2. Cases with insufficient tissue for CBs.

The sample size of eighty- four (84) was calculated from the formula using a prevalence of 5.8% (Cameroon) of female breast cancer from a study done in South Africa.[6] This was the minimum sample size for this study.

The sample size was determined based on the number of eligible consecutive cases available during the study period. Due to the nature of the study, which focuses on diagnostic concordance, a formal sample size calculation based on prevalence was not considered appropriate.

Data Collection/Procedure

This prospective study was conducted over a one-year period. Samples were collected from patients presenting with suspected breast cancer seen at Aminu Kano Teaching Hospital (AKTH) and Murtala Muhammadu Specialist Hospital (MMSH), Kano. The patient's sample was obtained using a 21-G needle and syringe, and the sample was processed into a cell block. When malignancy was detected, the patient was recruited into the study after obtaining consent.

Preparation of CBs

- A sample was aspirated from the breast lesion using a 21-G needle and syringe.
- The material was allowed to clot for a few seconds in the needle lumen
- 10% buffered formalin was also aspirated into the syringe so as to dislodge the clot from the syringe wall.
- This was then fixed for 24 hours inside the plunger with a syringe or by expressing the content into a labeled 10% formalin universal bottle.
- The sample was centrifuged at 1800 rpm for 5 minutes.
- The supernatant was poured off, and the cell pellets were allowed to settle.
- The cell pellets were packed into filter paper, wrapped, and put in a cassette.
- This was passed into a tissue processor and processed as a routine biopsy specimen.
- The Cell block-FFPE was prepared and thereafter stained using routine H & E.

After staining, slides from both CB and FFPE Tissue blocks were graded using Robinson's and Nottingham grading systems, respectively. To avoid bias in grading, the CB and final tissue biopsy specimens were assigned different identifiers and were randomized by an assigned third party.

The Nottingham grade was evaluated as follows:

Nottingham criteria for grading invasive breast carcinomas

Feature graded	**Criterion**	**Score**
Tubule (gland) Formation	>75%	1
	10-74%	2
	<10%	3
Nuclear pleomorphism	Small, regular, uniform cells	1
	Moderate increase and variability	2
	Marked variation	3
Mitotic count was counted using a field area of 0.264mm^2 and a field diameter of 0.58mm)		
	0-9	1
	10-19	2
	>20	3

Based on the above, the individual parameter scores were then added together, and the histologic grade and interpretation were rendered as:

Score: 3-5	Grade 1	Well differentiated
Score: 6-7	Grade 2	Moderately differentiated
Score: 8-9	Grade 3	Poorly differentiated

Robinson's cytological grading system was evaluated as shown in Table 1 below:

Table 1:Robinson's cytological grading system

Parameter	Score 1	Score 2	Score 3
Cell dissociation	Cells mostly in clusters	Mixture of single cells and clusters	Mostly single cells
Cell size	1-2 times the size of Red Blood Cells (RBCs)	3-4 times the size of RBCs	≥5 times the size of RBCs
Cell uniformity	Monomorphic	Mildly pleomorphic	Pleomorphic
Nucleoli	Indistinct	Noticeable	Prominent
Nuclear margins	Smooth and grooves	Slightly irregular/folds	Buds and clefts
Chromatin	Vesicular	Granular	Clumped and cleared

A score of 1-3 was assigned to each of these parameters, and the tumours were graded by adding up the scores. The cytological grade was also evaluated as follows:

Score: 6-11	Grade 1	Well differentiated
Score: 12-14	Grade 2	Moderately differentiated
Score: 15-18	Grade 3	Poorly differentiated

Immunohistochemistry

Cell blocks and corresponding FFPE Tissue blocks of the cases were sectioned at 3µm for HER-2 immunohistochemistry, using the Thermo-Fischer Scientific *Ultra Vision Quanto Detection system*, which is an immunoperoxidase technique.

HER2 immunostaining was performed using Ventana anti-HER2/neu (4B5) antibody. Appropriate positive and negative controls were included in each staining batch to ensure quality assurance.

Evaluation of Immunohistochemical Staining

Immunostaining of HER-2 was evaluated using the recommended scoring system for breast cancer. The staining intensity was scored on a scale of 0-3.

