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Research Article

Evaluation of the Common Practice of Retesting HER2 Status in Excision Specimen When Core Biopsy Tested Negative in Breast Cancer

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Abstract

Objectives: Our study aims to review the common practice of retesting HER2 in breast Excision Specimens (ES) that tested negative in Core Biopsies (CB) for its potential significance and effectiveness.

Methods: Our Quality Assurance (QA) data was queried for all breast cancers with HER2 tests from 2015-2021. Patients with negative HER2 results (defined as IHC score 0, 1+, and 2+/FISH-) in Core Biopsies (CB) and subsequent HER2 testing in Excisional Specimens (ES) of the same breast cancer were included in the study. Results: A total of 548 cases with HER2 negative results (IHC 0 or 1+, n = 522; IHC 2+/FISH-, n = 26) on CB were found, and the results of their repeat HER2 tests in subsequent ES were reviewed. 32 out of 522 (6%) cases were upgraded, which included 31 cases from the negative category (IHC 0, n = 7, and IHC 1+, n = 24) on CB specimens to the equivocal IHC 2+ category on ES, and a single case of IHC 1+ to the IHC 3+ category. FISH was performed on all 58 cases (31 upgraded IHC2+, 1 upgraded IHC 3+, and 26 IHC 2+). With the 2018 updated HER2 FISH criteria, only 3/548 (0.54%) cases were FISH amplified. The final conversion rate from negative HER2 to a positive status between CB and ES is only 0.54% in our cohort, with non-descriptive HER2 retesting in ES.

Conclusions: The overall discordance of HER2 status between CB and ES is only 0.54%. Hence, the CB test results should be considered reliable for pre-operative patient management. Although rare, the converted HER2 result in retesting could significantly impact the post-operative management of individual patients. Our study provides data for analyzing the practicality of this common practice of retesting HER2 in ES for tumors with negative HER2 test in CB, thereby discouraging retesting in low-grade disease as per ASCO/CAP recommendation.

BACKGROUND

Female breast cancer accounts for 11.7% (2.3 million) new cases of an estimated 19.3 million new cancers in both sexes, surpassing lung cancer as the most commonly diagnosed cancer worldwide, according to Global Cancer Statistics 2020 [1]. In the United States, 287,850 women were diagnosed with invasive breast cancer, according to SEER data, in the year 2022. The estimated mortality rate is 6.9%, which depends on multiple factors, including the molecular subtypes of breast carcinoma. About 15% of breast cancers are HER2-enriched [2]. HER2-enriched tumors show higher histologic grade and stage, resistance to endocrine therapy, aggressive behavior, and poor prognosis, associated with a high rate of recurrence and mortality [3,4]. The survival rate at four years among women with Hormone Receptor-Negative(HR-) and HER2-positive (HR-/HER2+) is 82.7% compared to 92.5% of HR+/HER2- women [5]. However, with the introduction of trastuzumab, an anti-HER2 agent, the treatment and outcomes for HER2+ breast cancers have shifted dramatically in the last two decades [6,7]. Hence, an accurate and reliable laboratory evaluation of HER2 enrichment is essential for trastuzumab therapy and other neoadjuvant chemotherapy.

Core Biopsy (CB) is a universally accepted method of choice for tissue sampling of mammography-detected abnormalities for histologic diagnosis and breast cancer biomarker assessment when cancer is detected [8,9]. It has replaced fine needle aspiration as a diagnostic technique of choice with distinct advantages, including providing enough material to perform IHC for biomarkers evaluation and diagnosis, including HER2 status evaluation[10]. Testing of HER2 overexpression and amplification on CB samples is the standard of practice in every newly diagnosed, recurrent, and metastatic breast cancer.

The Human Epidermal Growth Factor Receptor 2 (HER2) is an epidermal growth factor receptor with tyrosine kinase activity located on chromosome 17 at q21. HER2-enriched breast cancers arise primarily due to the amplification of the proto-oncogene HER2 [11]. In clinical practice, immunohistochemistry for HER2 over-expression and/or in situ hybridization is used to determine the HER2 status of invasive breast cancer for patient care. The American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) published the first guidelines on HER2 testing in breast cancer in 2007, with subsequent updates in 2013, 2018, and 2023 as more data became available to improve clarity and address uncommon clinical scenarios. One of the recommendations is to consider repeating HER2 testing at excision if the initially tested core biopsy is negative, especially if the tumor is of a higher grade on ES [2]. The rationale behind retesting is that negative HER2 results in core biopsy could result from tumor heterogeneity or potential issues with antigenicity preservation in CB.

