Receptor Status Concordance in Breast Carcinoma: A Comparative Study of Core Needle Biopsy and Surgical Specimens

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Abstract

Background: Accurate assessment of estrogen receptor (ER), progesterone receptor (PR), and HER2/neu status is essential for the optimal management of breast cancer. Core needle biopsy (CNB) is frequently used for initial diagnosis, but discrepancies in receptor status compared to surgical specimens may influence therapeutic decisions.

Objectives: The objective of this study was to evaluate to evaluate the concordance of ER, PR, and HER2/neu expression between CNB and surgical specimens in patients undergoing upfront surgery for breast carcinoma.

Methods: This prospective observational study included 62 female patients with biopsy-proven breast carcinoma who underwent surgery without prior neoadjuvant therapy. Biomarker expression from CNB was compared with postoperative surgical specimens using Cohen's kappa statistic.

Results: Perfect agreement was observed for tumor histologic type, Nottingham grade, ER, and PR status (Kappa = 1.0, $p < 0.001$). The HER2/neu status showed substantial agreement (Kappa = 0.82, $p < 0.001$), with discordance in 4.8% of cases. Subgroup analysis revealed lower HER2 concordance in patients with T4 tumors, advanced nodal stage, and rare histologic variants. Treatment regimens were modified in three patients due to HER2 discordance. These findings support the clinical impact of biomarker mismatch and emphasize the need for confirmatory testing in equivocal cases.

Conclusions: The study concludes that core needle biopsy (CNB) demonstrates high concordance with surgical specimens for ER, PR, and HER2/neu status. However, even minor HER2 discordance can significantly alter treatment plans. Reflex testing or reassessment should be considered in select cases to ensure accurate classification and appropriate therapy.

Keywords: Breast Neoplasms; Core Needle Biopsy; HER2 Neu receptor; Immunohistochemistry

Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide and a leading cause of cancer-related mortality. In 2020 alone, it accounted for 2.3 million new cases and over 685,000 deaths globally.[1] Breast cancer in India has overtaken cervical cancer as the most prevalent cancer in women, with more than 160,000 new cases and over 87,000 deaths reported in the same year.[2] These figures reflect not only the scale of the disease but also its profound impact on individuals, families, and healthcare systems.

Core needle biopsy (CNB) is widely used for the initial diagnosis of breast cancer. It allows pathologists to examine tissue architecture and assess key tumor biomarkers such as estrogen receptor (ER), progesterone receptor (PR), and HER2/neu. Though minimally invasive and generally accurate, CNB has limitations. It may miss crucial features due to sampling error or tumor heterogeneity, especially when the lesion is small or difficult to access. In contrast, surgical specimens provide a more comprehensive and detailed view of the tumor, offering definitive information for diagnosis, staging, and treatment planning.

Hormonal and growth factor receptors play a critical role in determining breast cancer behavior and therapeutic response. The presence of ER and PR typically indicates a better prognosis and a higher likelihood of response to endocrine therapy. The HER2/neu overexpression, while associated with a more aggressive clinical course, has become a valuable therapeutic target with the advent of HER2-directed treatments. The ability to accurately assess these markers is central to delivering personalized and effective care.

However, discrepancies in receptor status between CNB and surgical specimens have been reported in various studies, with discordance rates ranging from 5% to 40%.[3-5] These inconsistencies can stem from several factors, including technical variation in testing, differences in tumor sampling, and biological diversity within the tumor itself.[6] Such discordance may lead to misclassification of tumor subtype and, in turn, suboptimal treatment decisions.

The present study, therefore study aims to evaluate the concordance of ER, PR, and HER2/neu status between core needle biopsy and surgical specimens in breast cancer patients.

Methods

This prospective comparative observational study was conducted at the Departments of General Surgery and Pathology, ABVIMS & Dr. RML Hospital, New Delhi, between May 2023 and June 2024 after approval from the Institutional Ethical Committee. Female patients aged 18 years or older with a biopsy-proven diagnosis of breast carcinoma and scheduled for upfront surgery were eligible for inclusion. Patients who had received neoadjuvant chemotherapy, presented with metastatic disease, or had recurrent breast cancer were excluded.