Her-2/neu	Staining pattern	Her-2/neu protein over-expression
0	No reactivity seen	Negative
1	Weak, incomplete staining in any proportion of tumours	Negative
2	Non-uniform or weak to moderate complete membranous reactivity in >10% of the tumour cells or Intense complete staining of <30% of the invasive tumour cells.	Equivocal
3	Uniform, intense, complete membranous reactivity in >30% of the invasive tumour cells.	Positive

Overall, the scoring of HER-2 was as follows;
Scores of 0 and 1+ were considered negative
A score of 2 was considered to be Equivocal
A score of 3 was considered positive.

HER2 immunohistochemistry scoring was performed in accordance with the American Society of Clinical Oncology/College of American Pathologists ASCO/CAP 2018 guideline. Equivocal (2+) HER2 cases were included in the analysis; however, confirmatory FISH testing was not performed due to resource limitations, which were acknowledged as a limitation. Scoring was based on membranous staining intensity and completeness.

To minimize observer bias, HER2 scoring was performed independently and blinded to the corresponding paired sample results.

Data Management and Statistical Analysis
Statistical analysis was utilized using SPSS software package (version 23; SPSS, Inc., Chicago, IL, USA). Results were presented as photomicrographs, figures, charts, and tables. Quantitative data were summarized and presented using mean, median, range, standard deviation, and frequency distribution tables, while qualitative data were summarized and presented using frequencies and percentages.

Agreement between cell block and tissue block HER2 expression was assessed using Cohen's kappa statistic. Diagnostic performance indices, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated using histological tissue block results as the reference standard with 95% confidence intervals (CI).

Overall concordance between the two methods was calculated. Equivocal (2+) HER 2 cases were included in concordance analysis but treated as negative for diagnostic performance calculations due to lack of confirmatory FISH.

McNemar's test was used to compare paired categorical data and assess systemic differences between the two methods, while the Chi-square test was used to evaluate associations between categorical variables. A two-tailed p-value <0.05 was considered statistically significant.

Ethical Consideration

Ethical Clearances were obtained from the Ethical Committee of Aminu Kano Teaching Hospital and Murtala Muhammad Specialist Hospital (MMSH), Kano for the study on 6th December, 2022 and 23rd November, 2022 (reference number: AKTH/MAC/SUB/12A/P-3/VI/3538, NH|REC/28/01/2020/AKTH/EC/3438) and (reference number: SHREC/2022/3525, NHREC Approval Number, NHREC/17/03/2018 respectively. Additionally, written and verbal informed consent was obtained from the patients while maintaining confidentiality of the information.

Results

In the one-year study period spanning November 2023 and November, 2024, 768 fine needle aspirations were conducted, 262 (34.1%) of these were breast cases. A total of 98 (37.4%) of the breast cases were malignant, but only 83 cases in which both cell blocks and histological tissues were available were eventually included in this study. The excluded cases included 4 that were acellular/hypocellular and 11 that were lost to follow-up during the period, and no corresponding histological tissue could be obtained.

The patients' ages ranged from 23 to 80 years. The mean age of the study participants was 43.1 ± 13.1 years. The age distribution peaked in the 40-49 year age group. The age pattern shows numbers of cases rising progressively from the 20-27 age group, with a peak age group of 40-49 years, and declining progressively to the 80-89 age group. Patients within the age range of 40-49 years (28.9%) constituted the predominant age group, followed by those within the age range of 50-59 years (21.7%), while those within the age range of 80-89 years were the least, with 2.1% (as shown in Figure 1).

Out of the 83 cases, 80 (96.4%) were female, and 3 (3.6%) were male giving a female to male ratio of 27:1. Laterality showed that 48 (57.8%) presented with right breast mass, 34 (41.0%) on the left side and 1 (1.2%) presented bilaterally (as shown in Table 2).

Both Cell block and Tissue Block ratings were carried out by me, and 5 other raters, and the inter- and intra-rater Kappa coefficient of Cohen's and Fleiss were 0.794and 0.768, respectively; corresponding to a good strength of agreement. For HER-2 evaluation, the kappa rating was 0.935, corresponding to a very good strength of agreement.

HER2 scoring was performed independently and blinded to the corresponding cell block/tissue results to minimize observer bias.

