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Outcome of Breast Carcinoma between ER, PR with HER-2/Neu Positive Receptor Status

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Abstract **Original Research Article**

Background: The most frequent kind of cancer among women is breast cancer. Evidence shows that the receptor profile of primary and metastatic breast cancer tissue differs. Archival-paired pathology samples were evaluated to determine the level of hormone receptor discordance. ***Objective:*** To evaluate the efficacy of the most frequently used biological indicators in breast cancer for predicting how well a patient would respond to surgical management and their outcome. ***Materials and Methods:*** This comparative Study was conducted in the surgery department, Rajshahi Medical College, Bangladesh, with a Matricentred base Study from January 2019 to December 2021. They also included patients (n=100) for whom tissue from either the main or secondary metastatic location was detectable. Cancers were compared and analyzed for their ER, PR, and Her-2/neu status in both the primary and the metastatic. ***Results:*** The discordance rate for ER was 17.7% (2-sided p=0.0039), with 9.7% of tumors changing from ER-positive to ER-negative and 8.0% changing from ER-negative to ER-positive. The discordance rate for PR was 37.3% (2-sided p<0.0001), with Each and every one of these tumors going through a transition from PR-positive to PR-negative. As far as Her-2/neu is concerned, no major discrepancies were discovered. ***Conclusions:*** Hormone receptor status is significantly different between primary and metastatic breast cancer samples, as suggested by this dataset. Common instances of PR decline were observed. More than half of the patients had a positive hormone status, and it was found that the illness had spread to other organs in most of these cases.

Keywords: Breast Cancer, Hormone receptors, metastases, Discordance, Her-2/neu.

INTRODUCTION

Discordance in estrogen receptor (ER) [1] and progesterone receptor (PR) expression between primary and metastatic breast cancer tissues from the same patient has been documented (PR) [2]. There is also a description of Her- 2/neu receptor discordance, although the results are less reliable (3). There is a paucity of data on hormone receptor discordance in the context of Her-2/neu receptor status, which warrants further investigation. This is especially important given the postulated interactions between the hormone and Her-2/neu receptors. Following the pivotal trial by Slamon *et al.,* It showed that adding trastuzumab to chemotherapy improved survival for patients with advanced disease [4], many cancer centers began performing Her-2/neu testing of primary tumor specimens in patients who had subsequently developed metastatic disease. In fact, it wasn't until much later, after the outcomes of the postoperative immunotherapy studies [5], that routine Her-2/neu testing on primary breast cancer specimens was performed at the time of diagnosis. There is less information available for Her-2/neu receptor discordance rates than for hormone receptors, even though some centers were testing for Her2/neu prior to these dates for prognostication.

There is a lot of debate over hormone receptor incongruity, and many postulated processes haven't been universally accepted. Furthermore, it is suspected that technical issues related to specimen analysis and variation in staining methodology may contribute to "pseudo-discordance." True receptor discordance, however, may have important clinical implications with respect to systemic therapy decisions. Therefore, the existence of true Discordance would support an argument for obtaining metastatic tissue in patients with clinical or radiological suspicion of disseminated breast cancer. This Study determined how often hormone and Her-2/neu receptors were mismatched across primary

and metastatic breast cancer samples from the same patient.

MATERIALS AND METHODS

Pathology databases at the department of surgery, Rajshahi Medical College, Bangladesh, with Matricentred base Study from January 2019 to December 2021. The aim of this Study was to find n=100 individuals for whom primary and metastatic breast cancer tissues could be analyzed. The main search terms used were "metastatic" and "breast" but excluded "axillary" lymph node samples. Such ipsilateral lymph node samples are often termed "metastatic breast cancer" in node-positive patient pathology reports; these specimens were not included in the current analysis. Patients were only included in this analysis if they had an accessible clinical record for review and pathology information (i.e., a report) on both the primary and the metastatic specimens, including at least one of ER, PR, or Her- 2/neu status. The patient's chart and pathology reports were reviewed, and demographic, tumour, and treatment characteristics were recorded. Combination therapy hormone treatment, Her-2/neu status, adjuvant chemotherapy use, the period between main diagnosis and metastatic biopsy, site of metastatic biopsy, and primary tumor grade were all included in a logistic regression analysis to determine their potential impact on hormone receptor discordance.

