Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.2024114385-391

Evaluating Biomarker Dynamics in Breast Cancer Post-Neoadjuvant Chemotherapy: A Retrospective Cross-sectional Study

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ARTICLE INFO

Received:
4 July 2024
Revised:
15 August 2024
Accepted:
15 August 2024

Keywords:
Neoadjuvant chemotherapy, hormone receptors, histological grade, biomarker, breast cancer

ABSTRACT

Background: Neoadjuvant chemotherapy (NACT) is integral to breast cancer management, yet its influence on biomarkers, notably androgen receptor (AR), remains underexplored. This study examines post-NACT alterations in receptor status, including ER, PR AR, HER2, and Ki67 index in breast cancer patients.

Methods: A cross-sectional study, spanning three years at a tertiary care center, enrolled patients with invasive breast cancer undergoing mastectomy post-NACT. Pre- and post-NACT specimens underwent histological grading and immunohistochemistry for hormone status, HER2 status, and Ki67 index. Discordance between pre- and post-NACT receptor statuses and expression levels of biomarkers was assessed using McNemar's and Wilcoxon signed rank tests, respectively.

Results: Among 100 patients, 35 were assessed. The mean age was 43.83 years, with prevalent T1 tumors (34.3%) and N1 nodal involvement (37.1%). Post-NACT, 54.2% showed no histological grade change. Notable alterations included changes in ER (14.2%), PR (14.2%), and HER2 status (8.57%). AR expression showed a significant change following NACT (p=0.03), while ER expression exhibited a trend towards significance (P=0.06). Ki67 index decreased in only 5.7% of cases.

Conclusion: This study unveiled intricate biomarker dynamics following NACT in breast cancer, with particular emphasis on AR, hitherto not evaluated. Larger investigations are imperative to elucidate clinical implications and tailor treatment strategies for breast cancer patients undergoing NACT.

INTRODUCTION

Breast cancer is a leading cause of cancer mortality in the world. It is now the fifth leading cause of cancer-related fatalities. According to Global Cancer Statistics 2020, breast cancer in females is now the most commonly diagnosed cancer (11.7%) exceeding lung cancer (11.4%). In females, breast cancer is both the most commonly diagnosed malignancy as well as the leading cause of mortality due to cancer.[1] Breast cancer is known to be a heterogeneous disease, showing variable morphological and clinical features, with variable response to treatment. Assessment of breast cancer mainly comprises the evaluation of histologic type, grade, and stage of the tumor. Apart from these, assessment of Estrogen receptor (ER), Progesterone receptor (PR), Human epidermal growth factor receptor 2 (HER2) expression is also done routinely in the evaluation of breast cancer.[2] The molecular subtyping emphasizes the biological heterogeneity of breast cancer, paving the way for the evolution of new therapeutic strategies for breast cancer.[3]

Treatment of patients with operable breast cancer is multidisciplinary and combines local treatment and

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systemic therapy. Local treatment includes surgical excision and radiation therapy. Systemic therapy in breast cancer includes chemotherapy, endocrine therapy and anti-HER2 therapy. The molecular subtype of the tumor guides the appropriate choice of therapy for the patient. Systemic therapies aim to improve survival by controlling micro-metastasis. Based on the timing, systemic therapy can either be adjuvant which is given after surgery or neoadjuvant that is given before surgery. Neoadjuvant chemotherapy (NACT) is mainly used in locally advanced breast cancer to downstage the disease and enable breast conserving surgery.[4]

Several factors may cause alteration in the biomarker profile in surgical specimens of breast cancer. They include tumor heterogeneity, a limited amount of tissue evaluated in a biopsy being poorly representative of the tumor, and changes in tumor biology due to chemotherapy given to the patient.[5]

The Ki67 proliferation index is also expected to change with the administration of NACT. As Ki67 has been reported to have predictive and prognostic value in patients with invasive breast cancer who received NACT. The post-therapy Ki67 proliferation index level could provide an additional prognostic value where the pathological complete response is not being achieved.

Substantial evidence from various studies has shown significant alteration in biomarker expression following neoadjuvant chemotherapy in breast cancer. Such a change in receptor status calls for evaluation as the conversion of receptor status from negative to positive may warrant a change in the treatment plan. However, there is still only limited evidence on whether such a change in treatment plan benefits the patient and also on the impact of alterations in biomarker profile on the survival of the patient. Still more controversial is whether targeted therapies should be stopped or continued if the receptor status becomes negative in a patient.[6] Therefore, all of the above warrant evaluation of receptor status post neoadjuvant chemotherapy in breast cancer. Only a few studies have been conducted in the Indian population evaluating changes in receptor status post neoadjuvant chemotherapy. Through this study, we intend to evaluate the alterations in receptor status and Ki67 index post-neoadjuvant chemotherapy in breast cancer.

