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Breast Cancer

Study of Biomarker Discordance between Primary and Recurrent Sites and its Clinical Implications in Metastatic Breast Cancer : A Single Institutional Study from India

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Abstract

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Immunophenotypic discordance of receptors between primary and metastatic sites significantly impacts treatment outcomes. Current international guidelines recommend rebiopsy of accessible metastatic lesions to reassess tissue biomarkers. While existing literature on biomarker changes is conflicting and heterogeneous, similar studies on the Indian cohort of breast cancer patients are lacking. In this context, we aimed to evaluate the frequencies of biomarker changes between biopsies from primary and recurrent sites, and their association with various clinicopathological characteristics, including the type of metastasis and treatment in metastatic breast cancer (MBC) patients. This is an ambispective study performed at a single center. Immunohistochemical (IHC) expression of paired primary and recurrence samples of MBC patients was reviewed for the expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2), and Ki-67. Concordance, loss, and gain of receptors were assessed based on the Allred scores for ER, PR, and HER2. Ki-67 was assessed based on a 14% cutoff. Further, receptor changes were studied in relation to age, menopausal status, morphology, grade, stage, metastatic sites, interval between biopsies, and treatment. At progression, biopsies were obtained from 41.18% of locoregional recurrence and 58.82% of metastatic sites. Despite high discordance of 47% for ER and 68.6% for PR, true receptor conversion was observed in 9.8%, 21.56%, and 5.88% for ER, PR, and HER2, respectively. There was a significant correlation between age and ER discordance ($p = 0.029$). Loss in PR significantly correlated with a gain in Ki-67. Of all the metastatic sites, the lung was significantly associated with PR and Ki-67 concordance ($p = 0.008$ and $p = 0.0425$, respectively). Discordance of receptors was neither related to the sites of biopsy (local recurrence or metastatic site) nor to the time interval between biopsies, prior chemotherapy, or hormone therapy. In conclusion, metastatic progression of the disease is accompanied

Keywords

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- metastatic
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by age-dependent discordance of ER. Unparalleled changes in PR in relation to ER suggest that ER-independent pathways may influence PR expression in MBC. Furthermore, the concurrence of PR loss with Ki-67 gain indicates an aggressive phenotype with disease progression. Hence, follow-up testing of samples for receptor expression is beneficial in determining prognosis and guiding therapeutic decisions.

Introduction

Breast cancer is one of the most prevalent cancers in women contributing to 2.26 million new cases and 684,996 deaths in 2020 globally.[1] Breast cancer accounts for 13.5% of all cancer cases and 10.6% of fatalities in India, according to GLOBOCAN statistics from 2020, with a 39% increase in incidence.[2,3] Breast cancer has malignant potential irrespective of the size of primary tumor.[4] It can relapse with local recurrence or distant metastasis even a decade after complete treatment and remission.[5,6] Despite having a better prognosis than other aggressive tumors, the 5-year overall survival rate for breast cancer drops from 99% for localized disease to 27% for distant metastases.[7]

Treatment of metastatic breast cancer (MBC) depends on several important factors such as site of metastases, severity of recurrence, time to progression, previous treatments, as well as tumor biology. While the histopathological features of primary tumor are usually preserved, studies have indicated receptor conversion in metastatic sites.[4,8,9]

Receptor discordance may occur due to gain or loss of receptors with progression of disease from primary breast to regional recurrence or distant metastases. Although pathophysiology of the hormonal receptor discordance still needs to be elucidated, it is evident that changing receptor status can impact choice of therapeutic regimen and clinical outcome.[8–10]

Recent international guidelines recommend rebiopsy of accessible metastatic lesions,[11–13] so that targeted treatment could be offered to patients even if one of the biopsies (either primary or metastatic) is positive for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2).[12] Frequencies of discordance or conversion of ER, PR, and HER2 have been inconsistent across different Western studies.[14–16] In India, rebiopsy is not usually performed from metastatic sites in breast cancer, and biomarker discordance studies from Indian cohort are sparse which could impact the survival outcome of our breast cancer patients.[17] Hence, the present study was undertaken to explore frequencies of ER, PR, and HER2 discordance and related Ki-67 changes in Indian females with breast cancer.