RESULTS

Patient and Primary Tumour Characteristics

The Study included 100 patients who fulfilled all inclusion criteria. Details on the patient's main tumor and background are displayed (Table I).

Table I: Patient demographics with primary tumor features and patient characteristics

Variable	Patient (n=100)
Gender (%)	
Male 50	Female 50
Age at diagnosis (years)	
Median	50
Range	29-79
Histology (%)	
Ductal	77
Lobular	8
Mixed	3
Unknown	12
Grade (%)	
I	6
II	30
III	47
Unknown	17
T stage (%)	
I	48
II	35
III	5
IV	3
Unknown	9
N stage (%)	
0	62
I	15
II	13
III	2
Unknown	8

Metastatic Biopsy Details

Table II describes the metastatic biopsy findings. Over one-third of samples were collected prior to 2019 to 2021 when Her-2/neu testing was rarely performed. The most common site from which a metastatic biopsy was taken was the bone or bone marrow. Several of these specimens were obtained through surgical intervention for the treatment of a pathological fracture or during research into cytopenia.

Table II: Metastasis biopsy details

Variable	Patient (n=100)
Time to metastasis biopsy (years)	
Median	4.0
Average	5.4
Range	1-35
Date of metastasis biopsy (%)	
Pre 2019	36
During or post-2019	64
Site of metastasis biopsy (%)	
Bone or bone marrow	33
Lymph node or skin	24
Thorax/lung	24
Abdomen/liver	15
Central nervous system	3
Other	1

Table III displays the many types of receptor assays that were performed. The type of assay used for the hormone receptor analysis in the primary [predominantly enzyme-linked immunoassay (EIA)] differed greatly from that used for the metastasis [predominantly immunohistochemistry (IHC)]. This mirrors a shift in practice over time towards using IHC hormone receptor assays. In assessing methods of Her-2/neu testing, there was proportionally more fluorescent in situ hybridization (FISH) testing compared to IHC performed on the metastasis compared with the primary specimen. This may be because many pathologists prefer FISH testing since it is regarded to be more technically trustworthy and because metastatic specimens were more likely to be in the form of core biopsies.

Table III: Strategies for assessing receptors (n=100)

	EIA	IHC	FISH	Not available
HR-primary	53	29		18
HR-metastasis	1	57		42
Her-2/neu-primary		41	7	52
Her-2/neu metastasis		29	11	60

EIA: Enzyme-linked immunoassay, IHC: immunohistochemistry, FISH: fluorescent in situ hybridization.