Because of this recommendation, it has been a common practice to retest HER2 in an Excision Specimen (ES) when the test was negative in CB in many institutions despite some earlier studies showing high concordance of HER2 test results between CB and ES [12-14]. At our institution, we estimated that about 80% more HER2 tests are done due to this practice. We evaluated this practice retrospectively for its real-time effectiveness at our institution.

MATERIALS AND METHODS

Our institution's immunohistochemistry lab quality assurance data of breast cancer cases with HER2 tests from 2015 to 2021 were retrospectively reviewed and analyzed. Inclusion criteria: all cases that had tested negative for HER2 by IHC and FISH in CB and subsequently retested in ES of the same tumor. All cases were first evaluated by IHC and reflexed to FISH when equivocal IHC result (score 2+ >10%) was encountered according to the current guidelines or criteria set by ASCO and CAP. Cases with inadequate tissue for HER2 IHC studies on CB samples and post-neoadjuvant ES samples were excluded.

All specimens were processed in a single laboratory with a uniform pre-analytics process (more than 6 hours and less than 72 hours fixation) as per ASCO/CAP guidelines (3). The HER2/neu immunocytochemical assay was performed on 4-micron paraffin sections using the FDA 501 (k) cleared Ventana PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal antibody on a fully automated Ventana BenchMark ULTRA autostainer according to the manufacturer's guidelines. According to the current ASCO/CAP guideline for breast cancer*, a score of 3+ in more than 10% of the tumor cells is considered positive; 2+ >10 or 3+ < or =10% is considered equivocal, and 1+ or 0 is considered negative. The current low HER2 1+ reporting will be evaluated in a separate study and not the scope of this study. Our lab fulfilled and followed the CAP recommendation of at least a 95% concordance between IHC 3+ and FISH-amplified cases and 95% between IHC negative (score 0 and 1+) with FISH non-amplified cases.

HER2 FISH assay was performed on a 4-micron paraffin section using the FDA-approved PathVysion HER2 DNA probe kit from Vysis (Abbott Molecular). The signals of both HER2 and CEP17 were counted in more than 20 carcinoma cells. According to the current 2018 ASCO/CAP guideline*, the HER2 gene is reported as amplified (POSITIVE) when a ratio of HER2/CEP17 greater than or equal to 2.0 and HER2/cell greater than or equal to 4.0 is identified by dual-probe assay, or HER2/cell greater than or equal to 6.0 in an IHC equivocal (2+) case. HER2 IHC stain was evaluated and reported by subspecialized breast pathologists, and HER2 FISH was assessed and documented by one FISH-specialized pathologist with more than 20 years of experience. Other baseline clinicopathological characteristics such as age, size, modified Bloom-Richardson grade, histologic subtype, and stage were collected. The HER2 result on core biopsy and excision and discordance rate were recorded.

RESULTS

During the study period, 548 breast cancer cases met the inclusion criteria. The patients were all female; the mean age was 61.2 years (29-87 years). The mean tumor size was 1.92 cm (0.5 to 9.8 cm). The baseline clinical-pathological characteristics of these IHC-upgraded 32 tumors are outlined in (Table 1). The type of surgical excision was wide local lumpectomy in 17 (53.1%) cases and mastectomy in 15 (46.9%) cases (Figure 1).

The cohort of 548 cases included HER2 negative (IHC 0 or 1+, n=522) and equivocal (IHC 2+/FISH-, n = 26) in a preceding CB and had HER2 retesting in subsequent ES by IHC and/or FISH analysis. 32 out of 522 (6%) cases were upgraded, which included 31 negative cases (IHC 0: n = 7, IHC 1+:n = 24) on CB specimens to the equivocal 2+ category, and a single case of IHC1+ to the IHC 3+ category on excision specimens. There were 26 cases with IHC 2+/FISH- in CB, and all 26 remained IHC 2+ in ES. FISH was performed on ES of all these 58 cases (31 upgraded from 1+ or 0, 1 upgraded from 1+, and 26 remained 2+). By FISH, three cases were converted to HER2 positive status (n = 2 with IHC 1+: 6%, 1 with IHC 2+/FISH indeterminate: 4%).