METHODS

Study design and participants

The study was conducted in a tertiary care center over two years (January 2022 to December 2023). It was a cross-sectional study in which patients with invasive breast cancer, diagnosed on core needle biopsy, who later underwent mastectomy following neoadjuvant chemotherapy (involving combinations of anthracyclines (such as doxorubicin or epirubicin) and taxanes (such as paclitaxel or docetaxel) were included. Patients received a total of 4-6 cycles of neoadjuvant chemotherapy. The exact number of cycles was determined based on individual patients' responses and tolerability to the treatment. This approach ensured that the patients received an optimal dose of chemotherapy to maximize tumor reduction while minimizing adverse effects. All patients who had pathological complete response [Miller Payne classification] following NACT were excluded. Out of 100 patients, 65 had complete pathological response; therefore, a total of 35 patients could be evaluated to compare the biomarker dynamics between pre and post NACT. This study was done in accordance with the Declaration of Helsinki, after receiving approval from the Institutional Ethics Committee [Vardhman Mahavir Medical College and Safdarjung Hospital, IEC/VMMC/SJH/Thesis/06/2022/CC-229].

Measurements of hormone receptors

All the core needle biopsies and resected breast specimens were fixed in 10% neutral buffered formalin. Respective paraffin blocks were made and sections of 2-3µ were cut. The slides were stained with hematoxylin and eosin (H & E) and evaluated under microscope to diagnose invasive breast carcinoma followed by Modified Bloom Richardson (MBR) scoring for histological grading. Immunohistochemistry was performed for hormone status (ER & PR), Her2neu status, androgen receptor expression and Ki67 proliferation index for all the core needle biopsies. Based on the above, surrogate molecular classification was also done. The tumor size, hormone receptor status, Her2neu status, AR expression, and Ki67 proliferation index were evaluated in all the post NACT mastectomy specimens. For IHC interpretation of ER and PR, a validated semiquantitative scoring system (Allred score) was used.[7] For Her2neu evaluation positive staining (3+) was considered when >10% of the tumor cells showed complete, intense and circumferential membranous staining.[7] The expression of AR was evaluated similar to ER, considering into account the percentage of nuclear staining as well as the intensity.[8] IHC interpretation for Ki67 was obtained by calculating the percentage of the total number of tumor cells with nuclear staining regardless of the staining intensity.[8,9] The changes in the receptor status and Ki67 proliferation index were observed and evaluated.

Statistical analysis

Discordance between pre- and post-NACT receptor statuses was assessed using McNemar's test,

which is suitable for paired nominal data. This test was used to determine if there was a significant change in the proportion of positive and negative cases for each biomarker (ER, PR, Her2neu, AR) after NACT. A P-value ≤ 0.05 was considered statistically significant. Quantitative data were summarized as mean and standard deviation. Differences in the expression levels of biomarkers between pre- and post-NACT samples (the paired groups) were compared by the Wilcoxon signed rank test. Qualitative data were summarized as proportions and analyzed by Chi-square/Fisher exact test. All statistical analyses were performed using SPSS software (version 21.0).

RESULTS

The mean age of the participants was 43.83±9.40 years with ages ranging from 26-65 years. There were 31.4% of the patients in the 36-45 and 46-55 year age groups. Twenty-four (68.6%) patients had lesions in the right breast and the most common quadrant was central (20%), followed by upper outer and upper inner quadrants (17.1% & 14.3%), respectively. The distribution of the "T" stage of the tumor among study subjects included 34.3% of T1, followed by T3 (28.6%). Thirteen patients (37.1%) had no nodal involvement while 13 patients (37.1%) belonged to N1 stage. Nodal status could not be assessed in one patient as lymph node resection was not done. We observed no change in MBR scoring in 54.2% of patients following NACT. A decrease in MBR scoring was seen in 31.4%, whereas 14.2% showed an increased MBR score. In four patients, no tumor was left and one had in situ carcinoma (nodal involvement present in both) post chemotherapy; therefore, no comparison was done. Histological grade decreased post chemotherapy in 17.1% of the patients, whereas 8.6% of the patients showed an increase in histological grading. However, the majority of the patients (74.3%) observed no change in their histological grade. Also, 51.4% of patients were ER-negative and 48.6% of patients were ER-positive before chemotherapy. Five patients had a change in ER status from positive to negative; however, this change was not statistically significant (P=0.06). Similar observations were made for PR expression as five patients had a change in PR status after chemotherapy, although the change was not significant. Changes in Her2neu expression were also observed as two 3+ positive patients changed to 1+ and 2+ staining (Table 1, 2). In addition, 100% of the participants had Ki67 index of >14% in their prechemotherapy biopsy samples, two of whom (5.7%) observed a change in the Ki67 index to <14% post neoadjuvant chemotherapy.