Patients presenting with a breast lump to the General Surgery Department were clinically assessed. After triple assessment, the patients with suspicious findings were selected for core needle biopsy (CNB). The Core Needle Biopsy (CNB) samples were processed for histopathological examination to assess tumor type, grade, and the status of estrogen receptor (ER), progesterone receptor (PR), and HER2/neu. Based on clinical and pathological findings, patients were stratified for treatment. Those not requiring neoadjuvant chemotherapy underwent upfront surgery, and the surgical specimens were further examined histologically. This included re-evaluation of receptor status, tumor grade, margin status, and other relevant features.

To estimate the required sample size for this study, Cohen's kappa statistic was used as the basis, considering the primary objective of assessing concordance between biomarker expression (ER, PR, and HER2/neu) in CNB and surgical specimens. Concordance values from previously published data (Damodaran et al.)[7] were used: 0.82 for ER, 0.77 for PR, and 0.60 for HER2/neu. Assuming a kappa value of 0.60 for the most variable marker (HER2/neu), with a confidence level of 95% ($\alpha = 0.05$) and a statistical power of 90% ($\beta = 0.10$), the sample size was calculated using the formula derived from Cohen's method for estimating agreement between two raters:

$$m\kappa = \left[\frac{4(1-\kappa)}{WD^2}\right]\left[(1-\kappa)(1-2\kappa) + \frac{\kappa(2-\kappa)}{2\pi_D(1-\pi_D)}\right] Z^2_{1-\alpha/2}$$

Where:

- κ is the expected kappa value (0.60)
- πD is the probability of disagreement ($1 - \kappa = 0.40$)

- Z is the Z-score for a 95% confidence level (1.96)
- W is the margin of error (10%)

The calculated minimum sample size, using these parameters, was 56. Accounting for an anticipated dropout rate of 10%, the final sample size was rounded to 62 patients to ensure sufficient power for detecting meaningful agreement levels.

All data collected were first compiled in Microsoft Excel and then analysed using IBM SPSS Statistics version 25. The normality of continuous variables was evaluated using both the Kolmogorov-Smirnov and Shapiro-Wilk tests. Quantitative data were summarized as mean ± standard deviation for normally distributed variables and as median with interquartile range for skewed distributions.

For comparison between independent groups, the Student's t-test was used if data were normally distributed, and the Mann-Whitney U test was applied for non-normally distributed data. Paired t-tests or Wilcoxon signed-rank tests were employed for pre- and post-intervention comparisons, as appropriate. Categorical variables were presented as frequencies and percentages. Associations between categorical variables were tested using the chi-square test or Fisher's exact test where applicable.

The degree of agreement between biomarker results from CNB and surgical specimens was assessed using Cohen's kappa statistic. Interpretation of kappa values followed standard guidelines: values ≤0.20 were considered slight agreement, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and ≥0.81 almost perfect agreement. A p-value of less than 0.05 was considered statistically significant throughout the analysis.

Results

A total of 62 patients were included in the study. The demographic and clinical characteristics are summarized below:

The age of the patients ranged from 31 to over 70 years, with a mean age of 50.5 ± 10.04 years. The most represented age group was 41–50 years 32.3% (20), followed by 51–60 years 27.4% (17) and 31–40 years 21% (13). Only a small fraction were over 70 years of age 4.8% (3). This suggests that breast carcinoma most commonly affected middle-aged women in this cohort.

Tumors were more commonly seen in the left breast 69.4% (43) compared to the right 30.6% (19).

According to size, the majority of tumors 72.6% (45) were categorized as T2, indicating medium-sized tumors at the time of diagnosis. Smaller tumors (T1b and T1c) constituted 19.3%(12), while large tumors (T4) made up 8.1%(5) [Table 1].

Table 1: Distribution of Clinical and Pathological Tumor (T) and Nodal (N) Staging among the Study Cohort of Patients with Breast Carcinoma (n=62).

