Journal of Advanced Biomedical Sciences
Homepage: http://jabs.fums.ac.ir
Online ISSN: 2783-1523
Fasa University of Medical Sciences

Concordance of HER2 Status between Core Needle Biopsy and Surgical Resected Specimens of Breast Cancer: A Narrative Review

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[DOR: 20.1001.1.22285105.2023.13.4.7.4]
[DOI: 10.18502/jabs.v13i4.13902]

Article Info

Article Type:
Review Article

Article History:
Received
29 Sep 2023
Received in revised form
01 Nov 2023
Accepted
06 Nov 2023
Published online
07 Oct 2023

Publisher:
Fasa University of Medical Sciences

Abstract

Background & Objective: HER2, a molecular biomarker, is routinely evaluated in breast cancer patients to guide therapeutic decisions. However, the concordance of HER2 status between core-needle biopsy (CNB) and surgical specimen (SS) samples is not always high, potentially affecting the accuracy of diagnosis and treatment. This study aims to review recent studies assessing the agreement of HER2 status between CNB and SS samples in breast cancer patients.
Materials & Methods: A literature search was conducted in PubMed, Scopus, and Google Scholar databases from January 2018 to August 2023 using the keywords: concordance, core needle biopsy, resection, HER2 status. Ten articles meeting the inclusion criteria were selected for this review.
Results: The results demonstrated variable concordance rates of HER2 status between CNB and SS samples, ranging from 83.3% to 99.5%. The primary factors influencing discordance were tumor heterogeneity, preoperative treatment, sampling error, and differing testing methods. Discordance was more prevalent in HER2-negative and HER2-low tumors compared to HER2-positive tumors.
Conclusion: The concordance of HER2 status between CNB and SS samples is generally high but not perfect. Therefore, retesting HER2 status on SS samples is recommended to ensure optimal treatment decisions for breast cancer patients.

Keywords: Core needle biopsy, Surgical specimen, Concordance, HER2

Cite this article: Maghbool M, Samizadeh B. Concordance of HER2 Status between Core Needle Biopsy and Surgical Resected Specimens of Breast Cancer: A Narrative Review. JABS.2023; 13(2): 265-270.
DOI: 10.18502/jabs.v13i4.13902

Introduction

Cancer, a leading cause of mortality worldwide, ranks among the most prevalent cancers globally, with a rising incidence (1, 2). Accurate diagnostic testing is crucial for effective breast cancer management. Core-needle biopsy (CNB) stands as the gold standard for breast cancer diagnosis (3). This technique facilitates high-precision pathological evaluation of adequate samples, aiding in preoperative treatment planning. Upon biopsy confirmation of malignancy, cancer typing and receptor studies can be readily conducted (4). Molecular biomarkers, including estrogen receptors (ERs), progesterone receptors (PRs), and human epidermal growth factor receptor 2

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[DOI: 10.18502/jabs.v13i4.13902]

(HER2), are routinely assessed in the clinical management of invasive breast carcinoma patients. These receptors serve as targets for breast cancer therapies beyond systemic chemotherapy, including anti-HER2 therapy for HER2-positive patients. Accurate HER2 analysis is therefore essential (5, 6). The concordance of biomarker status between CNB and the surgical specimen (SS) has emerged as a vexing issue for pathologists and clinicians, particularly for HER2, which exhibits the lowest concordance rate (2). This discordance can have significant implications for treatment decisions (2). Evaluating HER2 status concordance between CNB and SS specimens and identifying influencing factors is therefore paramount. In this narrative review, we aim to synthesize the current literature on this topic and provide recommendations for clinical practice and future research.

Materials and Methods

This review conducted a comprehensive search across three databases (PubMed, Scopus, and Google Scholar) from January 2018 to August 2023 to identify relevant articles investigating the concordance of HER2 status between core-needle biopsy (CNB) and resected surgical specimens (SS) in breast cancer patients. The keywords employed for this search were: concordance, core needle biopsy, resection, HER2 status. The retrieved articles were meticulously screened for both relevance and quality. Articles with low quality (e.g., those published in journals with low credibility) were excluded, resulting in the selection of ten articles for this review.

