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Cytologic assessment of estrogen receptor, progesterone receptor, and HER2 status in metastatic breast carcinoma

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Abstract

BACKGROUND—Discordance in the receptor status between primary breast carcinomas (PBC) and corresponding metastasis is well documented. Interrogation of the receptor status of metastatic breast carcinoma (MBC) in cytology material is common practice; however, its utility has not been thoroughly validated. We studied patients with MBC, and evaluated the concordance rates of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) between PBC surgical specimens and corresponding MBC cell blocks (CBs). We correlated the findings with clinicopathologic variables and with the fixation methods used.

METHODS—We searched for patients with MBC diagnosed on cytology from 2007 to 2009 and selected those with ER, PR and HER2 tested in both the PBC surgical specimens and the MBC CBs. We included CBs fixed in formalin and methanol based solution (CytoLyt®). All slides were reevaluated by cytopathologists. Clinical information was retrieved from the medical records.

RESULTS—We studied 65 patients with PBC and MBC paired specimens. The concordance rates between PBC and MBC were 78.5%, 58.5% and 96.9%, for ER, PR and HER2, respectively. When discordant, PR status switched from positive (PBC) to negative (MBC) in most cases (23/27). The PR concordance rate was 45.2% for CBs fixed in formalin and 70.6% for those fixed with CytoLyt® (p=0.047).

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- MF, OL, ME Contributed to the planning of the study
- FP, MPM, RDJ, FK, ME, OL contributed to the conduct of the study
- FP, RDJ, MPM, FK, MF, OL, ME contributed to the reporting of the study
- FP, ME are responsible for the overall content of the study as guarantors

CONCLUSION—The ER, PR and HER2 concordance rates between the PBC and MBC CBs are similar to those reported in paired surgical specimens. PR status was the most prevalent discordance and was not accompanied by a switch in ER.

Keywords

estrogen receptor; progesterone receptor; HER2; cytology; FNA; metastasis; breast cancer

INTRODUCTION

The clinical management of patients with breast carcinoma is largely dictated by the receptor status of their tumor. Accurate assessment of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression is critical to identify populations that could benefit from hormonal or anti-HER2 targeted therapies.

Optimization of therapies for patients with early breast cancer has led to dramatic improvements in outcome, in contrast, metastatic breast cancer (MBC) remains incurable.¹ Even though median survival following occurrence of metastasis is short, 23.1 months in a recent report, survival times of MBC patients show great variation.²

In current practice, the management of patients with MBC is mainly based on the receptor status of their primary tumor.³ Nonetheless, biomarkers should be evaluated at least once in MBC, if clinically feasible, as per recent recommendations.⁴ In patients whose primary and metastatic tumors have a dissimilar immunoprofile, it is recommended to consider the use of endocrine or anti-HER2 therapy if hormone receptors (HRs), ER and PR, or HER2 were positive at least once, irrespective of timing.⁴

The heterogeneity of breast carcinoma is both spatial and temporal. While in general, the immunoprofile of a primary breast carcinoma (PBC) and its corresponding metastatic sites is expected to be analogous, discordance in the receptor status has been documented for several decades.^{3, 5–7} A recent meta-analysis of 48 different studies reported pooled discordance rates of 20% for estrogen receptor (ER; range 3–62%), 33% for progesterone receptor (PR; range 12–54%), and 8% for HER2 (range 0–24%).⁵ Notably, Amir et al. have shown that receptor discordance in MBC has an impact in therapeutic decisions.⁷ Some authors have suggested that receptor status discordance between PBC and MBC is associated with poorer patient outcome, presumably due to suboptimal treatment, not adjusted to the changes in receptor status.^{8, 9} Cytological evaluation of MBC has become common practice.^{10–13} The minimally invasive nature of fine needle aspiration (FNA) procedures facilitates tissue sampling of metastasis, and malignant effusions can be evaluated solely by cytology. Guidelines for receptor evaluation in surgical specimens are well established.^{14–16} However, the accuracy of receptor status in metastatic breast disease diagnosed in cytology specimens has not been thoroughly evaluated despite cytology's widespread use. Receptor concordance rates between PBC and MBC in surgical pathology specimens have been widely studied, whereas studies comparing PBC in surgical specimens with MBC in cytology material are scarce. Furthermore, pre-analytical factors, such as the specimen fixative, can have an effect on receptor immunoreactivity in breast carcinoma.