Immunohistochemistry for HER-2 expression performed on both cell blocks and histological blocks showed that cell blocks, 15 cases (18.1%) were positive, 65 cases (78.3%) were negative and 3 cases (3.6%) were equivocal (as shown in Table 3) while from histologic tissues, 15 cases (18.1%) were positive, 63 cases (75.9%) were negative and 5 cases (6.0%) were equivocal (as also shown in Table 3).

In comparison with corresponding histologic biopsies, 2 cases were found to be discordant on the cell block. Of the 5 cases that showed HER2 equivocal expression on final histology, 2 cases were discordant on cell block (cases 67 and 77) (as shown in Table 4). All histologic cases showed no discordance on cell blocks with HER-2 negativity and HER-2 positivity expression.

The concordance rate was highest with HER-2 positive overexpression accounting for 100%, followed by HER-2 negative (96.9%), and the least concordance was with equivocal cases in which concordance was only 60%. The data was found to be statistically significant. The overall concordance was 93.5% (as shown in Table 4).

Using histological tissue blocks as the reference standard, the sensitivity and specificity of HER2 assessment on cell blocks were 96.9% (95% CI: 82.0-99.9) and 100% (95% CI: 94.3-100.0), respectively. The positive predictive value (PPV) of HER2 assessment on cell block was 100% (95% CI: 78.2 – 100.0) while the negative predictive value was 97.1% (95% CI: 89.9-99.6) as shown in Table 5.

The overall agreement between the two methods was excellent, with a Cohen's kappa coefficient of 0.935. McNemar's test showed no statistically significant difference between paired proportions ($\chi^2 = 0.50$, $p = 0.480$), while Chi-square analysis showed a strong association between the two methods ($\chi^2 = 74.89$, $p < 0.0001$) as shown in Table 6. Equivocal (2+) cases were included without FISH confirmation.

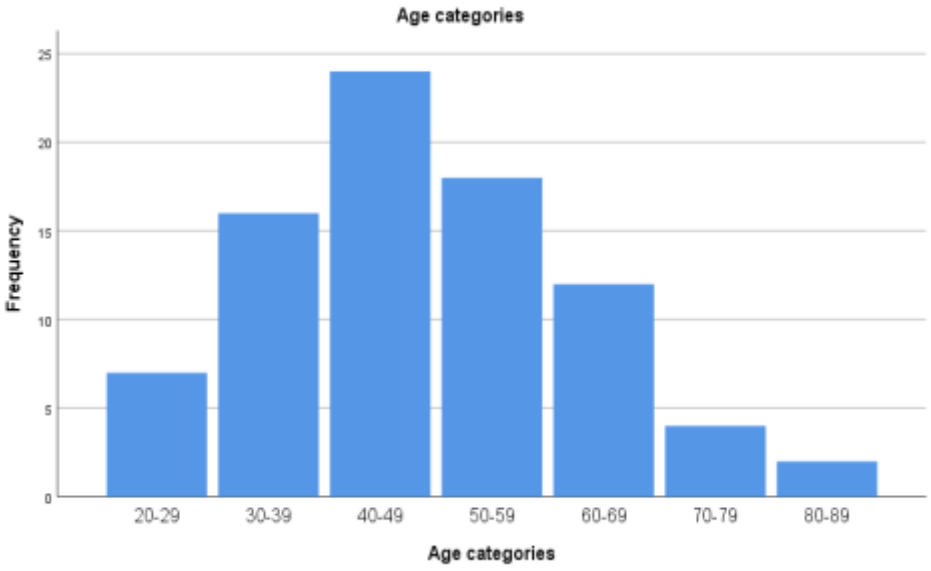


Figure 1: Distribution of cases by age group

Table 2: Distribution of cases according to gender and site of the breast carcinoma

		Frequency	**%**
Gender	Male	3	3.6
	Female	80	96.4
	Total	**83**	**100**
Site	Bilateral	1	1.2
	Right	48	57.8
	Left	34	41.0
	Total	**83**	**100**

Niger Med J 2025;67(2): 138 - 147, **ISSN**: 0300-1652, **E-ISSN**: 2229-774X, **Publisher**: Nigerian Medical Association. March – April **2026**