T stage	No.	%	N stage	No.	%
T1b	3	4.8	**N0**	40	64.5
T1c	9	14.5	**N1a**	11	17.7
T2	45	72.6	**N2**	5	8.1
T4	5	8.1	**N3a**	5	8.1
			N3b	1	1.6

In axillary nodal status, a significant proportion of patients 40(64.5%) had no lymph node involvement (N0), while others showed varying degrees of nodal spread: N1a 11(17.7%), N2 5(8.1%), N3a 5(8.1%), and N3b 1(1.6%) [Table 1].

In tumor Grading as per Nottingham Grade, out of 62 cases assessed, most tumors were classified as grade 2 45(72.5%), followed by grade 1 15(24.1%), with only two case of grade 3 (3.22%). This suggests that moderately differentiated tumors were most prevalent [Table 2].

Table 2: Comparison of Nottingham Histologic Grade in Core Needle Biopsy (CNB) and Final Surgical Resection Specimens in Patients with Breast Carcinoma (n=62).

Nottingham grade	CNB Specimen	Surgical Specimen
1	15	15
2	45	45
3	2	2

Histologically, Invasive ductal carcinoma was the predominant type observed in both CNB and surgical specimens 59(95.16%). Less common types included metaplastic carcinoma 2(3.22%) and mucinous carcinoma 1(1.61%). [similar for both samples i.e. CNB and Surgical Specimen] [Table 3].

Table 3: Comparison of Histopathological Subtypes of Breast Carcinoma Identified in Preoperative Core Needle Biopsy (CNB) and Final Postoperative Surgical Specimen Analysis (n=62).

Histopathological type of tumor	CNB Specimen	Surgical Specimen
Invasive Ductal Carcinoma	59	59
Metaplastic Carcinoma (Spindle type)	2	2
Mucinous carcinoma of breast	1	1

Estrogen Receptor (ER): ER was positive in 28(45.16%) of cases, while 34(54.83%) were negative, both in the CNB and Surgical Specimen [Table 4].

Table 4: ER status, PR status and Her2neu status (N=62) in Core Needle biopsy (CNB) and Surgical Specimen.

		CNB Specimen	Surgical Specimen
ER status	**Negative**	34	34
	Positive	28	28
PR status	**Negative**	41	41
	Positive	21	21
HER 2 NEU status	**Negative**	50	53
	Positive	12	9

Progesterone Receptor (PR): PR positivity was observed in 21(33.87%) of cases, with 41(66.12%) testing negative, both in the CNB and Surgical Specimen [Table 4].

HER2/neu Status: HER2 was negative in 50(80.64%) of CNB specimens and 53(85.48%) of surgical specimens. Positive HER2 expression was seen in 12(19.36%) and 9(14.51%) of cases respectively, suggesting a relatively low HER2 positivity rate in the population [Table 4].

Concordance Between CNB and Surgical Specimens

Tumor Type: Both CNB and surgical specimens showed identical results. This consistency is reflected in a Kappa value of 1.0, which indicates perfect agreement, and the p-value was less than 0.001, confirming that the agreement was statistically significant [Table 5, Figure 1].

Table 5: Agreement Metrics Between Core Needle Biopsy and Surgical Specimen.

Parameter	**Kappa Value**	**Interpretation**	**P-value**
Tumor Type	1.0	Perfect agreement	<0.001
Nottingham Grade	1.0	Perfect agreement	<0.001
ER Status	1.0	Perfect agreement	<0.001
PR Status	1.0	Perfect agreement	<0.001
HER2 Status	0.82	Substantial agreement	<0.001