Thus, determining the utility of cytology samples for HRs and HER2 evaluation in MBC is of paramount importance.

In the present study we compared the ER, PR and HER2 status of matched pairs of PBC in surgical specimens and MBC in cytology samples, to determine receptor concordance rates and unveil characteristics of discordant cases. We also aimed to evaluate the impact of the fixative used for the cytology specimen on concordance rates.

MATERIALS AND METHODS

Case selection

The study was approved by the Institutional Review Board. A computerized search for patients with cytology specimens yielding the diagnosis of MBC between for 3 consecutive years (2007 to 2009) was conducted in the pathology archives of our institution. Cases selected included cytology specimens fixed in either methanol-based fixative (CytoLyt®) or formalin and in which a cell block was processed and used for immunohistochemistry. As the laboratory was transitioning to meet ASCO/CAP guidelines, the laboratory changed its cytology fixative CytoLyt® to formalin for any case in which there was a prior history or clinical suspicion of breast carcinoma.¹⁷ Patients, in whom ER, PR and HER2 were tested in corresponding PBC surgical specimens and MBC cytology samples, were included in the study. Cases with non identifiable tumor content or in which slides/material was unavailable for review were excluded from the study. Receptor status was re-evaluated in the MBC cytology specimen in cases with discrepancies between primary and metastatic tumors, when material was available. HER2 FISH results were also recorded. Patient clinical information, including gender, age at PBC diagnosis, and interval between the PBC and MBC were also annotated.

Assessment of receptor status

Fixation times ranged from six to 48 hours. Immunohistochemical (IHC) stains for ER, PR and HER2 were performed in 5 µm-thick whole tissue sections, or in cell blocks (CBs) fixed in CytoLyt® or formalin. FDA approved monoclonal antibodies for ER (Ventana; clone 6F11), PR (Ventana; clone 1E2), and HER2 (Ventana; clone 4B5) were utilized for IHC testing, with positive and negative controls. The hematoxylin and eosin (H&E) and IHC slides were re-reviewed by 2 pathologists (ME and RDJ); interpretation of ER, PR and HER2 IHC, and HER2 fluorescence in situ hybridization (FISH) results were done following the ASCO/CAP guidelines.^{14,15} ER and PR discordance between the PBC and the MBC was defined as a switch in the receptor status from positive to negative, or from negative to positive. HER2 status was determined following the integrated evaluation of IHC and FISH results. HER2 discordance between the PBC and MBC was defined as a switch from HER2 positive to negative, or HER2 negative to positive. Cases with HER2 status changes between the PBC and MBC from positive or negative to equivocal, or vice-versa, were considered concordant.

Statistical analysis

The statistical analysis was conducted using SPSS Statistics for Windows, version 22.0 (IBM; Armonk, NY, U.S.A). Evaluation of categorical variables was performed using Chi square or Fisher exact test, wherever appropriate. Continuous variables were assessed using one-way analysis of variance (one-way ANOVA). Comparison of receptor status between PBC and corresponding MBC was performed by calculating the Cohen κ coefficient. A p value <0.05 was considered significant.

RESULTS

Our study population ($N=65$) was comprised of 64 (98.5%) women and one (1.5%) man. The mean patient age was 52.4 years (± 1.5 ; range 25–79). The PBC was invasive ductal carcinoma (IDC) in 56 (86.2%) cases, invasive lobular carcinoma (ILC) in 5 (7.7%), and mammary with mixed ductal and lobular features (IMC) in 4 (6.2%). IHC analysis for ER and PR, and IHC (+/–FISH) studies for HER2 were performed in core needle biopsy (CNB) in 10 cases (15.4%), and in excision specimens in 55 (84.6%). The excision specimen was a lumpectomy in 26 cases (47.3%) and a mastectomy in 29 (52.7%).

The most common metastatic site was the liver (16; 24.6%), followed by bone (14; 21.5%), lung and lymph node (12; 18.5% each), chest wall (3; 4.6%), and adrenal, mediastinum, pleura and soft tissue (2; 3.1% each). The median time interval between the PBC and MBC histologic diagnosis was 26 months (range 1–170) (Table 1).