Discussion

A comprehensive study by Yujie Lu et al., encompassing 5610 cases of early-stage breast cancer treated at the Comprehensive Breast Health Center, Ruijin Hospital in China between January 2009 and March 2022, stands as one of the largest investigations into the concordance of CNB with SS in HER2 status. All patients underwent both CNB and Excisional (EB) biopsies. The study revealed that 3209 (57.2%) of CNB and 3320 (59.2%) of EB cases exhibited HER2-Low status (1+ or 2+ IHC and FISH-negative). Notably, among 1066 HER2 Zero cases in CNB, 530 were classified as HER2-Low tumors. Conversely, 387 out of 3209 patients with HER2-Low tumors in CNB were HER2 Zero in EB, indicating a relatively low concordance (discordance rate of 23.13%) between CNB and EB in HER2-Negative breast cancer. These findings underscore the importance of EB examination in identifying patients who may benefit from anti-HER2 antibody-drug conjugates (7). Another large study conducted by Pölcher et al. retrospectively analyzed paired CNB and SS samples from patients with primary breast carcinoma treated in Germany over a three-year period. The study included 1307 paired specimens devoid of preoperative treatment. Concordance rates for ER, PR, Her2neu, and Ki67 status exhibited substantial to near-perfect agreement (κ = 0.91, 0.75, 0.89, and 0.61, respectively). While the concordance rates for individual markers were impressive, a significant proportion of molecular subtypes differed between CNB and SS, highlighting the mandatory nature of retesting markers to ensure optimal treatment decisions (8).

Slostad et al. conducted a retrospective analysis of patients with histologically confirmed invasive breast cancer who underwent CNB and SS pathology at their institution in the USA between January 2010 and May 2020. Among the 961 patients in their cohort, 259 (26.95%) exhibited complete concordance between CNB and SS for ER, PR, and HER2 IHC. Concordance, minor discordance, total concordance (concordance plus minor discordance), and major discordance between CNB and SS were reported for HER2 IHC (52.5%, 20.9%, 73.4%, and 26.6%), respectively. Discordance was more prevalent in PR and HER2 IHC. Their study suggests that retesting ER and HER2 can be clinically beneficial (9).

Robertson et al. conducted a retrospective study involving two cohorts of patients with primary breast cancer diagnosed between 2016 and 2017 in Sweden: one group underwent primary surgery (n = 526) and the other received neoadjuvant chemotherapy (NAC) (n = 216). The agreement between preoperative CNB and paired tumor specimens regarding biomarker assessment was evaluated in both cohorts. In the primary surgery cohort, HER2 IHC assessment demonstrated only moderate agreement (κ = 0.462). HER2 status, combining IHC and in situ hybridization, was discordant in 3.6% of cases, potentially influencing HER2-targeted therapy decisions. Generally lower concordance rates for HER2 were observed in the NAC cohort, where HER2 status was discordant in 7.4%.

Among the discordant cases in the primary surgery cohort, 6 equivocal cases (IHC 2+) with identical IHC scores between CNB and surgical specimen exhibited HER2 amplification only on the surgical specimen. This highlights the importance of retesting HER2, even for equivocal cases with a negative ISH on CNB, as HER2 status guides clinical treatment decisions. In the NAC cohort, the agreement of HER2 status between pre-NAC CNB and post-NAC histopathology was only moderate for HER2 IHC assignment. Of clinical interest, 10 tumors were HER2-positive on CNB but lost either HER2 expression or gene amplification after NAC. Conversely, one tumor assessed as HER2-negative on CNB had a positive HER2 status after NAC. Robertson et al. concluded that the concordance of HER2 and Ki67 between CNB and paired surgical specimens in primary breast cancer is inadequate, indicating a significant clinical value of biomarker retesting on surgical specimens.