Table 2 shows the characteristics of 32 IHC negative CB specimens upgraded to IHC 2+/3+ in ES. In 5 cases, the tumor histologic grade was upgraded based on an increase in two or three parameters, including a combination of mitoses and nuclear pleomorphism. One displayed a degree of morphologic heterogeneity between CB and ES, as the CB contained a classic lobular carcinoma. In contrast, the ES had a higher-grade variant, the pleomorphic type, that was morphologically distinct. In three cases (n = 3), there was a discrepancy in the HER2 status between the core CB and ES by IHC. Characteristics of those three discordant cases are outlined in (Table 3). In the core biopsy, two cases showed IHC 1+, and one showed IHC 2+/FISH-. However, in the excisional specimen, two cases showed IHC 2+, and one showed IHC 3+.

Table 4 shows the HER2 FISH signal enumeration results of the 3 IHC upgraded cases with a HER2/CEP17 ratio of > 2.0, HER2/CELL > 4.0 in two, and > 6 in one. Another IHC upgraded

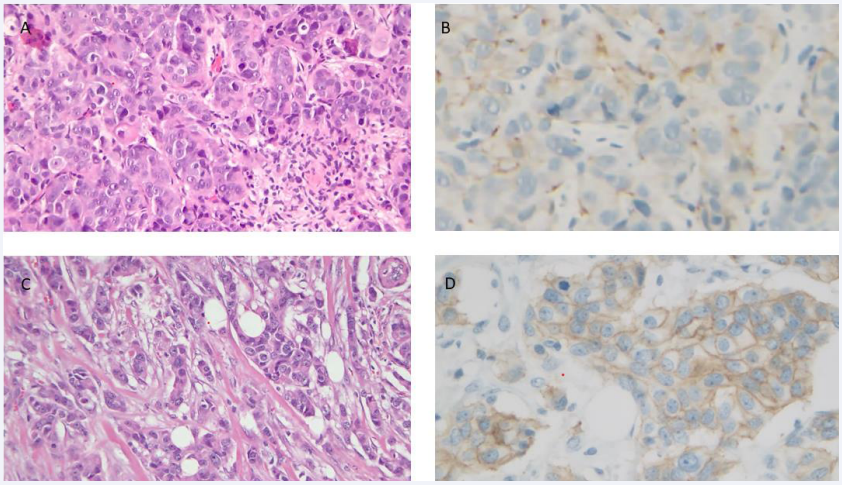

Figure 1 A. Invasive poorly differentiated ductal carcinoma on core biopsy (H&E, x20),
B. HER2 IHC showing weak, incomplete membranous (score 1+) staining on core biopsy (HER2 IHC, x20),
C. Invasive poorly differentiated ductal carcinoma on excision specimen (H&E, x20),
D. Subsequent HER2 IHC test in ES of the same breast cancer showing weak to moderate complete membranous (score 2+) staining (HER2 IHC, x20).

Table 1: Pathology of ES with 2+ or 3+ HER2 IHC that were previously CB HER2.

Characteristics	N	(%)
Surgery		
Partial mastectomy	17	(57)
Total mastectomy	15	(43)
Final histologic subtype		
IDC	25	(78.8)
ILC	3	(9)
ICDLF	3	(9)
IMC	0	(0)
Mixed IDC and IMC	1	(3.2)
Grade		
I	2	(6.3)
II	19	(59.4)
III	11	(34.3)
pT stage		
pT1	23	(71.8)
pT1a	2	(9)
pT1b	6	(26)
pT1c	15	(65)
pT2	7	(21.8)
pT3	2	(6.4)
pN stage		
pNX	3	(9)
pN0	21	(66)
pN1	7	(21.8)
pN2	1	(3.2)
LVI		
Positive	7	(21.8)
Negative	25	(78.2)
Estrogen Receptor (ER)		
Positive	29	(90.6)
Negative	3	(9.4)
Progesterone Receptor (PR)		
Positive	29	(90.6)
Negative	3	(9.4)

IDC: Invasive Ductal Carcinoma; ILC: Invasive Lobular Carcinoma; ICDLF: Invasive Carcinoma With Mixed Ductal And Lobular Features; IMC: Invasive Medullary Carcinoma; LVI: Lymph Vascular Space Invasion

Table 2: Change in histologic grade, HER2 status in 32 ES specimens in which HER2 IHC status was upgraded in ES.

	CB n (%)	ES n (%)
Tumor Grade		
1	3 (9.4)	2 (grade 1), 1(grade 2)
2	19 (59.4)	15 (grade 2), 4 (grade3)
3	10 (31.2)	7 (grade 3), 3 (grade 2)
HER2		
0	7 (21.9%)	7 (2+)
1+	24 (75%)	22 (2+/FISH-),
		1 (3+/FISH+)*
		1 (2+/FISH+)*
2+	1 (3.1%)	1 (2+/FISH+)*
Total	32	32

*Upgrades cases which are finally turned out to be HER2 amplified.