The most common subtype before chemotherapy was Luminal B (48.6%), whereas triple-negative breast cancer was the most common (42.9%) post-chemotherapy (Table 3).

Table 1. Comparison of PR, ER, AR & HER2 status (Pre and post chemotherapy) in study subjects (n=35)

	Pre-chemo (n=35)	Post-chemo (n=35)	P-value
PR			
Negative	20(57.1%)	25(71.4%)	0.06
Positive	15(42.9%)	10(28.6%)	
ER			
Negative	18(51.4%)	23(65.7%)	0.06
Positive	17(48.6%)	12(34.3%)	
AR			
Negative	15(42.9%)	21(60.0%)	0.03
Positive	20(57.1%)	14(40.0%)	
HER2neu			
Negative	25(71.4%)	26(74.3%)	0.22
Equivocal	1(2.9%)	2(5.7%)	
Positive	9(25.7%)	7(20.0%)	

McNemar's test

When AR expression was compared before and after chemotherapy, we observed a statistically significant change (P=0.03). Six AR-positive patients changed to negative after receiving NACT and also showed a decrease in Allred score.

Table 2. Comparison of HER 2 score (Pre and post chemotherapy) in study subjects (n=35)

SCORE (HER 2)	Pre-chemo (n=35)	Post-chemo (n=35)	P-value
0	25(71.4%)	26(74.3%)	0.89
2+	1(2.9%)	2(5.7%)	
3+	9(25.7%)	7(20.0%)	

Wilcoxon signed rank test

The discordance was highest in Luminal B subtype with a total of seven cases showing differences in pre and post chemotherapy and most of them changed to TNBC (5 cases). (Table 3).
A significant change in the Allred mean score of ER expression (from 3.17 ±3.45 to 2.31 ±3.31, P=0.03) and AR expression (3.86 ±3.48 to 2.46 ±3.12, P=0.001) was observed between pre and post chemotherapy samples (Table 4, 5). A significant association was also observed between histological grade and change in Her2neu status (P=0.01).

Treatment for breast cancer is multidisciplinary and combines local and systemic therapy. Systemic therapy, essential for reducing tumor size and eradicating micrometastasis, encompasses hormonal therapy, anti-HER2 therapy and chemotherapy.

Table 3. Comparison of Molecular subtypes (Pre and post chemotherapy) in study subjects (n=35)

	SURGICAL SPECIMEN (frequency)				DISCORDANCE	
BIOPSY	Luminal A	Luminal B	HER2 enriched	Triple Negative	No of pairs	%
Luminal A	0	0	0	0	0	0%
Luminal B	2	10	3	2	7/17	41.2%
HER2 enriched	0	0	4	2	2/6	33.3%
Triple Negative	0	0	0	12	0/12	0%

McNemar's test

Table 4. Association between Molecular subtype and Androgen receptor expression

Molecular class	AR Negative	AR positive
Her2 neu enriched	2 (33.3%)	4 (66.7%)
Luminal B	3 (17.7%)	14 (82.3%)
Triple Negative	9 (75%)	3 (25%)

Chi square test; p value = 0.01

Table 5. Comparison of Allred mean score (Pre and post chemotherapy) in study subjects (n=35)

Allred mean score	Prechemotherapy (n=35)	Post chemotherapy (n=35)	P-value
ER	3.17±3.45	2.31±3.31	0.03
PR	2.71±3.34	2.0±3.15	0.08
AR	3.86±3.48	2.46±3.12	0.001

Wilcoxon signed rank test

When the change in receptor status was compared to TNM staging, no significant associations were observed (Table 6, 7).