Materials and Methods

Study Design

This was a prospectively planned retrospective single-center cohort study conducted at a regional cancer center in India. The study duration was 4 years, from January 2019 to December 2022. The main sources of collected data were pathology department and patients' medical records.

To begin with 95 cases of chest wall recurrence (CWR) and metastatic sites were noted from pathology departmental records. About 32 cases of CWR without evidence of metastatic disease at progression were excluded. Corresponding primary sites were searched and Allred scores of ER, PR, and HER2, and Ki-67 percentage were recorded. Twelve patients who did not have complete immunohistochemistry (IHC) work-up for ER, PR, or HER2 were excluded from the study. The final study population included a total of 51 patients with paired samples of primary and recurrence/metastatic sites. Allred scores of receptors from primary and metastatic biopsies were recorded. Paired slides of primary and recurrent tumors were reviewed for majority of cases to ascertain IHC scores.

The time interval between the biopsies from primary and recurrent/metastatic sites (Bx interval), and history of various treatments received during this time interval were noted for all patients.

Immunohistochemistry Analysis

IHC technique was performed according to standard laboratory protocol at our center for all patients, including those who were referred from outside. The procedure was performed on formalin-fixed and paraffin-embedded sections as a part of routine diagnostic work-up. Appropriate cold ischemia time and fixation time were ensured constantly. IHC was done using rabbit monoclonal, ready to use antibodies on an automated slide processing system BenchMark* XT, Ventana Medical Systems, Inc., Tucson, Arizona, United States. Assessment of ER, PR, and HER2 expression was done complying with the latest recommendations of American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) 2013/2018 guidelines.[18,19] Allred scoring system was adopted for evaluation of hormonal receptors and HER2. For ER and PR, Allred score of 0 to 2 was considered as negative and 3 to 8 was considered as positive. With regard to HER2 status, scores of 0 and 1+ were considered as negative, 2+ as equivocal, and 3+ as positive. Patients with equivocal HER2 results were further subjected for fluorescent in situ hybridization (FISH) using ERBB2/CCP17 FISH probe kit and positive or negative status was assigned based on ASCO/CAP 2013 HER2 testing guidelines.[19]

Definitions: Discordance in our study refers to any variations in Allred scores of receptors; conversion refers to switch in the positive or negative status of receptors.

Statistical Analysis

Data were analyzed using SPSS software version 21 and Excel. Categorical variables were given in the form of

frequency table. Continuous variables were given in mean ± standard deviation/median (minimum, maximum) form. Chi-square test was used to check the dependency between categorical variables. Normality of variable was checked by Shapiro–Wilk's test and QQ plot. Kruskal–Wallis' test was used to compare mean age over ER, PR, and Ki-67. Confidence intervals were set at 95%, and a p-value ≤ 0.05 was considered statistically significant.

Results

Demographic Characteristics

►Tables 1 and 2 summarize the demographics and clinicopathological characteristics of our study cohort. The key findings were mean age of patients was 47.39 ± 11.23 years and majority (82.4%) being postmenopausal. Invasive ductal carcinoma of no specific type was the most common morphologic type, followed by invasive lobular carcinoma. Majority (70.6%) had grade 2 tumors and ~25.5% had grade 3. Out of total 51 cases, 30 patients presented in stage 4 (referred to as upfront metastatic breast cancer or UMBC) and the remaining 21 patients diagnosed in stage 2 or 3 later progressed to metastatic disease with or without local recurrence (referred to as recurrent metastatic breast cancer or RMBC). Overall bone was the most common (78.43%) site of metastasis followed by distant lymph nodes (35.29%), lung (29.41%), liver (29.41%), and ovaries (25.49%). However, the most commonly biopsied site at disease relapse was CWR (29.41%), followed by ovary (19.61%) and distant lymph nodes (13.7%).

