*Original Article*

# Impact of shifting of hormonal receptor and human epidermal growth factor receptor 2 on survival of non-metastatic breast cancer

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## ABSTRACT

**Objectives:** This study explores variations in hormone receptor (HR) status between biopsy and post-operative reports, as well as changes following neoadjuvant chemotherapy (NACT). The correlation between HR status alterations and patient survival outcomes is the key focus of this investigation.

**Material and Methods:** This retrospective study conducted at a tertiary care center in Kolkata, Eastern India, from 2013 to 2018.

**Results:** The parameters of 482 breast cancer patients meeting inclusion criteria were studied. The majority were >40 years (68.2%), with 300 receiving NACT. Clinical staging distribution was I (2.9%), IIA (10.4%), IIB (22.2%), IIIA (34.3%), IIIB (28.6%), and IIIC (1.6%). Preoperative and postoperative staging changes occurred in 47.7%, with 38.8% downstaging and 13.5% upstaging. Estrogen receptor (ER), progesterone receptor (PR), and Her2neu positivity at diagnosis were observed in 46.3%, 41.9%, and 36.9% of patients, respectively. Postoperative ER, PR, and Her2neu positivity were 46.1%, 40%, and 37.3%, respectively. Recurrence in 33.6% of patients correlated with factors like age, tumor grade, lymphovascular invasion (LVI), Perineural invasion (PNI), postoperative stage, ER, PR, and their changes. Multivariate analysis identified age, PNI, postoperative stage, stage change, ER, and PR changes as independent factors for recurrence. The correlation study demonstrated a significant association between NACT and changes in PR status ($\chi2 = 16.56$; $p = 0.001$), while no significant associations were found for ER and Her2neu changes. Analysis of variance (ANOVA) revealed a substantial association between NACT and PR status changes ($p = 0.001$). Post Hoc tests indicated significant differences in PR status changes related to NACT. Kaplan-Meier survival analysis revealed a significant difference in disease-free survival (DFS) based on changes in ER and PR status, with ER-positive patients having a median DFS of 76 months and PR-positive patients showing a median DFS of 47 months. No significant DFS difference was observed for changes in Her2neu status.

**Conclusion:** Changes in hormone receptor status, particularly ER and PR, significantly impacted recurrence and DFS. The study highlights the importance of personalized management strategies, with age, tumor grade, lymphovascular invasion (LVI), and changes in ER and PR status identified as key factors influencing prognosis.

**Keywords:** Breast cancer, Estrogen and progesterone receptor, Neoadjuvant chemotherapy, Hormonal receptor change, Survival

## INTRODUCTION

The number of new breast cancer cases in India is 178,361 (13.5%), with 90,408 (10.6%) reported deaths, as per the global cancer observatory (GLOBOCAN) data (2020).[1] The role of neoadjuvant chemotherapy (NACT) is now established for the treatment of locally advanced breast cancer. It helps to reduce the tumor size and, most importantly, decrease micrometastasis, increasing the chances of breast-conserving surgery.[2,3] The receptor's status needs to be determined as per protocol before initiating the treatment of breast cancer. These receptors include estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 neu (Her2neu), and Ki 67%. Hormone receptors (HR) and molecular markers are used to determine the status of breast cancer, and they may change after neoadjuvant chemotherapy.[4] This retrospective study seeks to illustrate the variations in HR status between biopsy specimens and final histopathological reports post-operatively, along with assessing changes in HR status following NACT at a tertiary care center in Eastern India. Additionally, the study aims to establish a correlation between the alterations in HR status and the survival outcomes of the patients.

## MATERIAL AND METHODS

The clinical data of breast cancer patients treated at the Institute of Post Graduate Medical Education and Research (IPGMER), Kolkata, from January 2013 to December 2018 were collected. The staging was done based on the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system (7th edition, 2010).[5] The diagnosis was validated by histopathological examination. The inclusion criteria for the patients were as follows: age > 18 years; females; unilateral histopathologically confirmed invasive breast carcinoma; availability of pre and post-operative histopathological examination report including the immunohistochemistry (IHC) report of ER, PR, Her2neu, and Ki67%; nonmetastatic breast carcinoma. Exclusion criteria were as follows: metastatic breast cancer; non-availability of pre and post-operative IHC report of ER, PR, Her2neu, and Ki67%; previous history of breast cancer treatment.