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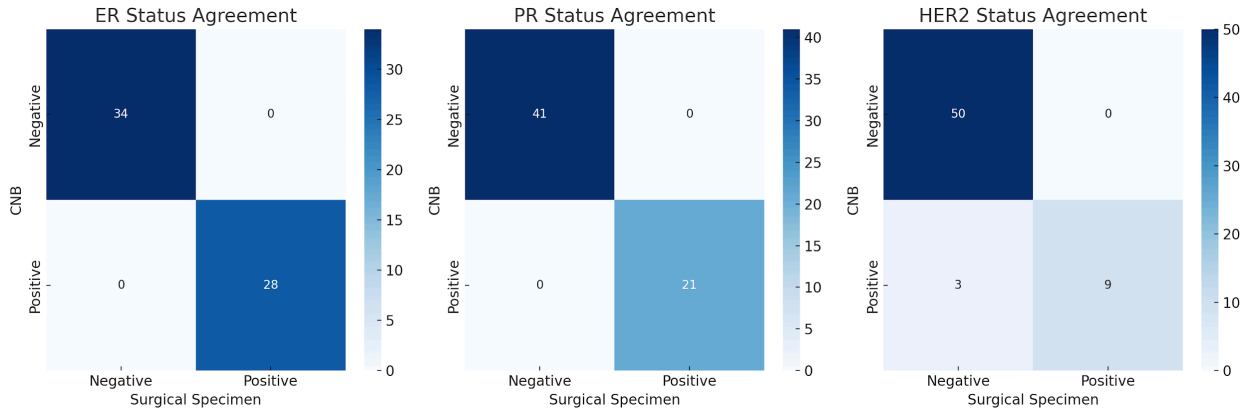

Figure 1: Agreement Plot (Confusion Matrices for Biomarkers)- These plots illustrate the agreement between core needle biopsy and surgical specimens for ER, PR, and HER2 status. Diagonal values indicate agreement; off-diagonal cells indicate discordance. HER2 showed minor discordance, whereas ER and PR were perfectly concordant.

ER and PR Status: ER and PR status were consistent between CNB and surgical specimens, each demonstrating perfect agreement (Kappa = 1.0; $p < 0.001$) [Table 5, Figure 1].

HER2/neu Status: The level of agreement between core needle biopsy (CNB) and surgical specimens for Her2Neu status demonstrated substantial concordance. The Kappa value for the agreement between CNB and surgical

specimens was 0.82, indicating a substantial level of agreement. This concordance was further supported by a p-value of less than 0.001, confirming the statistical significance of the findings [Table 5, Figure 1].

As discordance was seen in HER2 receptors, we did a Subgroup Analysis of HER2 Receptor Agreement. HER2 receptor agreement was evaluated by tumor stage, nodal status, and tumor histological type. While most subgroups exhibited excellent agreement, slightly lower values were observed in rare tumor types and advanced stages [Figure 2].

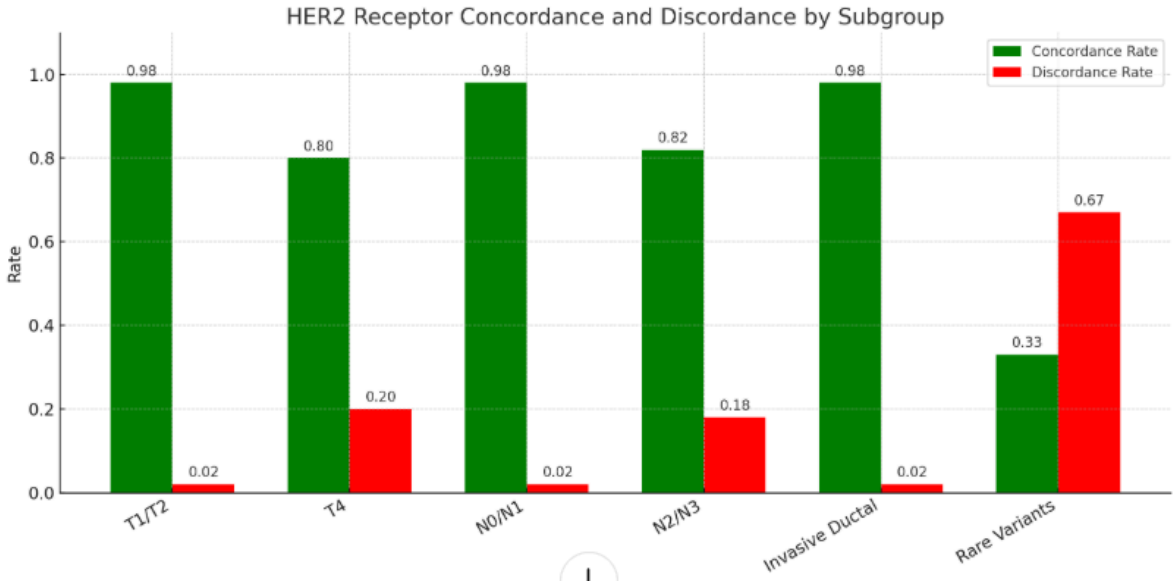

Figure 2: HER2 Agreement by Tumor Stage, Nodal Stage, and Tumor Type.