Table 6. Association of histological grade of tumor with change in receptor status

	Grade II (n=25)	Grade III (n=10)	P-value
Change in ER status	5 (20%)	0	0.29
Change in PR status	4 (16%)	1 (10%)	1.0
Change in HER2 status	0	3 (30%)	0.01
Change in AR status	4 (16%)	2 (20%)	1.0
Ki67 change	2 (8%)	0	1.0

Chi square test

Neoadjuvant systemic therapy, which is administered before surgical resection, is based on the hormone receptor expression and HER2 status of the patient which is now routinely assessed in the core needle biopsies sent to confirm a histological diagnosis of breast carcinoma.[4,10] The existing literature regarding the alterations in receptor status due to neoadjuvant chemotherapy ranges from studies showing no alterations to ones reporting significant alterations. Due to the inconsistency in the literature, there is uncertainty about whether re-evaluation of the receptor status is essential in the residual tumor and if the treatment options are to be modified according to the final molecular profile of the tumor. The pathogenesis behind the change in hormone receptor profile following neoadjuvant chemotherapy is multifactorial. Chemotherapy can induce changes at the molecular level that affect the expression of hormone receptors on cancer cells.

These changes may be due to direct cytotoxic effects on cancer cells, selective pressure exerted by chemotherapy, or alterations in the tumor microenvironment. Additionally, chemotherapy may lead to the clonal selection of subpopulations of cancer cells with different receptor profiles, contributing to the observed discordance in receptor status pre- and post-treatment.[10,11]

Table 7. Association of T And N stage of tumor with change in receptor status

	T0 (n=4)	T1 (n=12)	T2 (n=4)	T3 (n=10)	T4 (n=4)	Ti (n=1)	p value	N0 (n=13)	N1 (n=13)	N2 (n=5)	N3 (n=3)	Nx (n=1)	P-value
Change in ER status	1 (25%)	1 (8.3%)	1 (25%)	0	1 (25%)	1 (100%)	0.10	2 (15.4%)	2 (15.4%)	1 (20%)	0	0	0.93
Change in PR status	1 (25%)	2 (16.7%)	1 (25%)	0	1 (25%)	0	0.69	2 (15.4%)	2 (15.4%)	1 (20%)	0	0	0.93
Change in HER2 status	0	0	0	2 (20%)	1 (25%)	0	0.41	1 (7.7%)	1 (7.7%)	0	1 (33.3%)	0	0.10
Change in AR status	2 (50%)	0	0	4 (40%)	0	0	0.05	1 (7.7%)	3 (23.1%)	2 (40%)	0	0	0.43
Ki67 change	0	2 (16.7%)	0	0	0	0	0.40	0	1 (7.7%)	0	1 (33.3%)	0	0.24

Chi-square test

The patient cohort in the present study exhibited a younger age profile with a mean age of 43.83 years when compared to similar studies by Gahlaut *et al.* and Avci *et al.* who all observed a mean age of 47 years. This may be due to the smaller sample size of our study and the patients belonging to a different geographical area.[10,11]

Ramteke *et al.* and Gahlaut *et al.* reported that most of their patients exhibited histological grade 3 (57% and 48.6%, respectively). However, our observations aligned more closely with a previous study by Rey *et al.*, in which most of the patients belonged to histological grade 2 (59.7%).[5,7,10]

In this study, we observed a change in histological grade from higher to lower in 17.10% of cases and vice versa in 8.6% of the cases. The percentage of change is lower in comparison to a previous study by Gahlaut *et al.*, who documented change to a lower grade in 28.8% and upgradation to a higher histological grade in 13.8%, which could be possibly due to a larger sample size.[10] We found that five patients experienced a change in ER and PR expression from positive to negative, post neoadjuvant chemotherapy. However, changes in both ER and PR (5/35 patients – 14.2%) were statistically not significant (P = 0.06 for both ER and PR). Our findings are consistent with those of prior studies by Katayama *et al.* and Rey *et al.* who also documented insignificant changes in ER and PR expression post-chemotherapy. Katayama *et al.* reported a change in ER expression in 19.9% (4/143 patients) and a change in PR expression in 11.4% (16/140), both of which were not significant (P =0.13 and 0.56). Rey *et al.* evaluated 78 patients post chemotherapy and observed a change in ER expression in 2.56% (2/78 patients) and a change in PR expression in 8.97% (7/78 patients), which were both statistically not significant (P= 0.82 and 0.71). In a study on 38 patients, Kinsella *et al.* found a statistically significant change only in the PR expression in 23.6% of the patients (P= 0.03). However, a significant change in ER alone (P= 0.0016) was observed by Ramteke *et al.* with alterations in ER expression in 17% (17/100 patients), with an insignificant change in PR expression (P=0.13) in 13% of the sample (13/100 patients). Contrary to our findings, significant changes in both ER and PR expression had been observed in an earlier study by Gahlaut *et al.* who observed changes in ER and PR expression in 12% and 14.5% of the patients (out of 133 patients) with p values of <0.001 in both.[5,7,10,12,13]