Table 1 Baseline demographics and pathological characteristics of our study cohort

Variables	Subcategory	Number of subjects (%)
Age (y)	Mean ± SD	47.39 ± 11.23
	Median (minimum, maximum)	46 (24, 68)
Menopausal status	Postmenopausal	42 (82.4%)
	Premenopausal	9 (17.6%)
Laterality	B/L	10 (19.6%)
	LT	21 (41.2%)
	RT	20 (39.2%)
Morphology	IDC, NST	44 (86.3%)
	IDC, ST	5 (9.8%)
	ILC	2 (3.9%)
Grade	1	2 (3.9%)
	2	36 (70.6%)
	3	13 (25.5%)
Stage	2	14 (27.5%)
	3	16 (31.4%)
	4	21 (41.2%)
ER	Positive	47 (92.16%)
	Negative	4 (7.84%)
PR	Positive	42 (82.35%)
	Negative	9 (17.65%)
HER2	Positive	5 (9.80%)
	Negative	46 (90.20%)
Ki-67	Low (<14%)	23 (45.10%)
	High (≥14%)	28 (54.90%)

Abbreviations: B/L, bilateral; HER2, Human Epidermal growth Factor Receptor 2; IDC-NST, invasive ductal carcinoma, no special type; IDC-ST, invasive ductal carcinoma, special type; ILC, invasive lobular carcinoma; LT, left; RT, right; SD, standard deviation.

Table 2. Clinical and treatment characteristics of our study cohort

Metastatic sites	Bones	40 (78.43%)
	Ovaries	13 (25.49%)
	Liver	15 (29.41%)
	Lung	15 (29.41%)
	Adrenals	3 (5.88%)
	Distant LN	18 (35.29%)
	Pleura	6 (11.76%)
	Bone Marrow	2 (3.92%)
	Brain	4 (7.84%)
	Cervix	1 (1.96%)
Site of biopsy at recurrence	Local recurrence	21 (41.2%)
	Metastasis	30 (58.8%)
Metastatic biopsy sites	Bone	4 (7.84%)
	Brain	1 (1.96%)
	Liver	6 (11.76%)
	Distant lymph nodes	5 (9.8%)
	Lung	2 (3.92%)
	Ovary	10 (19.61%)
	Pleura	2 (3.92%)
Bx Interval #	Mean ± SD Median (Min, Max)	30.36 ± 34.25 19 (2, 180)
Exposure to HT	No	10 (19.6%)
	Yes	41 (80.4%)
Exposure to CT#	No	9 (17.6%)
	Yes	39 (76.5%)

Abbreviations: SD- Standard deviation; NCB- Needle core biopsy; CWR- Chest wall recurrence; # indicates missing information.

Treatment and Follow-up

Among 30 RMBC patients, 27 patients underwent surgery—2 patients had breast-conserving surgery with axillary lymph node dissection (ALND) and 25 patients had modified radical mastectomy (MRM) with ALND. Out of 27 patients who underwent surgical resection, 13 patients completed adjuvant treatment (chemotherapy [CT], radiotherapy, and hormone therapy [HT]), of which 5 of them had received

neoadjuvant CT before surgery. The remaining 14 patients defaulted one or the other adjuvant treatments.

Out of 21 UMBC patients, 9 patients underwent surgery (palliative mastectomy 2; bilateral salpingo-oophorectomy 3; MRM + ALND 4). About 20 patients received first-line HT (tamoxifen/aromatase inhibitor).

Evaluation of ER

ER discordance was observed in 47% of patients. Patients with ER gain were significantly older than patients with ER loss (►Table 3; $p = 0.029$, one-way analysis of variance). However, no significant association was noted between receptor changes and menopausal status, laterality, morphology, or grade. ER loss was most frequently noted in biopsies from metastatic sites and vice versa was observed for local recurrence, which was not statistically significant. ER loss was most frequently associated with stage 4 and ER gain with stage 2 or 3. Ki-67 indices did not alter much in relation to ER discordance. Time interval between biopsies did not significantly influence receptor changes nor the type of prior treatment.