In the subgroup analysis of HER2 receptor status, stratification was performed by tumor stage (T stage), nodal status (N stage), and histological tumor type. While most subgroups exhibited strong agreement, certain patterns emerged that warrant further discussion.

For tumor stage, HER2 concordance was highest among T1 and T2 tumors, likely due to relatively uniform tumor morphology and easier sampling. However, among T4 tumors, which are typically more heterogeneous and biologically aggressive, the level of agreement slightly declined. This suggests that tumor size and extent may influence biomarker heterogeneity, highlighting the importance of thorough sampling or repeat testing in large lesions.

With respect to nodal involvement, patients with N0 and N1 disease showed excellent HER2 concordance. In contrast, those with advanced nodal disease (N2 and N3) exhibited lower concordance levels. This might reflect increased genomic instability or clonal evolution in more advanced disease, which may lead to phenotypic variability between primary and metastatic sites or within the primary tumor itself.

Histological subtype analysis showed that concordance was perfect in invasive ductal carcinoma (IDC), the most common type. However, in the rare subtypes such as metaplastic carcinoma and mucinous carcinoma, HER2 status concordance was less consistent. These variants are known for their atypical biological behavior and may not follow the standard expression patterns seen in IDC. Therefore, in non-IDC histology, caution is advised when interpreting HER2 results based on CNB alone.

These subgroup findings emphasize that while CNB is generally reliable, receptor heterogeneity may be more pronounced in biologically aggressive or rare tumor types, warranting confirmatory testing or multidisciplinary discussion before finalizing treatment plans.

Impact on Treatment: The final treatment plan showed minor variations due to HER2 neu discordance. Although these differences were statistically insignificant, chemotherapy plans differed in 3 patients when based on core needle biopsy (CNB) results compared to those based on surgical specimen analysis.

Discussion

In this prospective analysis of 62 breast carcinoma patients, the mean age was 50.5 ± 10.04 years, with the majority falling within the 41–60 years range. This aligns with earlier findings by Dutta et al, 2023.[8] and national cancer registries,[2] where middle-aged women constitute the largest affected group. However, the rising incidence among women aged below 40 underscores the growing need for awareness and screening in younger populations.

Left-sided breast involvement was more prevalent (69.4%), a finding consistent with prior epidemiological studies suggesting a slight but unexplained predominance of left-sided tumors. Most patients presented with T2-stage tumors (72.6%), indicating that although surgical resectability was feasible, early detection efforts must be intensified to capture disease at T1 stages. Nodal assessment revealed that while 64.5% of patients were node-negative (N0), a considerable proportion (35.5%) had nodal involvement, reinforcing the necessity of comprehensive axillary evaluation.

Invasive ductal carcinoma (IDC) was the most common histologic subtype (95.16%), consistent with global pathology trends. Tumor grading revealed a predominance of grade 2 tumors (73.8%), suggesting moderately differentiated disease that may reflect a transitional biological behavior between indolent and aggressive patterns.

Concordance of Receptor Status Between CNB and Surgical Specimens

Estrogen receptor (ER) and progesterone receptor (PR) statuses demonstrated perfect agreement between core needle biopsy (CNB) and surgical specimens (Kappa = 1.0, $p < 0.001$). The findings exceed the concordance rates reported in prior studies, such as those by Li et al, 2022.[9] and Dutta et al, 2023,[8] which typically note substantial agreement (Kappa = 0.75–0.90). These results reinforce the reliability of CNB in determining hormonal receptor expression, supporting its use in guiding endocrine therapy decisions without the need for repeat testing postoperatively.