Data on age group, menopausal status, histopathological status, clinical stage, surgical information, post-operative staging, systemic chemotherapy information, IHC status, and follow-ups was collected. Disease-free survival (DFS) was defined from the start of primary therapy to the date of disease recurrence (local or distant). Overall survival (OS) was defined as the time from the date of the start of primary therapy to the date of death or the last follow-up.

### Statistical analysis

IBM SPSS (Statistical Package for the Social Sciences) for Windows version 25.0 was used.[6] Descriptive statistics were used to characterize the patient population using frequencies, mean, median, and quartile values. Continuous variables were analyzed using the Student's *t*-test. Univariate and multivariate Cox regression analyses were performed to identify the factors associated with disease recurrence. Analysis of variance (ANOVA) test done to identify the pre and post-NACT receptor status changes. DFS and OS were analyzed with the Kaplan–Meier test, and survival curves were compared with the log-rank test. P-values <0.05 were accepted as significant.

## RESULTS

Patients meeting the inclusion criteria were selected for analysis. The majority of the patients were in the age group > 40 years (68.2%). NACT was received by 300 patients whereas 182 were considered for upfront surgical intervention.

### Clinicopathological characteristics

The distribution of clinical staging of patients at stage I, IIA, IIB, IIIA, IIIB, and IIIC was 2.9%, 10.4%, 22.2%, 34.3%, 28.6%, and 1.6% respectively. The ER, PR, and Her2neu were positive in 46.3%, 41.9%, and 36.9% of patients respectively, at diagnosis of the core needle biopsy specimen. The distribution of grades of the tumor at grade 1, 2, and 3 were 20.5%, 40.5%, and 39%, respectively.

The post-operative stages IA, IIA, IIB, IIIA, IIIB, and IIIC were distributed as 5%, 19.5%, 30.5%, 25.3%, 13.1%, and 6.6%, respectively. The comparison between pre-and post-operative staging revealed that there was no change in 47.7% of patients. Down-staging was observed in 38.8% of patients, and up-staging was seen in 13.5%. The IHC study on the post-operative specimen revealed that the ER, PR, and Her2neu were positive in 46.1%, 40%, and 37.3% of patients, respectively.

The analysis of the pattern of changes in the ER of the post-operative specimen showed that the status remained positive for 41.9% of patients. and negative in 49.6%. ER from positive to negative was observed in 4.4%, and from negative to positive change in 4.1% of patients. The PR change pattern in the post-operative specimen showed that 35.7% remained positive and 53.7% remained negative. The change of PR from positive to negative and from negative to positive were 6.2% and 4.4%, respectively. Similarly, the Her2neu status of the post-operative specimen remained positive and negative in 34.4% and 60.2% of patients, respectively. The change of Her2neu from positive to negative and from negative to positive was in 2.5% and 2.9% of patients, respectively, in the post-operative specimen. At the time of analysis, 162 (33.6%) of the patients had recurrence. The comparative clinicopathological characteristics have been given in Table 1.

### Univariate and multivariate Cox regression analysis

The Cox regression analysis was performed to identify the factors associated with recurrence; details have been given in Table 2. The univariate Cox regression analysis showed that age group (p = 0.043), tumor grade (p = 0.002), LVI (p < 0.001), PNI (p < 0.001), post-operative stage p < 0.001), change of stage (p = 0.037), post-operative ER status (p < 0.001), post-operative PR status (p < 0.001), change of ER status (p < 0.001), change of PR status (p < 0.001) were dependent factors for recurrence in breast cancer patients. Menopausal status (p = 0.508), NACT (p = 0.114), and change of Her2neu (p = 0.245) were not associated with recurrence. The multivariate Cox regression analysis of dependent factors showed that age group (p < 0.001), PNI (p = 0.015), post-operative stage (p < 0.001), change of stage (p = 0.041), post-operative ER status (p = 0.013), change of PR status (p = 0.030) were the independent factors associated with recurrence in breast cancer patients.