Table 3: Characteristics of Cases with HER2 Discordance between CB and ES (n = 3).

Age	53	84	72
CB Histology	Ductal	Ductal	Ductal
CB DCIS	Yes	Yes	No
CB Grade	3	3	2
CB ER (%)	90	95	100
CB PR (%)	90	5	90
CB HER2 IHC	1+	1+	2+/Indeterminate
ES Type	Partial	Partial	Partial
ES Histology	IDC	IDC	IDC
ES DCIS	Yes	Yes	Yes
ES Grade	3	3	3
ES Tumor Size	2.4	0.5	2.1
ES LN (+)/Total	16-Apr	N/A	N/A
HER2 IHC	2+, 60%	3+	2+
HER2 FISH*	3.42, 5.89, 1.72	2.77, 7.17, 2.58	2.25, 5.34, 2.37

*Ratio of HER2 to CEP17, HER2/cell, and CEP17/cell, respectively.

Table 4: Detailed IHC and FISH test results of CB and ES in 3 converted cases.

Cases	CB IHC/ FISH	ES IHC*	ES FISH**
1	1+	2+ 60%	3.42, 5.89, 1.72
2	1+	3+ 10%	2.77, 7.17, 2.58
3	2+/indeterminate	2+ 15%	2.25, 5.34, 2.37

CB: Core Biopsy; ES: Excision Specimen; FISH: Fluorescent In Situ Hybridization.
*% refers to the percentage of tumor cells showing 2+/3+ staining.
**Ratio of HER2 to CEP17, HER2/cell, and CEP17/cell, respectively.

case showed HER2/CEP17 ratio > 2.0 but HER2/CELL < 4.0 (not shown in Table 4). With the 2018 updated HER2 FISH criteria, only the first 3 cases were considered amplified. For all IHC 2+ upgraded ES (n = 32), only 3 (9.4%) cases were finally found to be HER2+ cases by FISH, while all 26 previously IHC 2+/FISH- cases remain negative in ES. The final positive conversion rate between CB and ES is only 0.54% in our cohort of 548 cases. Clinical follow-ups for the three patients with converted HER2 status in ES showed that two received adjuvant treatment with HER2-targeted therapy. These two patients were recurrence-free after follow-up intervals (60 and 55 months, respectively). The third patient declined and did not receive any further treatment due to several comorbidities [15].

DISCUSSION

The ASCO/CAP guideline on HER2 testing recurrently recommends repeat testing in specific following scenarios: 1: Grade 3 tumors because the higher grade tumors are more associated with positive HER2 status, 2: when the tumor appears morphologically different at excision, 3: the amount of invasive tumor in the core biopsy is small, 4: HER2 status is equivocal by both IHC and ISH in core biopsy and lastly 5: when there is a suspect that pre-analytical factors such as long ischemic time and short fixation of < 6 hours at play [16].

Although prior studies have shown high reliability of HER2 testing in CB with ~a 90% to 98.8% concordant rate in ES [12-15], we assessed the real-time effectiveness of retesting HER2 in excision in cases that tested negative in CB at our institution. We found true discordance or negative to positive conversion in only 3 out of 548 cases (99.5%). There were 77 (14%) grade 1 tumors in our cohort; 3 of them (4%) were IHC upgraded from negative (0 or 1+) to equivocal (2+), but none converted to positive by FISH in the subsequent ES specimens. Out of 471 tumors with grades 2 and 3, 58 (12.3%) of them either got upgraded to equivocal (2+) or remained equivocal (2+) or positive (score 3+) in ES. 31 (6.5%) of these cases were upgraded to equivocal (2+) and one (0,4%) to 3+ from CB negative (0,1+). 26 of 26 cases with 2+/FISH- in CB remained 2+. Finally, only three negatives on CB (2 IHC 1+, 1 IHC 2+/FISH-) were converted to HER2 amplified status after FISH assay on ES. Detailed analysis of these three converted cases is summarized as follows:

1. The first case was ER (90%, 3+) and PR (90%, 3+) positive invasive ductal carcinoma with IHC 1+ on CB, upgraded to equivocal 2+ on ES (Fig 1), which reflexed to FISH, which confirmed amplification (Ratio 3.42, HER2/cell 5.89). This finding prompted us to do FISH on the original CB sample. The HER2 FISH assay was performed retrospectively on the original CB and showed a similar result as ES. Hence, the IHC negative finding on the CB specimen likely resulted from true IHC negative/FISH amplified, a very unusual but well-recognized phenomenon, either due to technical or non-technical factors, including intratumoral heterogeneity, monosomy 17 and polysomy 17 [17,18]. The patient completed post-lumpectomy radiation, with 5000 cGy in 25 fractions to the ipsilateral breast/nodal regions, followed by a boost to the surgical bed to 6000 cGy. The patient received Herceptin for 33 weeks (63.5% of therapy), discontinued due to cardiomyopathy. Currently, she is on anastrozole and disease-free after 60 months of follow-up.