However, conversion of ER was observed in only 5 out of 51 patients (9.8%)—positive conversion in 3 (5.88%) patients and negative conversion in 2 (3.92%) patients.

Evaluation of PR

Overall PR discordance was observed in 68.6% of patients. Similar to ER, older age was noted among patients who had PR concordance or PR gain compared with patients who had PR loss, though it was not statistically significant. Among different metastatic sites, lung metastasis was most significantly associated with PR concordance (►Table 3) ($p = 0.008$). Stage 3 patients had maximum gain of PR, whereas stage 4 patients had maximum PR loss. PR loss was found to be associated with longer biopsy interval time compared with patients who had gain or concordance of receptors. From chi-square test, it was noted that PR loss was significantly associated with gain of Ki-67 ($p = 0.0058$). Receptor changes did not differ much in relation to other parameters such as menopausal status, morphology, laterality, or prior CT or endocrine therapy.

Actual receptor conversion rate was found to be 21.56% (11 out of 51)—negative conversion in 7 patients (13.72%) and positive conversion in 4 patients (7.84%).

Evaluation of HER2

Out of total 51 cases, 46 cases were HER2 negative, and 5 cases were HER2 positive. As noted in ►Fig. 2, HER2 showed most consistent expression between the primary and metastatic sites with majority showing no conversion ($n = 48$, 94.12% concordance rate). Negative conversion was noted in two patients (3.92%) and positive conversion was noted in one patient (1.96%) accounting for total discordance/conversion rate of 5.88%.

Evaluation of Ki-67

No change in Ki-67 was observed in 15 patients (29.4%), gain in 25 patients (49%), and loss in 11 patients (21.6%). Patients with bone metastasis (84%) followed by liver (44%) had highest gain of Ki-67 biomarker. Maximum Ki-67 discordance was noted in stage 4 patients (maximum Ki-67 gain of 36% and loss of 63.64%).

Majority of the patients with discordance had received HT and CT regime. The biopsy interval was longer in patients who had no change or increase in Ki-67 index (mean 34.27 ± 37.11 months, median 18 months; and mean 32.83 ± 37.99 months, median 24.5months, respectively) compared with patients with Ki-67 loss (mean 19.64 ± 18.36 months, median 16 months). From chi-square test, a significant association was noted between Ki-67 concordance and lung metastasis ($p = 0.0425$ on chi-square test with Monte Carlo simulation). No significant association was observed between Ki-67 changes and other clinicopathological characteristics.

A Subgroup Analysis of ER/PR Concordance and ER Concordance/PR Loss

To delineate the effects of ER-dependent PR expression, we divided patients into two groups—Group 1 ($n = 23$) with ER/PR concordance and Group 2 ($n = 16$) with ER concordance/PR loss. The mean age of group 1 was found to be 49 ± 13.02 years and group 2 was 48.06 ± 8.7 years. On comparison of two groups, we noted significant association of—(1) ER/PR concordance with lung metastasis ($p = 0.007$) and (2) Ki-67 gain with ER concordance/PR loss ($p = 0.03$) (►Fig. 1). A slightly higher frequency of PR loss was noted in patients who received endocrine treatment, compared with those who had both ER/PR concordance (81.25 vs. 73.91%, respectively). A representative image of biomarker changes between primary breast and metastatic site, wherein PR loss and Ki67 gain were observed along with ER concordance.

Discussion

Breast cancer is highly heterogenous with regard to its biological and clinical behavior.[20]

Hormonal receptor variations between primary and metastatic tumors were demonstrated by scientists in 1970s itself by protein assays.[21] Currently, rebiopsy for IHC reassessment of biomarkers from recurrent lesions is not mandatory, though few international guidelines advocate to do it, especially where the IHC status of primary tumors is negative or unknown.[22] In India, rebiopsy of metastatic lesion is performed most importantly to rule out secondary malignancies and repeat IHC to check the biomarker status in metastatic lesions is not well established in routine clinical practice.