Table 3: Distribution of HER2 Expression

HER 2 Status	Cell Block n (%)	Tissue Block n (%)
Negative	65 (78.3)	63 (75.9)
Equivocal	3 (3.6)	5 (6.0)
Positive	15 (18.1)	15 (18.1)
Total	83 (100)	83 (100)

Table 4: Concordance Between Cell Block and Tissue Block

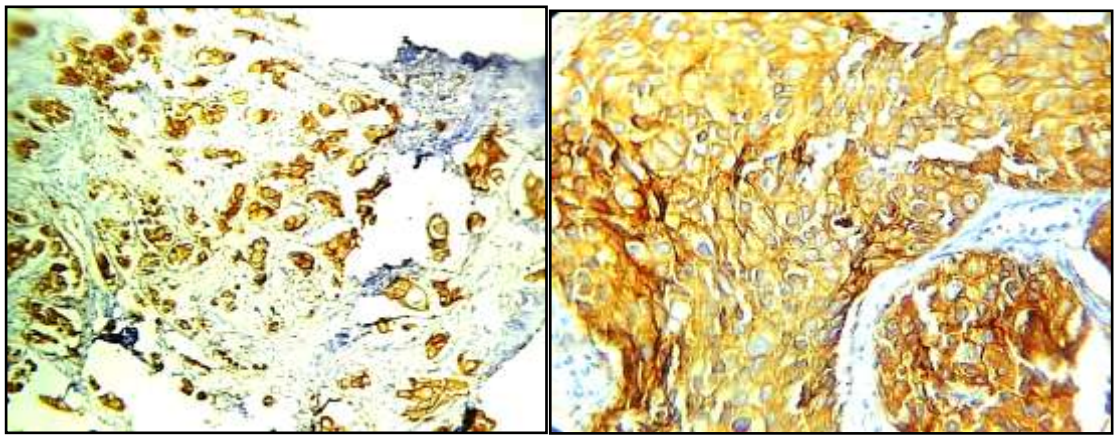
HER2 Category	Concordant Cases	Total Cases	Concordance (%)
Positive	15	15	100.0
Negative	63	65	96.9
Equivocal	3	5	60.0
Overall	78	83	93.5

Table 5: Diagnostic Performance of Cell Block (Reference = Tissue Block)

Parameter	Value %	95% Confidence Interval
Sensitivity	96.9	(82.0 - 99.9)
Specificity	100.0	(94.3 – 100.0)
Positive Predictive Value (PPV)	100.0	(78.2 – 100.0)
Negative Predictive Value (NPV)	97.1	(89.9 – 99.6)