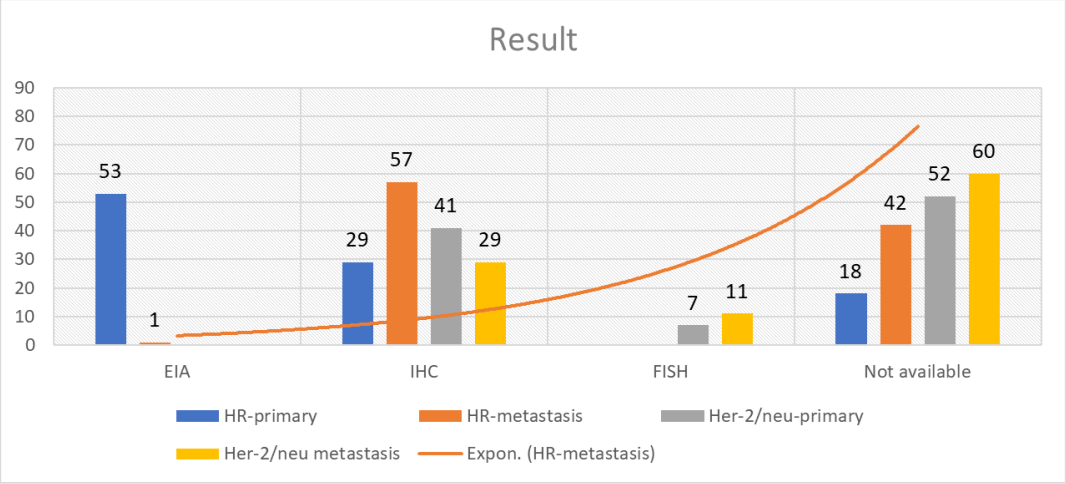

Fig. 1: Receptor assay methods

The end outcome of the hormone receptor study Table IV shows the hormone receptor status of all primary and metastatic samples. Unfortunately, over a third of patients did not complete hormone receptor status testing on the metastatic lesion. Out of the 100 patients included in this analysis, there were paired estrogen receptor samples available in 62 patients. Discordance for ER was found in 17.7% of these cases, with 6 tumours (9.7%) switching from being positive in the primary to negative in the metastasis and 5 tumours (8.0%) switching from negative to positive. This discordance rate for ER was statistically significant, with a two-sided p-value of 0.0039.

Table IV: Hormone receptor results (n=100)

Variable	ER		PR	
	Primary	**Metastasis**	**Primary**	**Metastasis**
Positive	73	52	60	26
Negative	24	12	35	36
Not available	3	36	5	38

A total of 59 patients had paired progesterone test findings available. Among these patients, there was a PR discordance rate of 37.3% ($p<0.0001$), and all of the 22 tumours that changed status switched from PR-positive to PR- negative.

Her-2/neu receptor results. The Her-2/neu status in patients' primary or metastatic specimens is shown in Table V. Although most patients were not tested for Her-2/neu on both their primary and their metastatic specimens, 70% of patients were tested for Her-2/neu on either one of their samples. Paired Her-2/neu samples were available in 18 patients, and one (5.5%) of these patients exhibited Discordance ($p=0.114$). This patient switched from being positive in the primary to negative in the metastasis.

Table V: Her-2/neu receptor results (n=100)

Variable	**Primary**	**Metastasis**	**Primary or metastasis**
Positive	7(14.6%)	6(15.0%)	13(18.6%)
Negative	41	34	57
Not available	52	60	30

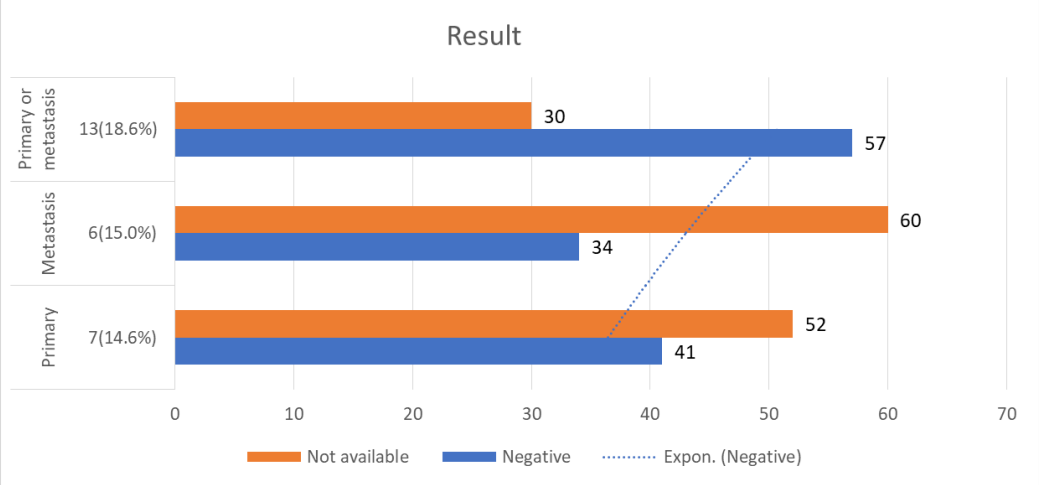

Fig. 2: Her-2/neu receptor results

The method of logistic regression a logistic regression analysis was used to determine if hormone therapy as an adjuvant treatment was effective. Her-2/neu status, adjuvant chemotherapy use, time from primary diagnosis to metastatic biopsy, site of metastatic biopsy or primary tumour grade influenced hormone receptor discordance. None of these variables were significantly associated with the occurrence of hormone receptor discordance.