### Correlation study of change of receptor status and NACT

The correlation study showed that a change in PR status ($\chi 2$ = 16.56; p = 0.001) was statistically significantly associated

**Table 1:** Clinicopathological characteristics.

| Variable | Characteristics | Neoadjuvant chemotherapy (NACT) | | | | P - value |
|---|---|---|---|---|---|---|
| | | No (N =182) | | Yes (N =300) | | |
| | | Count | N % | Count | N % | |
| Side | Left | 91 | 18.88% | 165 | 34.24% | 0.286 |
| | Right | 91 | 18.88% | 135 | 28.00% | |
| Age group | ≤ 40 years | 60 | 12.44% | 93 | 19.30% | 0.653 |
| | > 40 years | 122 | 25.35% | 207 | 42.91% | |
| Clinical T | T 1 | 20 | 4.14% | 0 | 0.00% | <0.001 |
| | T 2 | 112 | 23.24% | 20 | 4.14% | |
| | T 3 | 39 | 8.10% | 146 | 30.30% | |
| | T 4 | 11 | 2.28% | 134 | 27.80% | |
| Clinical N | N 0 | 75 | 15.57% | 24 | 4.97%% | <0.001 |
| | N 1 | 97 | 20.13% | 184 | 38.18% | |
| | N 2 | 10 | 2.07% | 84 | 17.43% | |
| | N 3 | 0 | 0.00% | 8 | 1.65% | |
| Clinical stage | IA | 14 | 2.90% | 0 | 0.00% | <0.001 |
| | IIA | 48 | 9.96% | 2 | 0.42% | |
| | IIB | 83 | 17.22% | 24 | 4.98% | |
| | IIIA | 26 | 5.40% | 139 | 28.81% | |
| | IIIB | 11 | 2.28% | 127 | 26.32% | |
| | IIIC | 0 | 0.00% | 8 | 1.66% | |
| ER (Biopsy specimen) | Negative | 93 | 19.30% | 166 | 34.44% | 0.366 |
| | Positive | 89 | 18.46% | 134 | 27.80% | |
| PR (Biopsy specimen) | Negative | 102 | 21.16% | 178 | 36.93% | 0.478 |
| | Positive | 80 | 16.60% | 122 | 25.31% | |
| Her2neu (Biopsy specimen) | Negative | 105 | 21.79% | 199 | 41,29% | 0.057 |
| | Positive | 77 | 15.97% | 101 | 20.95% | |
| Pathological T | T 1 | 22 | 4.56% | 8 | 1.65% | <0.001 |
| | T 2 | 125 | 25.95% | 92 | 19.09% | |
| | T 3 | 24 | 4.97% | 136 | 28.23% | |
| | T 4 | 11 | 2.28% | 64 | 13.27% | |
| Pathological N | N 0 | 80 | 16.60% | 120 | 24.90% | 0.026 |
| | N 1 | 62 | 12.86% | 90 | 18.68% | |
| | N 2 | 36 | 7.46% | 63 | 13.07% | |
| | N 3 | 4 | 0.83% | 27 | 5.60% | |
| Post-operative stage | IA | 17 | 3.52% | 7 | 1.48% | <0.001 |
| | IIA | 63 | 13.08% | 31 | 6.42% | |
| | IIB | 48 | 9.96% | 99 | 20.54% | |
| | IIIA | 40 | 8.29% | 82 | 17.01% | |
| | IIIB | 9 | 1.86% | 54 | 11.24% | |
| | IIIC | 5 | 1.04% | 27 | 5.56% | |
| Change of stage | Stable | 119 | 24.70% | 111 | 23.02% | <0.001 |
| | Upstaged | 31 | 6.45% | 34 | 7.05% | |
| | Downstaged | 32 | 6.64% | 155 | 32.16% | |