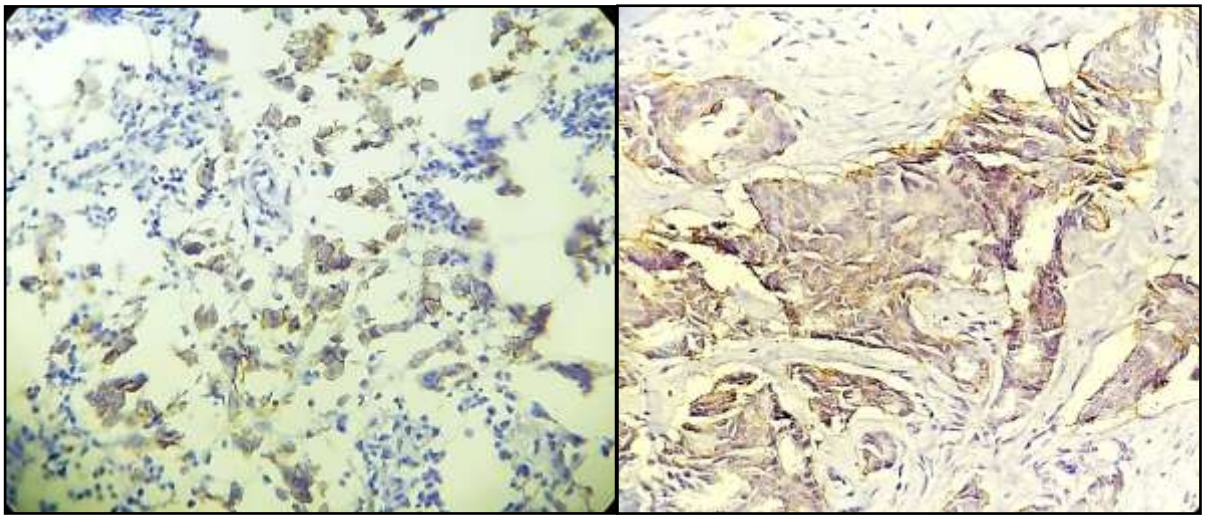
Table 6: Statistical Tests of Agreement

Test	Statistic	p-value	Interpretation
McNemar's Test	$\chi^2 = 0.50$	0.480	No significant difference
Chi-square Test	$\chi^2 = 74.89$	<0.0001	Strong association
Cohen's Kappa	0.935	-	Excellent agreement



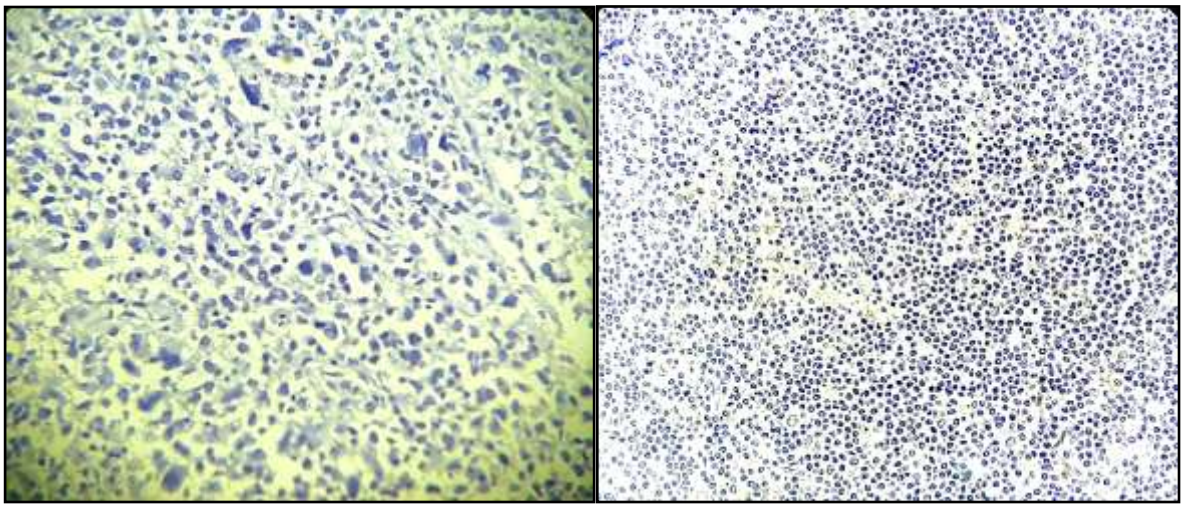
A **B**

Figure 2(A) HER-2 Positive overexpression on the cell block. 2(B) HER-2 Positive overexpression on the corresponding histological tissue block. (IHCx 200)



A **B**

Figure 3(A) HER-2 Equivocal expression on the cell block. 3(B) HER-2 Equivocal expression on the corresponding histological tissue block. (IHC x 200)



A **B**

Figure 4(A) HER-2 Negative expression on the cell block. 4(B) HER-2 Negative expression on the corresponding histological tissue block.(IHC x 200)

Discussion

The observation that breast cancer is more common among younger-aged women in large parts of Africa is corroborated by this study, where the average age at diagnosis is 43.1 years. Even though this index study is years later than the initial one carried out in the same facility, the average age of 42 years found then is no different.[7]A similar pattern has been established across other regions of Nigeria. The mean ages in Calabar,[8]Ilorin,[9] Gombe,[10] Zaria[11]and Enugu[12] are also all in the fourth decade. The mean ages across Africa, including those from Tanzania and Kenya, were 44.7 and 44 years, respectively.[13,14] This contrasts with the mean age of 60–64 years among Caucasians.[15]

The peak age in the index study was between 40 and 49 years old. This finding is similar to those of Adeniji *et al* in Ilorin, Omoniyi-Esan *et al* in Ile-Ife, and Ngadda *et al* in Maiduguri.[16,17,18] Comparable research has been done across Africa, including Libya[19] and Sudan.[20]