DISCUSSION

In this retrospective study, hormone receptor status was significantly different across primary and metastatic breast pathology samples. There was a long-term shift in ER status for 17.7 % (from positive to negative and vice versa) and for 37.3 % there was a shift in PR status (all of these tumors lost PR). That's right; 45.1% of patients showed evidence of hormone receptor alterations (i.e. a change in either ER or PR). The results are in keeping with previous studies. In an analysis of 232 patients, Hull *et al.* showed that 17% of participants in their series had a decline in ER and 13% had an increase [6]. Lower *et al.*, Study of 200 patient charts revealed a 30% ER discrepancy rate, with 19.5% of tumors losing ER and 10.5% gaining ER [7]. For PR, this group found a discordance rate of 39.3%. Mobbs *et al.*, discordance rates between ER and PR were 24% and 30%, respectively, when a retrospective pathology specimen assessment was done on 129 patients [8]. Gross *et al.*, in their series of 161 cases, found that 44% of patients lost PR, however, 8% of patients gained PR [9]. Finally, Franco *et al.*, conducted a meta-analysis including 8 observational studies with a total of 658 paired ER samples, and 418 paired PR samples [10]. They found a discordance rate of 29 and 27% for ER and PR, respectively.

Although there is a paucity of long-term data on Her-2/neu status, the reported time series all point to

increased stability [11]. Zidan *et al.*, identified the greatest rate of Her-2/neu discordance in a series of 58 patients with tumors examined by FISH or IHC [3]. They found a discordance rate of 14%, with 12% of patients losing Her-2/neu positivity and 2% gaining it over time. Other published series have found lower rates of Her-2/neu inconsistency, including a study that showed no status changes in 56 of 58 instances [12]. In the presented series of 100 patients with paired primary and metastatic pathology samples, who had had 'some' receptor analysis performed on both specimens, a significant discordance rate for Her-2/neu was not found, with only one patient losing Her-2/neu positivity. However, because Her- 2/neu testing had not been performed in both specimens from most of these patients, few paired Her-2/neu samples were available to analyse for Discordance. There are three possible reasons for the lack of Her-2/neu testing on the patients included in this series. Firstly, there may have been an assumption by clinicians and pathologists that Her-2/neu status in the metastasis is the same as in the primary; therefore the test was not requested. Secondly, over a third of metastatic samples were collected before 2019, when Her-2/neu testing was not routinely performed. Finally, technical difficulties may arise when conducting Her-2/neu testing in decalcified bone, which is the most prevalent site of metastatic biopsies.

In this group of patients with metastatic relapse, it was also observed that many of them had first been diagnosed with tumors that were both T1 and N0. One possible reason for this is that these patients would have been thought to have been at a lower risk of relapse and therefore when they presented with clinical or radiological evidence of metastatic disease, clinicians may have been more eager to obtain a biopsy to confirm or refute the diagnosis of metastatic breast cancer. This may have meant that this series of patients was skewed to be different from the typical population of patients with metastatic breast cancer with respect to their primary tumour characteristics. This is one limitation of this Study. There are also a number of additional significant caveats to this Study. The first issue is that there wasn't a comprehensive evaluation by central pathology. This was a chart review with the receptor status typically taken from the pathology report. Some patients had their primary tumour tested at a different pathology laboratory to that where their metastatic sample was analyzed.