Biomarker discordance rates have been inconsistent among different studies. A meta-analysis revealed discordance of ER by 3 to 54% and PR by 5 to 78%.[15] The current study observed variations of ER, PR, and Ki-67 in 47, 68.6, and 70.59%, respectively. The exact reason for tumor biomarker changes is not clear. However, scientists have attributed this to clonal selection and evolution of tumor cells, antigen repair, loss of receptors due to selective pressure from prior therapy, and limited reproducibility due to preanalytical and analytical variables.[4,23–25]

Table 3. Comparison of different variables in relation to concordance and discordance of Estrogen and Progesterone Receptors

	ER			P Value	PR			P Value
	Concordance	Gain	Loss		Concordance	Gain	Loss	
No of patients	27 (52.94%)	12 (23.53%)	12 (23.53%)		16 (31.37%)	12 (23.53%)	23 (45.1%)	
Age Mean + SD Median (Min, Max)	45.96 ± 11.5 45 (30, 68)	54.58 ± 8.62 55 (38, 68)	43.42 ± 10.39 44 (24, 65)	0.029^{A*}	49.38 ± 12.57 50 (30, 68)	46.92 ± 11.65 48 (32, 64)	46.26 ± 10.34 45 (24, 65)	0.695^{A}
Post-Menopausal	23 (85.19%)	11 (91.67%)	8 (66.67%)	0.279^{MC}	14 (87.5%)	11 (91.67%)	17 (73.91%)	0.456^{MC}
Pre- Menopausal	4 (14.81%)	1 (8.33%)	4 (33.33%)		2 (12.5%)	1 (8.33%)	6 (26.09%)	
Biopsy site -Metastasis	16 (59.26%)	5 (41.67%)	9 (75%)	0.295^{MC}	9 (56.25%)	8 (66.67%)	13 (56.52%)	0.866^{MC}
-Local Recurrence	11 (40.74%)	7 (58.33%)	3 (25%)		7 (43.75%)	4 (33.33%)	10 (43.48%)	
Metastatic site -Bone	22 (81.48%)	9 (75%)	9 (75%)	0.824^{MC}	12 (75%)	10 (83.33%)	18 (78.26%)	0.913^{MC}
-Distant LNs	11 (40.74%)	4 (33.33%)	3 (25%)	0.648^{MC}	8 (50%)	3 (25%)	7 (30.43%)	0.358^{MC}
-Lung	9 (33.33%)	4 (33.33%)	2 (16.67%)	0.627^{MC}	9 (56.25%)	4 (33.33%)	2 (8.7%)	0.008^{MC*}
-Ovaries	9 (33.33%)	3 (25%)	1 (8.33%)	0.258^{MC}	6 (37.5%)	2 (16.67%)	5 (21.74%)	0.508^{MC}
-Liver	8 (29.63%)	3 (25%)	4 (33.33%)	0.999^{MC}	5 (31.25%)	4 (33.33%)	6 (26.09%)	0.926^{MC}
Ki67- Same (n = 15)	9 (60%)	5 (33.33%)	1 (6.7%)	0.206^{C}	10 (66.67%)	3 (20%)	2 (13.33%)	0.0058^{C*}
Ki67- Gain (n = 25)	13 (52%)	6 (24%)	6 (24%)		5 (20%)	5 (20%)	15 (60%)	
Ki67- Loss (n = 11)	5 (45.45%)	1 (9.09%)	5 (45.45%)		1 (9.09%)	4 (36.36%)	6 (54.55%)	
Stage of Presentation -Stage 2	6 (22.22%)	5 (41.67%)	3(25%)	0.4498^{MC}	6 (37.5%)	1 (8.33%)	7 (30.43%)	0.4378^{MC}
-Stage 3	8 (29.63%)	5 (41.67%)	3 (25%)		4 (25%)	6 (50%)	6 (26.09%)	
-Stage 4	13 (48.15%)	2 (16.67%)	6 (50%)		6 (37.5%)	5 (41.67%)	10 (43.48%)	
Bx Interval Mean + SD Median (Min, Max)	23.41 ± 16 17 (2, 66)	46 ± 57.65 24 (5, 180)	31.67 ± 35.14 21 (2, 108)	0.734^{K}	22.69 ± 15.3 16.5 (2, 55)	24.36 ± 24.74 17 (5, 96)	38.57 ± 45.21 24 (2, 180)	0.726^{K}