HER2/neu showed substantial agreement (Kappa = 0.82, $p < 0.001$), with a discordance rate of 4.8%, where three CNB positive cases were HER2-negative on surgical specimen analysis. Although HER2 discordance was limited to 4.8%, its therapeutic implications are non-trivial. Previous studies suggest that omission or unnecessary administration of trastuzumab based on inaccurate HER2 status can significantly influence disease-free survival and quality of life.[10]

Notably, the HER2 discordance rate falls at the lower end of the range reported in literature[10,11] (typically 5–30%). Contributing factors may include:

- Tumor heterogeneity, where variable expression across tumor regions may result in different results depending on the sampled site.
- Sampling error during CNB, particularly in small or fibrotic lesions.
- Pre-analytic variables, such as delay in fixation or differences in staining protocols.
- Interpretive variability, especially in equivocal (IHC 2+) cases, where reflex testing by FISH is crucial.

In the subgroup analysis, slightly lower agreement was observed in metaplastic carcinoma and in patients with advanced nodal disease (N2/N3), possibly reflecting greater tumor heterogeneity or biological aggressiveness in these subsets.

Impact on Treatment Decisions and Management Modifications: While HER2 discordance was not statistically significant overall, it had direct therapeutic consequences in three patients, where HER2-targeted therapy was initially indicated based on CNB but ultimately withheld after final surgical pathology showed HER2 negativity. This led to changes in chemotherapy regimens and omission of trastuzumab. Although management in

these patients was guided by multidisciplinary review and clinical context, the necessity to modify treatment highlights the real-world clinical impact of biomarker discordance.

These cases emphasize the importance of reassessing receptor status on surgical specimens—especially in borderline HER2 cases—or confirming CNB findings with FISH when IHC results are equivocal. Failure to detect discordance early may result in overtreatment (e.g., cardiotoxicity from unnecessary trastuzumab) or undertreatment of HER2-driven disease.

Although the overall concordance of receptor status between primary breast tumors and surgical specimens was high in this study, the observed discordance—especially for HER2 remains clinically relevant. As seen in this cohort, even a small discordance rate (4.8%) led to therapeutic modifications in three patients. This aligns with findings by Patel et al, 2024,[12] who investigated immunohistochemical concordance between primary tumors and axillary lymph nodes. They reported discordance rates of 3.5% for PR and 12.9% for HER2, despite high overall agreement ($\kappa = 0.642$ for HER2). While statistically insignificant, such discordance can be clinically meaningful, potentially leading to overtreatment (e.g., unnecessary HER2-targeted therapy) or undertreatment (e.g., omission of targeted agents), thereby impacting patient outcomes. These results highlight the importance of confirmatory testing or re-evaluation of receptor status, particularly in equivocal or borderline cases.

Implications for Neoadjuvant Therapy: Neoadjuvant therapy is increasingly used in breast cancer to downstage tumors and assess treatment response. Decisions regarding such therapy are usually based on CNB findings. Inaccuracies in CNB receptor status, especially HER2, can therefore misdirect therapy selection. For example, initiating HER2-targeted therapy based on a false-positive CNB HER2 result may expose a patient to significant toxicity and cost without clinical benefit.

Equally problematic is the risk of missing a true HER2-positive tumor if CNB is falsely negative, denying the patient potentially curative therapy. If a patient does not respond to neoadjuvant therapy as expected, early reassessment is critical. Options include:

- Repeat biopsy (particularly if the lesion is accessible and measurable),
- Re-imaging and clinical correlation, and
- Post-surgical reassessment to confirm receptor status before adjuvant planning.

Guidelines from ASCO/CAP recommend confirming HER2 IHC 2+ results with FISH, especially in cases where treatment hinges on this determination.[13]

Conclusion

Core needle biopsy is a highly reliable tool for determining ER, PR, and HER2 status in breast cancer, showing strong concordance with surgical specimens. However, even infrequent HER2 discordance can lead to clinically meaningful changes in treatment. Reflex testing or confirmatory assessment should be considered, particularly when HER2 results influence therapeutic decisions. Larger, multicentre studies integrating molecular profiling and long-term outcomes are warranted to better understand and manage receptor discordance.

Study Limitations

The sample size, while adequately powered for concordance analysis, may limit the detection of rare discordant patterns or subgroup-specific trends.

The study was conducted at a single tertiary care centre, and receptor status assessments were performed without external review or dual-pathologist validation.

Patients undergoing neoadjuvant therapy were excluded by design; thus, findings cannot be extrapolated directly to that cohort.

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