Furthermore, there may be discrepancies in this Study across different labs. The second potential source of error is that primary and metastatic tissues were commonly analyzed using separate test techniques for hormone receptor and Her-2/neu receptor analyses. EIA was the main method utilized for hormone receptor analysis on the primary specimen, whereas IHC was almost invariably used when the metastasis was analyzed. This represents a change in practice over recent years. FISH (as the definitive test for Her-2/neu) was used proportionally more often in the analysis of the metastasis than the primary. This is likely because it is thought to be a more reliable method when a core biopsy is done. Thirdly, a positive or negative label was ascribed for each receptor as interpreted from the pathology report. It is possible that a tumour that changes its PR status from being weakly positive to negative may have less clinical meaning than a change of greater magnitude and the analysis did not capture this information. The definition of hormone receptor "positive" varied depending on which laboratory and by what method the analysis was done. As was previously indicated, the Study's power was diminished by a large number of missing data, notably on Her-2/neu status.

Despite the Study's limitations, this evaluation provides more evidence that there is substantial ER and PR hormone receptor discordance in the existing literature. This has a number of potential clinical implications for the management of patients. Firstly, a proportion of patients with metastatic disease may be sub-optimally treated without a biopsy. This may be especially so if a patient's receptor status has become positive over time and if this is not known, they may be deprived of potentially life-prolonging targeted treatment such as endocrine therapy. Secondly, patients may be inappropriately enrolled in clinical trials of systemic therapy. Many such trials are powered to detect small differences in efficacy between therapies. It is, therefore, possible that because of this discordance phenomenon, unknown imbalances in receptor status between the arms of trials (as eligibility is often based on the status of the primary tumour) may influence the results.

The high rate of "loss of PR" over time is a recurrent subject in both this article and others. Out of all three receptor discordance phenomena discussed here, loss of PR is the one that has generated the most biological research. PR is an ER-regulated gene that is expressed in two isoforms, PR-α and -β. PR mediates the effects of progesterone on the development of mammary glands in healthy individuals and is implicated in the development of breast cancer. Compared to individuals who received estrogen treatment only, those who received estrogen and progesterone had a higher risk of developing breast cancer [13]. Metastatic tumors that lose PR tend to progress more quickly and are linked to shorter overall lifetimes than those that keep PR [14]. The higher proportion of PR-negative tumors in the metastatic samples compared to the primary ones is not surprising. There is an increased association between Her-2/neu overexpression and ER-positive/PR-negative tumours (25%) compared to ER-positive/PR-positive (10%) tumours [15]. The presence of the ER+/PR- phenotype is also related to a more severe tumor grade [16]. In addition, ER-positive/PR-negative tumors express more EGFR than ER-positive/PR-positive tumors [17]. These associations with the ER-positive/PR-negative

phenotype implicate high growth factor activity with a decrease or loss of PR. Therefore, growth factor-mediated downregulation of PR independent of ER is a popular hypothesis for explaining PR loss.

There are several other postulated mechanisms for loss of PR. One is genetic loss of the PR gene locus or loss of heterozygosity. Another is hypermethylation of the PR promoter, which is found in 21-40% of ER-positive/PR- negative tumours compared with none of tumors with a positive ER and PR status [18]. One other theory attempting to explain the ER-positive/PR-negative phenotype is that in these tumors have ER that is dysfunctional and cannot promote PR generation. However, some ER-positive/PR-negative tumours may simply result from low levels of circulating endogenous estrogens in postmenopausal patients that do not adequately stimulate PR expression even when the ER mechanism is functional [19].

IN CONCLUSION

This Study has demonstrated significant Discordance in hormone receptor status between primary and metastatic specimens, which may have implications for the systemic treatment of patients' metastatic disease. The results of a confirmatory biopsy altered management in 20% of patients. These preliminary results further support the phenomenon of receptor discordance and reinforce the importance of obtaining a confirmatory biopsy when patients present with suspicion of metastatic disease.

CONFLICT OF INTEREST

None.

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