Immunohistochemical characteristics of the cohort

The immunohistochemical findings are summarized in Table 2. Fifty-two (80%) PBCs were ER positive and 13 (20%) ER negative. Thirty-three (50.8%) PBCs were PR positive, while 32 (49.2%) were PR negative. Ten (15.4%) PBCs were positive for HER2, whereas 55 (84.6%) were HER2 negative. We observed receptor status concordance rates between PBC and MBC of 78.5%, 58.5% and 96.9% for ER, PR and HER2, respectively (Table 3). The overall agreement in receptor status between PBC and MBC was moderate for ER (κ , 0.5), and HER2 (κ , 0.598), while only a slight agreement was observed for PR (κ , 0.176). There were five cases in which ER, PR and HER2 expression in MBC was evaluated in both a cytology specimen and a core needle biopsy. The ER, PR and HER2 status was the same in the cytology and the CNB specimen in 80%, 60% and 100% of cases, respectively. The correlation of receptor status between paired PBC and MBC is shown in Table 3.

Estrogen receptor status in corresponding primary and metastatic breast carcinomas

ER discordance between PBC and MBC was observed in 14 patients. Thirteen ER positive PBCs had a corresponding ER negative MBC specimen, while one patient had an ER negative PBC, with an ER positive MBC (21.5% discordance rate for ER) (Table 2). The mean patient age between the groups with ER concordant (52.4 ± 1.7) and discordant tumors (52.4 ± 2.6) was similar. The only male patient in the cohort had a tumor that showed ER concordance between PBC and MBC. No differences were seen in terms of PBC histologic type or type of PBC specimen tested between the ER concordant and discordant groups.

Notably, the ER PBC-MBC concordant cases did not differ from the discordant ones in terms of percentage of ER staining cells and intensity of staining in the PBC.

The mean interval between the PBC and MBC histologic diagnosis was comparable between ER concordant (43.8 ± 5.8 months), and ER discordant cases (35.3 ± 8.3 months).

Progesterone receptor status between corresponding primary and metastatic breast carcinomas

Twenty-seven cases showed PR discordance between the PBC and corresponding MBC. Of these, 23 cases showed PR positivity in the PBC specimen and were PR negative in the MBC (Fig 1), while four were negative for PR in the PBC sample and switched to PR positive in the MBC (41.5% discordance rate for PR) (Table 2).

The mean patient age was comparable between the PR concordant (51 ± 2 years) and PR discordant (53.6 ± 2.2 years) groups. The only male patient in the cohort had a tumor that showed PR concordance between PBC and MBC. All 5 ILCs were PR discordant, while 36 IDCs and 2 IMCs were PR concordant, and 20 IDCs and 2 IMCs were PR discordant ($p=0.019$). The mean interval between PBC and MBC histologic diagnosis was comparable between PR concordant (34.7 months ± 4.5) and discordant (52.3 months ± 9.7) groups.

No difference in the type of PBC surgical specimen used for receptor evaluation correlated with PR concordance. All PR discordant (27 cases) were also ER positive in PBC specimen (Table 4).

HER2 status between corresponding primary and metastatic breast carcinomas

Two cases showed a HER2 status switch, one positive (PBC) to negative (MBC), and the second one from negative (PBC) to positive (MBC) (3.1% discordance rate for HER2). Three HER2 negative and three HER2 positive PBCs were equivocal for HER2 in the MBC specimen (Table 2). The mean patient age in HER2 concordant (53.4 ± 1.6) and HER2 discordant cases (45.9 ± 4) was comparable. The only male patient showed a HER2 concordant tumor between PBC and MBC. The PBC histologic type or specimen used for receptor status evaluation was similar between HER2 concordant and discordant cases.

The mean interval time between the PBC and MBC histologic diagnosis was 43.4 months (± 5.3 ; 1–170) in the HER2 concordant group, and 32.1 months (± 12 ; 1–95) in the HER2 discordant group.

Characteristics of the cohort according to the MBC CB fixation method

Thirty-one patients had a MBC cytology specimen fixed in formalin, while in 34 patients the MBC sample was fixed in a CytoLyt®. No difference was seen in terms of clinicopathologic features between the two groups.

The IHC staining of PBC corresponding to the CytoLyt®-fixed cell blocks (CF-CB) and formalin-fixed cell blocks (FF-CB) showed comparable ER (70.6%; 90.3%), PR (44.1%; 58.1%), and HER2 (11.8%; 19.4%) positivity rates, respectively. PR discordance was the sole characteristic studied that was statistically different between the CF-CB and FF-CB.