On analyzing HER2 amplification, our result (18.1% HER2 positive on tissue blocks) is in accordance with the commonly reported rate of 15-20% on solid tissue blocks.[21,22] In this study, the concordance rate between the HER2 overexpression on cell blocks and tissue blocks was 93.5%, the sensitivity was 96.9%, and the specificity was 78.3%. A similar study was conducted by Bansal *et al* with a concordance rate of 93.75%, which is similar to this study; the sensitivity of 91.67% is also similar, but their specificity of 94.44% is higher than ours.[23] Similar results have been observed by other investigators, Kumal *et al* and Vohra *et al.,* with concordance rates of 90% and 96.7%, respectively.[24,25]However, the studies by Nishimura *et al* and Dong *et al* have also reported concordance rates of 77% and 83.1%, respectively, for HER-2 scoring between cytological and histological samples.[26,27]In addition to the foregoing, the finding that all of the tumors that stained positive (3+) for HER2 by IHC on cell block preparations also stained positive on the corresponding histological tissue block is helpful in our setting, where patients may not be able to afford the cost of having an incisional tissue biopsy.

The high concordance observed for HER2-positive cases suggests that cell block preparations may be particularly useful for identifying patients eligible for targeted therapy in settings where access to tissue biopsy is limited. However, the relatively lower specificity observed in this study indicates that negative or equivocal results on the cell block should be interpreted with caution and confirmed using tissue biopsy, where possible.

The lower concordance observed among equivocal cases may be attributed to borderline staining intensity, tumour heterogeneity, and variability in sample adequacy between cytological and histological preparation. Variations in fixation time, antigen retrieval, and technical processing may also contribute to discrepancies in immunohistochemical staining results.

Equivocal HER2 (2+) cases were included in the concordance analysis; however, no FISH confirmation was performed due to resource limitations.
The relatively lower specificity observed suggests that false-negative or equivocal interpretations on the cell block may occur, emphasizing the need for confirmatory issue-based assessment, particularly in borderline cases.

The study's discordance can be attributed to the limited number of clusters that were aspirated from the cell block and the challenging cell morphology grading process. In this investigation, a total of more than five clusters were used. The discordant cases, upon re-examination, were cases where the clusters were lowest.

In the current investigation, technical errors (sampling and staining errors) might be the primary cause of the discrepancy between the IHC results of cell blocks and tissue blocks. Inadequate manual assays and ineffective antigen retrieval are examples of technical errors.[28,29]Immunostaining for HER2 is linked to significant variation in sample preparation, fixation, staining, and interpretation, and these may underlie the differences observed.[24,30,31]

Summary

Breast cancer was found in patients between the ages of 23 and 80, with a mean age of 43.1 years, and was more common in women than in men. In this study, there is a strong concordance of HER2 overexpression scoring between the cell block and histological tissue block.

Limitations of the Study

This study has several limitations. The sample size was relatively small and derived from a single geographic region, which may limit generalizability. Fluorescence In-Situ Hybridization (FISH) was not

performed for equivocal HER2 cases, introducing potential verification bias. Additionally, variability in sample handling, fixation, and staining may have affected immunohistochemical results. A cost-effectiveness analysis comparing cell block and tissue methods was also not performed. Some patients were lost during follow-up or after FNAC or CB procedure.

Conclusion

With an overall concordance of 93.5%, cell block cytology demonstrates strong agreement with histological tissue in HER2 assessment. Cell block cytology demonstrates strong concordance with FFPE tissue for HER2 assessment. It may be useful as an adjunct or preliminary triaging tool in resource-limited settings. However, confirmatory testing on tissue biopsy remains essential, particularly for equivocal and borderline cases.

To achieve this and even greater concordance, adequate attention must be paid to obtaining enough cell clusters, prompt fixation, optimal cell block preparation, and careful sectioning and immunohistochemical staining.

Acknowledgement

The authors acknowledge the support of the management of the Department of Histopathology, Aminu Kano Teaching Hospital, Kano.

Funding

No financial funding

Conflict of interest

The authors declare that there is no conflict of interest.

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