(*Contd...*)

| Variable | Characteristics | Neoadjuvant chemotherapy (NACT) | | | | P - value |
| | | No (N =182) | | Yes (N =300) | | |
| | | Count | N % | Count | N % | |
|---|---|---|---|---|---|---|
| Post-operative ER | Negative | 94 | 19.50% | 166 | 34.50% | 0.431 |
| | Positive | 88 | 18.25% | 134 | 27.85% | |
| Post-operative PR | Negative | 101 | 21.00% | 188 | 39.00% | 0.119 |
| | Positive | 81 | 16.80% | 112 | 23.20% | |
| Post-operative Her2neu | Negative | 105 | 21.79% | 197 | 40.88% | 0.079 |
| | Positive | 77 | 15.97% | 103 | 21.36% | |
| Change of ER | Stable positive | 84 | 17.42% | 118 | 24.48% | 0.127 |
| | Positive to negative | 5 | 1.06% | 16 | 3.31% | |
| | Negative to positive | 4 | 0.82% | 16 | 3.31% | |
| | Stable negative | 89 | 18.47% | 150 | 31.13% | |
| Change of PR | Stable positive | 77 | 15.99% | 95 | 19.71% | 0.001 |
| | Positive to negative | 3 | 0.63% | 27 | 5.60% | |
| | Negative to positive | 4 | 0.82% | 17 | 3.52% | |
| | Stable negative | 98 | 20.33% | 161 | 33.40% | |
| Change of Her2neu | Stable positive | 74 | 15.35% | 92 | 19.08% | 0.088 |
| | Positive to negative | 3 | 0.62% | 9 | 1.87% | |
| | Negative to positive | 3 | 0.62% | 11 | 2.28% | |
| | Stable negative | 102 | 21.17% | 188 | 39.01% | |
| LVI | Negative | 81 | 16.80% | 110 | 22.82% | 0.088 |
| | Positive | 101 | 20.96% | 190 | 39.42% | |
| PNI | Negative | 90 | 18.67% | 114 | 23.66% | 0.014 |
| | Positive | 92 | 19.08% | 186 | 38.59% | |
| Tumor grade | Grade 1 | 59 | 12.24% | 40 | 8.30% | <0.001 |
| | Grade 2 | 70 | 14.52% | 125 | 25.94% | |
| | Grade 3 | 53 | 11.00% | 135 | 28.00% | |
| Recurrence | Yes | 52 | 10.78% | 110 | 22.82% | 0.068 |
| | No | 130 | 26.98% | 190 | 39.42% | |

LVI: Lymphovascular invasion, PNI: Perineural invasion, ER: Estrogen receptor, PR: Progesterone receptor, T: Tumor, N: Node.

| Table 2: Univariate and multivariate analysis of DFS using Cox Regression Analysis | | | | | | | |
| Variables | | Univariate | | | Multivariate | | |
| | N | P value | HR | 95% CI for HR | P value | HR | 95% CI for HR |
|---|---|---|---|---|---|---|---|
| Age group | | 0.043 | | | 0.001 | | |
| ≤ 40 years | 153 | | 1 | | | 1 | |
| > 40 years | 329 | | 0.71 | 0.52 – 0.99 | | 0.57 | 0.41 – 0.80 |
| Menopausal status | | 0.508 | | | | | |
| Pre-menopausal | 242 | | 1 | | | | |
| Post-menopausal | 240 | | 0.90 | 0.66 – 1.22 | | | |
| Neoadjuvant chemotherapy | | 0.114 | | | | | |
| No | 182 | | 1 | | | | |
| Yes | 300 | | 1.30 | 0.93 – 1.81 | | | |