Ten cases (29.4%) in the CF-CB group were PR discordant, whereas 17 discordant (54.8%) ($p=0.047$) in the FF-CB group. In the CF-CB group all PR discordant cases (10) showed a PR positive (PBC) to negative (MBC) switch, while in the FF-CB group 13 cases changed from being PR positive (PBC) to PR negative (MBC), and 4 cases from PR negative (PBC) to PR positive (MBC) (Table 5). The CF-CB and FF-CB groups showed comparable ER discordance rates, 17.6% and 25.8%, respectively. All six ER-discordant cases in the CF-CB group showed an ER positive (PBC) to negative (MBC) switch. In the FF-CB group seven cases underwent an ER positive (PBC) to negative (MBC) change, while one case showed an ER negative (PBC) to positive (MBC) change (Table 5). The CF-CB and FF-CB groups showed comparable HER2 discordance between PBC and MBC specimens, 0% and 6.5%, respectively. In the FF-CB group one HER2 discordant PBC was HER2 positive, and had a corresponding HER2 negative MBC, while the second HER2 discordant PBC was HER2 negative, with a matched HER2 positive MBC (Table 4).

DISCUSSION

Receptor discordance between PBC and MBC is a well-documented phenomenon. In a prospective study, Amir et al. showed 37.6% of MBC had discordance in any receptor, compared to the paired PBC.⁷ In our study we compare the receptor status in PBC surgical specimens to MBC cytologic specimens. We observed PBC to MBC discordance rates of 21.5%, 41.5%, and 3.1% in terms of ER, PR and HER2 status, respectively. Yang et al. observed comparable discordance rates: 18.8% for ER, 33.5% for PR and 6.8% for HER2.⁶

A meta-analysis of 48 studies showed that positive to negative receptor conversion is more frequent than the reverse. They observed a negative to positive status switch in 14%, 15% and 5% of cases for ER, PR and HER2, respectively, whereas the rates of ER, PR and HER2 positive to negative conversion were 24%, 46% and 13%, respectively⁵. In our cohort, HR positive to negative conversion was more frequent than negative to positive switches, while no differences were seen for HER2. In our cases, PR loss of expression in MBC was the most frequent receptor change, as previously reported by others.^{5, 7}

The evaluation of receptor status is known to be influenced by different factors, including fixation method. We compared patients in whom MBC cytology samples were evaluated in CF-CB vs FF-CB. Maleki et al. evaluated HR and HER2 expression in ER and PR positive, and HER2 overexpressing breast cancer cell lines following different CB fixation protocols, and showed that while ethanol-based and formalin fixation were comparable in regards to ER and PR status, HER2 results following ethanol-based CB fixation showed significant variability.¹⁰ The percentage of HER2 positive cells ranged from 5% to 95% across different fixation times. Ethanol fixation for longer than 48 hours resulted in very poor HER2 labeling.

Kinsella et al. compared the immunoprofile of 50 breast carcinomas (9 PBC and 41 MBC) evaluated in formalin fixed CB vs PBC surgical specimens. They report concordance rates of 92% and 78% for ER and PR status, respectively, higher than the ones we report for the FF-CB subgroup (74.2% and 45.2%, respectively). They reported IHC HER2 discrepancies, (changes from positive to negative, or negative to positive) in 2/50 cases (4%), and minor

discrepancies involving a positive or negative sample in one specimen and equivocal results in the other in 11/50 cases (22%).¹²

Hanley et al. compared the receptor status of primary or metastatic breast carcinomas, in CB fixed in 50% ethanol, followed by formalin, to formalin-fixed tissue blocks from CNB or excision specimens. They observed a 12.2% discordance rate between CB and CNB material, similar to the one we report in the CF-CB subgroup (17.6%). They also report a 26.8% PR status discordance rate between CB and CNB specimens, similar to what we observed in the CF-CB subgroup (29.4%). In their series, when excluding HER2 IHC equivocal cases from the analysis, they showed a 14.6% HER2 discrepancy rate. However, of 14 HER2 equivocal cases in CNB material, 7 were equivocal in CB, while 6 were positive and 1 negative.¹³ Since FISH for HER2 is routinely performed to resolve HER2 equivocal cases, discordance of HER2 equivocal status might not be clinically relevant.