*Abbreviation: A – One-way ANOVA, K – Kruskal Wallis test, MC – Chi square test with Monte Carlo simulation, * indicate statistical significance.*

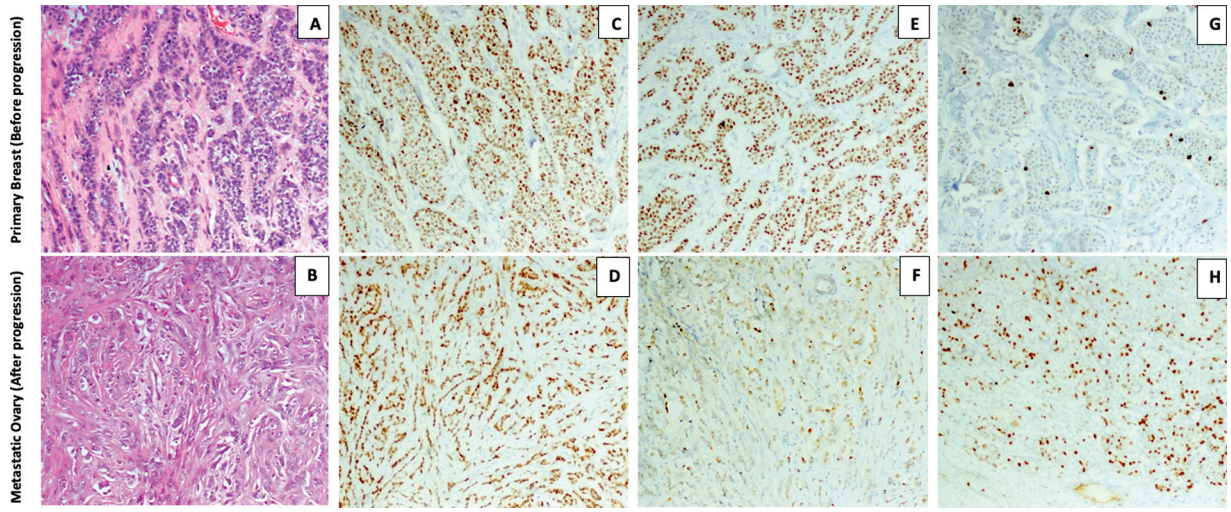

Fig. 1 A representative image of biomarker changes. The upper row is from primary breast (before progression of disease), and the lower row is from metastatic ovary (at the time of progression). (**A**) Breast (H & E, ×100); (**B**) ovary (H & E, ×100); (**C, D**) ER, Allred score of 8 in both breast and ovary; (**E, F**) PR, Allred score 8 in breast and 5 in ovary; (**G, H**) Ki-67, 5 to 8% in breast and 65% in ovary. ER, estrogen receptor; H & E, hematoxylin, and eosin; PR, progesterone receptor.