*(Contd...)*

| Variables | | Univariate | | | | Multivariate | | |
|---|---|---|---|---|---|---|---|---|
| | N | P value | HR | 95% CI for HR | | P value | HR | 95% CI for HR |
| Grade | | 0.002 | | | | 0.669 | | |
| Grade 1 | 99 | | 1 | | | | 1 | |
| Grade 2 | 195 | 0.021 | 1.77 | 1.08 – 2.87 | | 0.427 | 1.23 | 0.73 – 2.08 |
| Grade 3 | 188 | 0.001 | 2.31 | 1.43 – 3.72 | | 0.378 | 1.26 | 0.74 – 2.15 |
| LVI | | <0.001 | | | | 0.227 | | |
| Absent | 191 | | 1 | | | | 1 | |
| Present | 291 | | 1.99 | 1.41 – 2.80 | | | 1.25 | 0.86 – 1.82 |
| PNI | | <0.001 | | | | 0.015 | | |
| Absent | 204 | | 1 | | | | 1 | |
| Present | 278 | | 2.56 | 1.80 – 3.65 | | | 1.60 | 1.09 – 2.35 |
| Post-operative stage | | <0.001 | | | | <0.001 | | |
| Stage IA | 24 | | 1 | | | | 1 | |
| Stage IIA | 94 | 0.742 | 1.19 | 0.42 – 3.34 | | 0.559 | 0.72 | 0.24 – 2.12 |
| Stage IIB | 147 | 0.72 | 2.34 | 0.92 – 5.95 | | 0.385 | 1.55 | 0.57 – 4.22 |
| Stage IIIA | 122 | 0.004 | 3.95 | 1.54 – 10.14 | | 0.029 | 3.13 | 1.12 – 8.70 |
| Stage IIIB | 63 | 0.001 | 5.35 | 2.06 – 13.89 | | 0.018 | 3.50 | 1.24 – 9.58 |
| Stage IIIC | 32 | <0.001 | 7.784 | 2.89 – 20.90 | | <0.001 | 13.34 | 3.39 – 52.42 |
| Change of stage | | 0.037 | | | | 0.041 | | |
| Stable stage | 230 | | 1 | | | | 1 | |
| Upstaged | 65 | 0.478 | 1.173 | 0.75 - 1.82 | | 0.016 | 0.35 | 0.15 – 0.82 |
| Downstaged | 187 | 0.028 | 0.679 | 0.48 – 0.95 | | 0.647 | 1.10 | 0.718 – 1.70 |
| Post-operative ER | | <0.001 | | | | 0.013 | | |
| Negative | 260 | | 1 | | | | 1 | |
| Positive | 222 | | 0.460 | 0.33 – 0.64 | | | 0.49 | 0.28 – 0.86 |
| Post-operative PR | | <0.001 | | | | 0.737 | | |
| Negative | 289 | | 1 | | | | 1 | |
| Positive | 193 | | 0.520 | 0.37 – 0.72 | | | 0.90 | 0.51 – 1.59 |
| Post operative Her2neu | | 0.510 | | | | | | |
| Negative | 302 | | 1 | | | | | |
| Positive | 180 | | 0.897 | 0.64 – 1.24 | | | | |
| Change of ER | | <0.001 | | | | 0.074 | | |
| Positive to positive | 202 | | 1 | | | | 1 | |
| Positive to negative | 21 | 0.238 | 1.545 | 0.75 - 3.18 | | 0.211 | 1.61 | 0.76 – 3.42 |
| Negative to positive | 20 | 0.342 | 0.609 | 0.21 – 1.69 | | 0.605 | 1.38 | 0.40 – 4.76 |
| Negative to negative | 239 | <0.001 | 2.134 | 1.50 – 3.01 | | 0.013 | 2.03 | 1.15 – 3.56 |
| Change of PR | | <0.001 | | | | 0.030 | | |
| Positive to positive | 172 | | 1 | | | | 1 | |
| Positive to negative | 30 | 0.789 | 0.902 | 0.42 – 1.91 | | 0.368 | 0.69 | 0.32 – 1.52 |
| Negative to positive | 21 | 0.087 | 0.359 | 0.11 – 1.16 | | 0.025 | 0.20 | 0.05 – 0.81 |
| Negative to negative | 259 | 1.870 | 1.870 | 1.32 – 2.64 | | 0.737 | 1.10 | 0.62 – 1.93 |
| Change of Her2neu | | 0.245 | | | | | | |
| Positive to positive | 166 | | 1 | | | | | |
| Positive to negative | 12 | 0.275 | 0.567 | 0.20 – 1.57 | | | | |
| Negative to positive | 14 | 0.129 | 0.335 | 0.08 – 1.37 | | | | |
| Negative to negative | 290 | 0.663 | 1.076 | 0.77 – 1.47 | | | | |

ER: Estrogen receptor, PR: Progesterone receptor, LVI:Lymphovascular invasion, PNI: Perineural invasion, HR: Hazard ratio, CI: Confidence interval.

with NACT. Change of ER status ($\chi2 = 5.70$; $p = 0.127$) and Her2neu ($\chi2 = 6.53$; $p = 0.089$) were statistically significantly not associated with NACT. ANOVA between NACT and change of ER, PR, and Her2neu status of the post-operative specimen showed that change of PR status is statistically significantly associated with NACT ($p = 0.001$); details have been given in Table 3. The post Hoc test between NACT and change of PR showed that there is a statistically significant difference between change from positive to positive and positive to negative ($p < 0.001$); positive to positive and negative to positive ($p = 0.020$); positive to negative and negative to negative ($p = 0.003$); details have been given in Table 4. It can be said that there is maximum change in PR status in association with NACT is observed in the group of patients who showed change from positive to negative.