In our cohort, CF-CB and FF-CB were comparable in terms of ER and HER2 concordance rates, while PR discordances were more frequent in cases with FF-CB. Nevertheless, changes in PR status do not usually have clinical or therapeutic consequences, as long as they are not concomitant with a switch in ER status. Altogether, these findings suggest that CBs fixed in CytoLyt®, which remains current practice in some institutions, may be acceptable for assessment of receptor status in situations when another specimen fixed in formalin is not available or cannot be obtained.

Importantly, Dieci et al. showed that conversion to HR or HER2 negative status in a metastatic site predicts poorer post-recurrence and overall survival.¹⁸ Moreover, a receptor status change may lead to a modification of the previously planned treatment regimen, as it has been reported in 14% of cases.⁷ Caution should be exerted when interpreting a change in receptor status, as it can be influenced by numerous factors, both technical, such as choice of fixative and fixation time, or biological, such as tumor heterogeneity¹⁶. Multiple studies have shown that tumors evolve over time, and metastatic tumors show enrichment of mutations present in the PBC, as well as de novo molecular aberrations, absent in the primary site. Treatment history, which might lead to clonal selection, should also be taken into consideration.¹⁹

Limitations of our study include its retrospective nature, and lack of treatment information. To the best of our knowledge this is one of the largest studies comparing receptor status in MBC sampled by cytology with paired PBC results evaluated in surgical specimens.

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Highlights

Metastatic breast carcinoma sampled by cytology has a high concordance rate of ER, PR and HER2 when compared to paired primary breast carcinoma results and is a reliable method for assessment of receptor status.

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Figure 1.

Invasive ductal carcinoma with a discordant progesterone receptor status between the primary and metastatic site. (a) Primary breast invasive ductal carcinoma (H&E stain). (b) Immunohistochemical stain for progesterone receptor in primary breast carcinoma. (c) Formalin-fixed cell block preparation of metachronous metastatic breast carcinoma to lymph node (H&E stain). (d) Immunohistochemical stain for progesterone receptor in formalin-fixed cell block of metastatic breast carcinoma to lymph node (H&E stain).

Table 1

Clinicopathologic Characteristics of the Population

Total		65 (100%)
Gender	Female	64 (98.5%)
	Male	1 (1.5%)
Age	Mean ($\pm$ SEM)	52.4 ($\pm$ 1.5)
	Median (Range)	53 (25–79)
Primary Breast Carcinoma		
Histology	IDC	56 (86.2%)
	ILC	5 (7.7%)
	IMC	4 (6.2%)
Specimen	CNB	10 (15.4%)
	Excision	55 (84.6%)
Metastatic Breast Carcinoma		
Site	Liver	16 (24.6%)
	Bone	14 (21.5%)
	Lung	12 (18.5%)
	Lymph node	12 (18.5%)
	Chest wall	3 (4.6%)
	Adrenal	2 (3.1%)
	Mediastinum	2 (3.1%)
	Pleura	2 (3.1%)
	Soft tissue	2 (3.1%)
Interim PBC-MBC (months)		
	Mean ($\pm$ SEM)	42 ($\pm$ 4.9)
	Median (Range)	26 (1–170)

Abbreviations: SEM, standard error of the mean; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IMC, invasive mammary carcinoma with mixed ductal and lobular features; CNB, core needle biopsy; PBC, primary breast carcinoma; MBC, metastatic breast carcinoma.

Table 2

Immunohistochemical Characteristics of the Population

PBC (TB)						
MBC (CB)	ER		PR		HER2	
	Positive	Negative	Positive	Negative	Positive	Negative
Positive	39 (60%)	1 (1.5%)	10 (15.4%)	4 (6.2%)	6 (9.2%)	1 (1.5%)
Negative	13 (20%)	12 (18.5%)	23 (35.4%)	28 (43.1%)	1 (1.5%)	51 (78.5%)
Equivocal	N/A	N/A	N/A	N/A	3 (4.6%)	3 (4.6%)
Total	52 (80%)	13 (20%)	33 (50.8%)	32 (49.2%)	10 (15.4%)	55 (84.6%)

Concordant cases indicated by grey boxes.