Karaman et al. sought to compare the ER, PR, HER2, and silver in situ hybridization (SISH) results of CNB specimens and SS of their breast carcinoma cases in Turkey. They selected 97 cases with both CNB and SS, diagnosed with breast cancer at their center between 2017 and 2018. The correlation between CNB and SS in terms of HER2 was significant ($\chi 2$ = 74.19, P < 0.000; κ = 0.54, P < 0.000; and Spearman's Rho = 0.64, P < 0.000). HER2 status in CNB was positive in 15 (15.5%) patients, negative in 52 (53.6%), and "weak" in 20 (20.6%), while in SS, HER2 was positive in 13 patients (13.4%), negative in 69 (71.1%), and weak in 11 (11.3%). HER2 assessment had a sensitivity of 100% and a specificity of 73.4%. The authors concluded that if HER2 needle biopsy results are negative, assessments should be repeated in SS (11).

Verma et al. aimed to determine the concordance of CNB and SS for molecular profiling and to observe any changes following neoadjuvant chemotherapy. They conducted a cross-sectional study over one year, involving 95 cases in India. A total of 7 (7%) cases were HER2-positive on CNB and 8 (8%) on mastectomy, respectively. No change in HER2 status was observed after neoadjuvant therapy. The agreement of hormone receptor status between CNB and subsequent mastectomy was substantial (kappa values for ER, PR, and HER2neu were 0.608, 0.648, and 0.648, respectively). The study demonstrated that IHC is a cost-effective method for assessing hormone receptor expression. The authors concluded that ER, PR, and HER2 expression in CNB should be reassessed in excision specimens for optimal endocrine therapy management (12).

Damodaran et al. conducted a prospective study to assess the concordance between CNB and SS for ER, PR, and Her2 receptor status in breast carcinoma and its implications on treatment decisions. They enrolled 90 consecutive treatment-naïve operable breast cancer patients treated between September 2015 and April 2017 in India. All patients underwent core needle biopsy prior to definitive surgery. Immunohistochemistry (IHC) studies for ER, PR, and Her2 receptor assay were performed on both the CNB specimen and SS. The concordances

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[DOR: 20.1001.1.22285105.2023.13.4.7.4]
[DOI: 10.18502/jabs.v13i4.13902]

between CNB specimen and SS for ER, PR, and Her2 receptor were 92%, 88%, and 78%, respectively. Overall discordance for ER, PR, and Her2 status based on IHC tests on CNB specimen and its corresponding SS was 41% (37 out of total 90 patients), primarily for Her2 (20 patients). In total, a change in treatment decision based on IHC test results of the CNB specimen was made for 14 out of 37 discordant tests, translating to 15% of the overall study group. The study demonstrated near-perfect to substantial concordance between CNB specimen and SS for IHC tests of ER and PR status. However, the concordance for Her2 receptor was only moderate. The authors concluded that Her2 receptor assay by IHC is more sensitive in CNB specimens than in SS (13).

In two studies, CNB and SS biomarker assessment revealed high levels of concordance. One study, conducted by Shanmugalingam et al. in Australia, retrospectively collected histopathological biomarker information from preoperative CNB and SS on patients diagnosed with breast cancer through the Breast Screen Sydney West program over a four-year period between January 2017 and December 2020. Data were then analyzed to calculate the percentage of agreement and concordance using kappa values for ER, PR, HER2, tumor grade, and Ki-67. A total of 504 cases of invasive breast cancers were analyzed. Substantial concordance was observed for ER (96.7%; $\kappa = 0.687$) and PR (93.2%; $\kappa = 0.69$). Concordance for HER2-negative (IHC 0, IHC 1+) or HER2-positive (IHC 3+) tumors on CNB was 100% ($\kappa = 1.00$). Grade and Ki-67 showed moderate concordance, 72.6% ($\kappa = 0.545$) and 70.5% ($\kappa = 0.453$), respectively. The authors concluded that ER, PR, and HER2 exhibit high concordance, indicating that CNB is reliable in determining histopathological biomarkers for ER, PR-positive, and HER2-positive or -negative tumors. Therefore, retesting these biomarkers on SS may not be necessary (14).