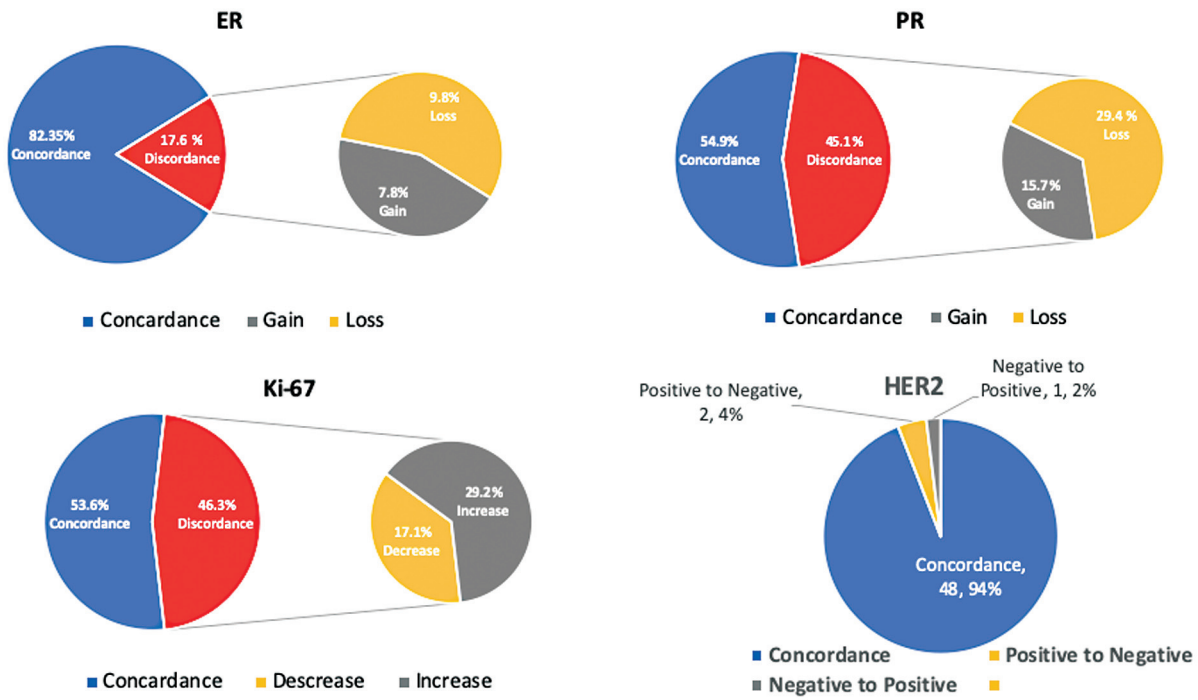

Fig. 2 Concordance and discordance rates for ER, PR, HER2, and Ki-67%. ER, estrogen receptor; PR, progesterone receptor.

Pooled analyses of different studies have shown conversion rates of 13, 31, and 6%, respectively, for ER, PR, and HER2.[4,26,27] Similarly, we noted receptor switch, either positive or negative, in 9.8% for ER, 21.56% for PR, and 5.88% for HER2. On the contrary, other researchers have documented conversion rates of up to 26.9% for ER, 38.8% for PR, and 22.4% for HER2, respectively.[28] A rather low conversion rates in our study could be substantiated by an extremely low chances of preanalytical variability, as procedures were performed by standardized automated system in a single center. Our observations are further supported by prospective standardized multicentric studies who also observed low conversion rates of 12.6, 31.2, and 5.5% for ER, PR, and HER2, respectively.[27,29]

Our analysis revealed higher discordance rates for PR than for ER, and PR loss was more frequent than PR gain. in agreement with other studies.[4,25–27,30] This phenomenon in relation to endocrine treatment could possibly occur due to high genetic sensitivity of PRs to hormonal treatment,[30] thus indicating the role of changes in tumor biology leading to receptor discordance.[27] However, we found that no prior

therapeutic regimes (HT/CT) have impact on the gain or loss of receptor expression in locally recurrent and metastatic sites, similar to earlier reported findings.[31]

Significant difference in discordance of receptors between local recurrence and metastatic sites have been reported[23] as local recurrences are formed directly from primary tumor cells and thus likely to maintain the same receptor expression status.[32] Though we observed a similar trend, it did not reach to the point of statistical significance. Majority of other larger studies also did not observe any significant relation between the receptor discordance and sites of recurrence.[4,26,28]

Ki-67 antigen levels reflect proliferative index of tumor. Increased Ki-67 levels indicate therapeutic failure or need to change the therapeutic regime.[33] In the present study, increased Ki-67 levels were found in 36% of stage 4 cases and in those who had already received adjuvant CT and hormonal treatment, thus indicating the need for change of therapeutic regimen. We noted a significant inverse correlation between Ki-67 indices and PR expression upon comparison of biopsies from local recurrence and metastatic sites.