2. For the second case, the patient had ER+/PR+/HER2- (IHC 1+) invasive poorly differentiated ductal carcinoma excised with negative margins in the right breast seven months ago with post-operative anti-hormonal therapy and then developed new lesions in the same area one of which was biopsied and proven to be poorly differentiated invasive ductal carcinoma again. The second core biopsy specimen was tested ER (70%, 3+) and PR (15%, 3+) positive and HER2 negative (IHC 1+). Another excision was performed in a month. Multiple small foci (up to 0.5 cm) of high-grade invasive ductal carcinoma were noted around the prior surgical site, consistent with recurrence. The HER2 was retested in the ES specimen and was upgraded to IHC 3+ (10%) on ES. FISH was performed due to the unusual IHC conversion (1+ to 3+), which showed a high amplification of HER2 by FISH (Ratio 2.77, HER2/cell 7.17). FISH retrospectively tested the prior IHC 1+ CB specimen and was negative for HER2 amplification. This case might represent a diverse clonal evolution and/or tumor heterogeneity, which are rare but tend to happen in recurrent or post-treatment settings. The patient chose to be on aromatase inhibitors and declined Herceptin due to several comorbidities. She subsequently developed metastasis in the right axilla after four years of second breast cancer diagnosis, followed by metastasis in the mediastinal lymph nodes, pulmonary nodules in the right lung, and right pleural effusion. She is currently in palliative care.

3. The third tumor was ER (95%, 3+) and PR (5%, 3+) positive invasive ductal carcinoma with histologic grade 2 in CB but grade 3 in ES. The HER2 IHC was negative on CB (score 2+, FISH indeterminate, due to lack of tissue block, consult case). On ES, IHC remained 2+, but the FISH assay was positive for HER2 amplification (Ratio 2.25, HER2/cell 5.34). In this case, HER2 over-expression was not detected by IHC in both CB and ES, while amplification was detected in ES but was unknown in CB. So, the scenario to explain the discordance could be the same as case 1 if FISH was negative in CB or case 2 if FISH was positive in CB. The patient completed Herceptin therapy and is currently on aromatase inhibitors. She is disease-free after 55 months of follow-up.

This is the first study to assess the real-time positive conversion rate of HER2 status at excision in cases tested negative in CB in a single institution with uniform pre-analytics testing conditions per ASCO/CAP guidelines. Our study evaluated

the impact or potential benefit of the positively converted HER2 status to patient care. Our findings suggest that in a subspecialty practice setting with a well-controlled testing environment (pre-analytic, analytic, and post-analytic), the concordance of HER2 test results between CB and ES could be even higher than previously reported. Nevertheless, the common practice of reflex HER2 retesting of all previously CB-tested negative breast cancers (non-descriptively) in ES could pick up rare HER2 positive cases (3/548, < 1%), which could potentially impact patient care. All positively converted cases in our cohort are histological grade 2 or 3 cancers, and none of them are grade 1 cancer. This finding supports the ASCO/CAP's recommendation of retesting high-grade tumors and discourages non-descriptive reflex retesting for a more cost-effective practice.

A limitation of this study is related to the emerging scenario of low HER2 expression as a distinct biological entity, which was not the scope of this study.

In summary, the final conversion rate of a negative HER2 status to a positive status between CB and ES is only 0.54% in our cohort with non-descriptive HER2 retesting in ES. In a tertiary and subspecialized practice setting, CB test results should be considered reliable for pre-operative patient management. The descriptive HER2 retesting in ES following ASCO/CAP recommendation is highly recommended for a more cost-effective operation and healthcare cost control. Meanwhile, HER2 status conversion in ES can rarely occur in CB negative (IHC 0 or 1+, and IHC 2+/FISH-) cases. Detecting these rare events could still majorly impact individual patient care. Our study provides data for analyzing the practicality and cost-effectiveness of the common practice of retesting HER2 status in ES when tested negative in CB.

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