## Survival analysis

The Kaplan-Meier survival analysis revealed a statistically significant difference in the DFS concerning changes in ER status (log-rank test, $\chi2 = 24.24$; $p < 0.001$). The overall

**Table 3:** ANOVA of Neoadjuvant chemotherapy with changes of ER, PR, and Her2neu.

| Receptor change | N | Mean | Std. Deviation | 95% Confidence Interval | P value |
|---|---|---|---|---|---|
| **NACT and Change of ER** | | | | | |
| Positive to positive | 202 | 1.58 | .494 | 1.52 - 1.65 | 0.127 |
| Positive to negative | 21 | 1.76 | .436 | 1.56 - 1.96 | |
| Negative to positive | 20 | 1.80 | .410 | 1.61 - 1.99 | |
| Negative to negative | 239 | 1.63 | .484 | 1.57 - 1.69 | |
| **NACT and Change of PR** | | | | | |
| Positive to positive | 172 | 1.55 | 0.499 | 1.48 - 1.63 | 0.001 |
| Positive to negative | 30 | 1.90 | 0.305 | 1.79 - 2.01 | |
| Negative to positive | 21 | 1.81 | 0.402 | 1.63 - 1.99 | |
| Negative to negative | 259 | 1.62 | 0.486 | 1.56 - 1.68 | |
| **NACT and Change of Her2neu** | | | | | |
| Positive to positive | 166 | 1.55 | 0.499 | 1.48 - 1.63 | 0.089 |
| Positive to negative | 12 | 1.75 | 0.452 | 1.46 - 2.04 | |
| Negative to positive | 14 | 1.79 | 0.426 | 1.54 - 2.03 | |
| Negative to negative | 290 | 1.65 | 0.478 | 1.59 - 1.70 | |

NACT: Neoadjuvant chemotherapy, ER: Estrogen receptor, PR: Progesterone receptor.

**Table 4:** Post Hoc Test analysis with NACT as a dependable variable for changes in PR.

| (I) Change of PR | (J) Change of PR | Mean difference (I-J) | P value | 95% confidence interval |
|---|---|---|---|---|
| Positive to positive | Positive to negative | -0.348* | 0.000 | 0.53 - 0.16 |
| | Negative to positive | -0.257* | 0.020 | 0.47 - 0.04 |
| | Negative to negative | -0.069 | 0.141 | 0.16 - 0.02 |
| Positive to negative | Positive to positive | 0.348* | 0.000 | 0.16 - 0.53 |
| | Negative to positive | 0.090 | 0.507 | 0.18 - 0.36 |
| | Negative to negative | 0.278* | 0.003 | 0.10 - 0.46 |
| Negative to positive | Positive to positive | 0.257* | 0.020 | 0.04 - 0.47 |
| | Positive to negative | -0.090 | 0.507 | 0.36 - 0.18 |
| | Negative to negative | 0.188 | 0.084 | 0.03 - 0.40 |
| Negative to negative | Positive to positive | 0.069 | 0.141 | 0.02 - 0.16 |
| | Positive to negative | -0.278* | 0.003 | 0.46 - 0.10 |
| | Negative to positive | -0.188 | 0.084 | 0.40 - 0.03 |