A unique finding in our study was significant correlation between concordance of PR and Ki-67 markers with lung metastasis ($p = 0.008$ and $p = 0.0425$, respectively). Very few authors have studied an association between the biomarker changes and metastatic sites, and some interesting correlations were observed such as liver metastasis with PR discordance, lymph node metastasis with HER2 loss, and CWR with ER/PR concordance.[34]

In MBC, PR has an independent role in predicting response to hormonal treatment and progression-free survival.[35] It has been postulated that in endocrine-resistant tumors, PR receptors might be lost due to suppression by certain growth factors, despite intact ER signaling.[36] Very few researchers have investigated PR changes in relation to ER. Vogel et al revealed that PR loss, while ER concordant, was significantly associated with endocrine treatment and a shorter postmetastatic survival compared with patients with ER/PR concordance.[34] In this context, we conducted a subgroup analysis of ER/PR concordance and ER concordance/PR loss, which showed significant association of later group with Ki-67 gain ($p = 0.03$), thus indicating evolution of primary tumor to more aggressive phenotype at metastatic site with PR loss.

We hypothesize that the time interval between biopsies from primary and metastatic lesions possibly influence the rates of biomarker discordance. The median time interval between biopsies in our study was longer in patients who showed discordance of receptors (►**Table 3**), especially PR loss and Ki-67 gain (24 and 24.5 months, respectively) compared with patients with concordance of biomarkers (median 16.5–18 months). However, the difference was not statistically significant. Similarly, Nguyen et al did not observe any significant difference in receptor discordance rates in relation to duration of time between primary and metastatic biopsies.[28] However, studies which demonstrated higher discordance rates than ours were found to have longer biopsy interval (median 45–51 months)[28,34,37] than that noted in the current study (overall median 19 months, as in ►**Table 1**).

Mean age of the present study participants was 47.39 ± 11.23 years. Statistically, significant correlation was found between mean age and ER discordance ($p = 0.03$). Also, ER and PR loss was found in younger females of age group ≤ 45 years. Similar findings were reported by Yang et al (2018)'s study in 231 breast cancer patients. Young females ≤ 50 years had high receptor conversion ($p = 0.0014$) with significantly worse disease-free survival ($p = 0.031$).[38]

Menopause does not cause cancer but increases the risk of cancer. It is one of the prognostic factors to determine the endocrine treatment options.[39] In the present study, high receptor discordance was observed in postmenopausal patients compared with premenopausal patients.

Conclusion

Overall, discordance rates of immunohistochemical biomarkers is highly heterogenous across different studies. Our study demonstrated considerably low receptor conversion rates on repeat biopsies, despite high variation of hormonal receptors. Salient findings of our study were, i) age dependant gain of estrogen receptors ii) Ki-67 gain concurrent with progesterone receptor loss on repeat biopsies indicating evolution of disease to an aggressive phenotype and iii) association of lung metastasis with progesterone receptor and Ki-67 concordance. We believe that the immunohistochemical discordance could be minimized to a substantial level by following standard laboratory protocol. Nevertheless, biopsies from recurrent sites in metastatic breast cancer is essential to re-stratify patients based on receptor expression on repeat immunohistochemical evaluation, in order to offer tailored and specific treatment to patients.

The strengths of our study were that the current study was conducted at a single center and IHC procedures were performed according to standardized laboratory protocol using automated systems. The main limitations were smaller sample size, retrospective design of the study, limited duration of follow-up because of which impact of receptor changes on postmetastatic survival, and overall survival could not be assessed.

Previous Presentation

This study was presented at the 3rd DALOS (Dr. Advani's Legendary Oncology Series) Conference, Mumbai, July 16, 2023.

Conflict of Interest

None declared.

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