Another study with a high concordance rate was conducted by Saghir et al. in Sweden, aiming to determine the concordance between biomarker status assessed as part of clinical workup on a CNB compared to a medically untreated surgical specimen. Paired CNB and surgical specimens from 259 patients that were part of the SCAN-B cohort were investigated. The concordance between immunohistochemical (IHC) -based biomarker status was examined. Biomarkers of interest included ER (specifically, the alpha variant), PR, Ki67, HER2, and tumor molecular subtype. In general, moderate to very good correlation in biomarker status between the paired CNB and surgical specimens was observed for IHC assessment (83-99% agreement, kappa range 0.474-0.917)(15).

In a single case study from Portugal, Vasques et al. presented a 33-year-old man with right breast cancer in April 2016, staged as cT4N1M0, HER2 2+ from IHC technique that was negative with silver in situ hybridization (SISH) technique. He received chemotherapy without anti-HER2 antibody-drug conjugates. In November 2016, due to the presence of lumbar metastasis, an oligometastatic approach and a modified radical right mastectomy were performed. HER2 in this specimen (post-chemotherapy) was positive using SISH. The authors commented that negative biomarkers in CNB should be repeated in the SS, particularly in patients who undergo neoadjuvant chemotherapy (6).

As discussed in the reviewed articles, varying results of concordance between biomarker status have been observed, with HER2 exhibiting the least concordance among these markers. This discrepancy can be attributed to various factors, including technical issues with the antibody kit used, the preparation, fixation, and staining process, interpretation protocol and interpreter experience, as well as tumor heterogeneity and the quality of the sample taken by the clinician during the biopsy. Since evaluating the status of

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[DOI: 10.18502/jabs.v13i4.13902]

this marker is crucial for determining the molecular profile and utilizing drugs like Herceptin, it is recommended to repeat the molecular biomarker results in surgical samples. In case of any discrepancy in the results, both biopsy and surgical samples should be reviewed again. If necessary, the staining and interpretation process should be re-performed on both samples to ensure the most accurate treatment plan for the patient and prevent tumor spread or recurrence.

Conclusion

This study underscores the significance of assessing HER2 biomarker status in breast cancer patients, as it influences the molecular profile and treatment options. It also acknowledges the factors that can contribute to discrepancies between biopsy and surgical sample results, such as technical issues, interpretation errors, tumor heterogeneity, and sample quality. We advocate for repeating the tests and reviewing the samples in case of any inconsistency to ensure optimal treatment outcomes and prevent tumor progression. Additionally, we emphasize the importance of retesting HER2 status in resection specimens, particularly for equivocal or negative cases on CNB, as it could impact the molecular profile and treatment decisions for breast cancer patients. This review further highlights that neoadjuvant chemotherapy may alter HER2 status and affect the concordance between CNB and resection samples.

Acknowledgments

The authors express their gratitude to the Clinical Research Development Unit at Valiasr Hospital, Fasa University of Medical Sciences.

Conflict of interest

None.

List of abbreviations

CNB: Core needle biopsy
EB: Excisional biopsy
ER: Estrogen receptor
FISH: Fluorescent in situ hybridization
HER2: Human Epidermal Growth Factor Receptor 2
IHC: Immunohistochemistry
NAC: Neoadjuvant chemotherapy
PR: Progesterone receptor
SISH: Silver insitu hybridization
SS: Surgical specimen

Funding

None.

Ethical Considerations

This article is written in compliance with all the ethical considerations.

Author's Contributions

All the authors have collaborated in collecting data and writing the article.

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