*The mean difference is significant at the 0.05 level, PR: progesterone receptor, NACT: Neoadjuvant chemotherapy
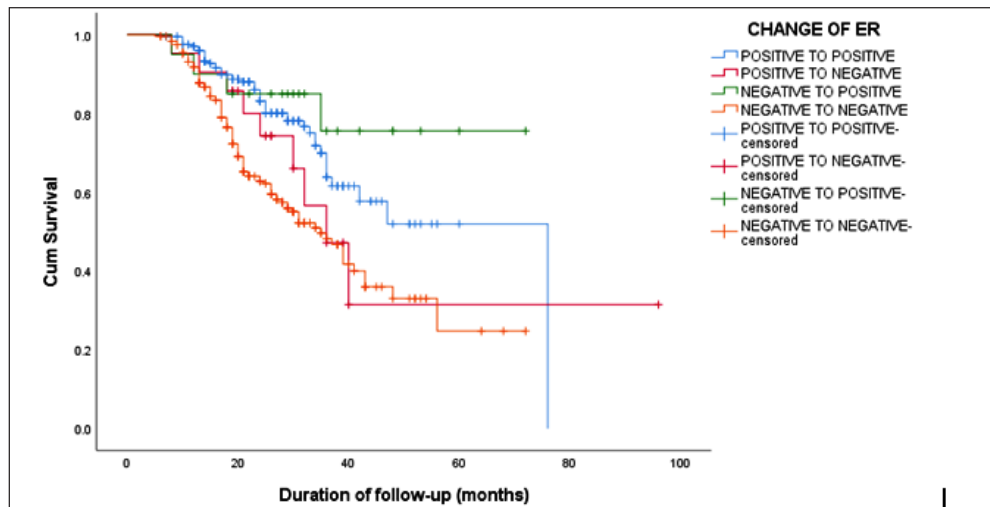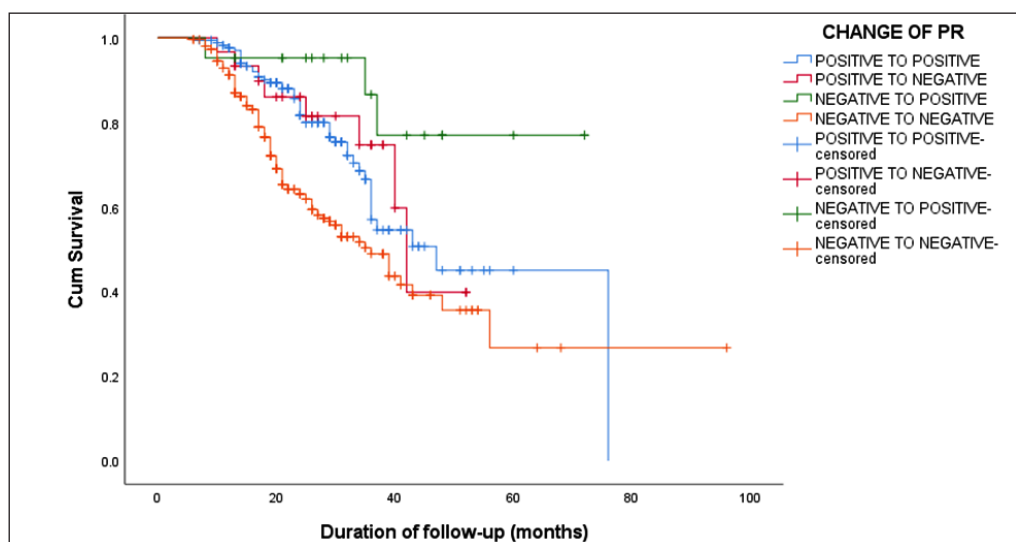
**Figure 1:** The Kaplan-Meier survival curve showing a statistically significant difference in the disease-free survival (DFS) concerning changes in estrogen receptor (ER) status (log-rank test, $\chi 2 = 24.24$; $p < 0.001$).

median DFS was 58.03 months. Patients maintaining ER positivity exhibited a median DFS of 76 months, while those remaining ER-negative had a median DFS of 35 months (CI of 29.56 – 40.43). ER changes from positive to negative resulted in a median DFS of 36 months (CI of 27.21 – 44.78), and DFS was not reached for ER changes from negative to positive [Figure 1]. Similarly, a significant difference in DFS was noted for changes in PR status (log-rank test, $\chi 2 = 22.92$; $p < 0.001$). PR-positive patients had a median DFS of 47 months (CI of 35.73–58.26), PR-negative patients showed a median DFS of 36 months (CI of 29.94–42.05), PR changes from positive to negative yielded a median DFS of 42 months (CI of 38.21–45.78), and those changing from PR negative to positive did not reach the median DFS [Figure 2]. No

statistically significant difference in DFS was observed when comparing changes in Her2neu status