Abbreviations: PBC, primary breast carcinoma; TB, tumor block; MBC, metastatic breast cancer; CB, cell block; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; N/A, not applicable.

Table 3

Correlation of ER, PR and HER2 expression between Corresponding Primary and Metastatic Breast Carcinomas

	Agreement	Kappa
ER	78.5% (51/65)	0.5
PR	58.5% (38/65)	0.176
HER2	96.9% (63/65)	0.598

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table 4

Clinicopathologic and Immunohistochemical Characteristics of the Population according to Progesterone Receptor Status Concordance

		PR concordant	PR discordant	Total	P value
Total		38 (100%)	27 (100%)	65 (100%)	
Age	Mean ($\pm$ SEM)	51.6 ($\pm$ 2)	53.6 ($\pm$ 2.2)	52.4 ($\pm$ 1.5)	0.496
	Median (Range)	51.5 (25–79)	53 (33–77)	53 (25–79)	
Gender	Female	37 (97.4%)	27 (100%)	64 (98.5%)	1.000
	Male	1 (2.6%)	0 (0%)	1 (1.5%)	
PBC					
Histologic type	IDC	36 (94.7%)	20 (74.1%)	56 (86.2%)	0.019
	ILC	0 (0%)	5 (18.5%)	5 (7.7%)	
	IMC	2 (5.3%)	2 (7.4%)	4 (6.2%)	
Specimen	CNB	7 (18.4%)	3 (11.1%)	10 (15.4%)	0.503
	Excision	31 (81.6%)	24 (88.9%)	55 (84.6%)	
PBC-MBC concordance					
ER	Concordant	31 (81.6%)	20 (74.1%)	51 (78.5%)	0.547
	Discordant	7 (18.4%)	7 (25.9%)	14 (21.5%)	
HER2	Concordant	37 (97.4%)	26 (96.3%)	63 (96.9%)	1.000
	Discordant	1 (2.6%)	1 (3.7%)	2 (3.1%)	
Interim PBC-MBC (months)					
	Mean ($\pm$SEM)	34.7 ($\pm$ 4.5)	52.3 ($\pm$ 9.7)	42 ($\pm$ 4.9)	0.075
	Median (Range)	25.5 (1–106)	38 (1–170)	26 (1–170)	

Abbreviations: PR, progesterone receptor; SEM, standard error of the mean; PBC, primary breast carcinoma; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IMC, invasive mammary carcinoma with mixed ductal and lobular features; CNB, core needle biopsy; MBC, metastatic breast carcinoma; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

Table 5

Immunohistochemical Characteristics of the Population according to Fixation Method

		PBC (TB)					
		ER		PR		HER2	
MBC		Positive	Negative	Positive	Negative	Positive	Negative
FF-CB	Positive	21 (67.7%)	1 (3.2%)	5 (16.1%)	4 (12.9%)	4 (12.9%)	1 (3.2%)
	Negative	7 (22.6%)	2 (6.5%)	13 (41.9%)	9 (29%)	1 (3.2%)	21 (67.7%)
	Equivocal	N/A	N/A	N/A	N/A	1 (3.2%)	3 (9.7%)
	Total	28 (90.3%)	3 (9.7%)	18 (58.1%)	13 (41.9%)	6 (19.4%)	25 (80.6%)
CF-CB	Positive	18 (52.9%)	0 (0%)	5 (14.7%)	0 (0%)	2 (5.9%)	0 (0%)
	Negative	6 (17.6%)	10 (29.4%)	10 (29.4%)	19 (55.9%)	0 (0%)	30 (88.2%)
	Equivocal	N/A	N/A	N/A	N/A	2 (5.9%)	0 (0%)
	Total	24 (70.6%)	10 (29.4%)	15 (44.1%)	19 (55.9%)	4 (11.8%)	30 (88.2%)

Concordant cases indicated by grey boxes. ER concordance rates=74.3% (FF-CB), 82.4% (CF-CB); PR concordance rates=45.2% (FF-CB), 70.6% (CF-CB); HER2 concordance rates=93.5% (FF-CB), 100% (CF-CB) Abbreviations: PBC, primary breast carcinoma; TB, tumor block; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast carcinoma; FF-CB, formalin-fixed cell block; CF-CB, CytoLyt-fixed cell block; N/A, not applicable.