## DISCUSSION

This study mainly focuses on the change of ER and PR status in the specimens, but Her2neu status was also compared. Most important changes of receptor status are negative to positive as this change altered the treatment modality.[7] Our study revealed that ER and PR receptor status conversion or change influences the recurrence of breast cancer, and similar findings in the other studies showed that the ER and PR receptor changes influence survival.[8] In an Italian series of 904 patients, ER was lost in 5% of HR+ cancers compared with 67% showing loss of PR (cut-off 20%); change in PR



**Figure 2:** The Kaplan-Meier survival curve showing a statistically significant difference in the disease-free survival (DFS) concerning changes in progesterone receptor (PR) status (log-rank test, $\chi 2 = 22.92$; $p < 0.001$).

status was associated with improved survival regardless of whether they received endocrine therapy.[9] The study found that change in PR receptor status is associated with improved survival which is in concordance with the findings of our study. A review of 45 studies addressing ER, PR, and Her2neu expression found an average prevalence of discordant results of 32% for PR and 13% for ER local recurrences showed higher rates of ER and PR conversion than the immediate post-NACT specimens.[10]

In our study, alterations in ER receptor status were observed in 8.5% (receptor changes of 1.88% in no NACT and 6.62% in the NACT group) of patients, while changes in PR receptor status were identified in 10.58% of patients. In a French series with 420 patients, ER status changed by 23%; 42% negative to positive and 13% positive to negative.[11] An Indian study by Anand AS et al. reported that ER discordance was 8.7 % and PR discordance was 13 %. PR positive to PR negative discordance was the predominant one. These findings were in concordance with the results of our study.[12] A study from China by WU YT et al. found a 15% change in ER status and 2a 7% change in PR status. These reports are higher than the findings of our study.[13] In this study, a statistically significant difference in patient DFS was observed based on changes in ER or PR status. Patients maintaining ER positivity exhibited a median survival of 76 months, while ER-negative patients had a median survival of 35 months. ER changes from positive to negative resulted in a median survival of 36 months, and for ER changes from negative to positive, the median survival was not attained. For PR, those remaining PR-negative had a median survival of 36 months, PR changes from positive to negative showed a median survival of 42 months, and those changing from PR-negative to positive did not reach the median survival. A study by Yang Z et al. reported findings similar to those of our study, except that their study involved metastatic breast cancers.[14]

A recent series of 482 patients by Ding et al. found changes in ER status in 10% of cases (36 positive to negative and 14 negative to positive) and PR status in 17% (57 positive to negative and 25 negative to positive). These changes influence the DFS and OS.[15] Yang L et al. described in their study that for patients who received adjuvant hormonal therapy after surgery, the 5-year DFS estimates for patients in any receptor conversion group (55.2%) was worse than patients in the receptor stable group (73.7%, Log-rank test, $P=0.015$). While the 5-year OS estimates for patients with or without receptor conversion were not statistically different (86.0 vs. 82.4%, Log-rank test, $P=0.587$).[16] We noted a lower survival rate in cases where ER expression was lost compared to those with continuous ER positivity. Likewise, DFS was compromised with the loss of PR expression and the shift from PR positive

to PR negative. However, survival was higher in cases where PR initially tested positive but later converted to negative, in contrast to those where PR positivity was sustained. Matsumoto et al. found that patients exhibiting a switch to positive hormonal receptors in metastatic lesions experienced improved survival.[17] In accordance with the recent recommendations from the National Comprehensive Cancer Network (NCCN), it is advised to tailor treatment based on recurrent ER/PR/HER2 status whenever possible.[18] Ensure biopsy provision and optimize the treatment approach for patients experiencing recurrence and metastasis.

Limitations of our study including single center study, retrospective, and small sample size. Further studies on cumulative data are needed for confirmation.

## CONCLUSION

In conclusion, changes in hormone receptor status, particularly ER and PR, significantly impacted recurrence and DFS. The study highlights the importance of personalized management strategies, with age, tumor grade, LVI, and changes in ER and PR status identified as key factors influencing prognosis. Further research is warranted to unravel the intricate relationships between molecular changes, treatment modalities, and long-term outcomes in breast cancer.

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