Change in HER2 status was seen only in 8.57% (3/35) patients (P=0.22). Results discordant with our study were observed by Katayama *et al.*, who found a significant change in the HER2 status in 19.9% (44/221) patients (P=0.01). However, their study included only Her2neu-positive patients either by IHC or FISH, which creates a selection bias when compared to the present study. However, findings similar to the present study were observed by Rey *et al.*, who reported a change in HER2 status in 11.5% (9/78) patients. Changes in HER2 status have been attributed to the internalization of the HER2 protein and lysosomal degradation.[5,12]

We observed a significant change in the androgen receptor expression in the post-chemotherapy surgical specimens (P=0.03). Six patients who had positive AR expression in the biopsy showed negative expression in the resection specimens. The data regarding the change in Androgen receptors after chemotherapy is limited and warrants evaluation in larger cohorts. In this study, only 2 cases out of 35 showed a change in the Ki67 index from >14% to <14%. This is in contrast to the literature, as most of the studies have shown a significant change in the Ki67 index post-chemotherapy possibly due to a larger sample size. Rey *et al.* documented a change in the Ki67 index in 18 out of 78 patients, which was statistically significant.[5]

The AR is not routinely assessed in breast cancer patients, despite emerging evidence suggesting its potential significance. AR expression has been found to play a role in the progression and prognosis of breast cancer, particularly in certain subtypes such as TNBC and ER+ cancers. Including AR assessment in the diagnostic and treatment planning process could provide a more comprehensive understanding of tumor biology and aid in the development of tailored treatment strategies.

Incorporating AR evaluation into routine practice could offer several benefits for patient care. For instance, AR positivity in TNBC patients, who traditionally lack targeted therapies, might identify a subset of patients who could benefit from anti-androgen therapies. This could open new avenues for treatment in a group that otherwise has limited options. Additionally, for ER+ breast cancers, understanding AR status might help in predicting resistance to traditional endocrine therapies and in developing combination treatment approaches that could improve outcomes.

In the setting of metastatic breast cancer, where treatment options are often limited and the disease is more aggressive, incorporating AR-targeted therapies for AR+ patients might help in controlling disease progression and managing symptoms, ultimately improving the quality of life and survival rates.

Lee *et al.* observed that the most common molecular subtype to have changed in the post-chemotherapy resection specimens is the Luminal B subtype (14 out of 92 cases), which is in line with the

findings of the current study. The resulting subtypes noted in the study were HER2 enriched (1 out of the 14), Triple negative (4 out of the 14 cases) and Luminal A (9 out of the 14 cases) which are also similar to the changes observed in the present study.[14]

CONCLUSION

The notable changes in the receptor status observed in this study were statistically not significant; however, they exhibited a trend toward significance, justifying the need for reassessment in post-chemotherapy specimens. While this study provides valuable insights into the dynamics of breast cancer biomarkers post-neoadjuvant chemotherapy (NACT), it is important to address certain limitations that may impact the interpretation and generalizability of the findings. One notable limitation is the relatively small sample size of 35 patients, which may limit the statistical power of the study and potentially influence the robustness of the observed changes in biomarker expression. The small cohort size might also affect the ability to detect subtle yet clinically significant alterations, thereby necessitating cautious interpretation of the results. Furthermore, the limited sample size can restrict the ability to perform subgroup analyses that could provide more nuanced understanding of biomarker dynamics across different patient populations. Future studies with larger cohorts are essential to validate these findings and to explore the broader applicability of the results, ensuring that the observed trends are not artifacts of sample size limitations but rather reflective of true biological and clinical phenomena.

ETHICAL CONSIDERATIONS

This study was done in accordance with the Declaration of Helsinki and after receiving approval from the Institutional Ethics Committee [IEC/VMMC/SJH/Thesis/06/2022/CC-229].
Informed consent was taken from the patients.

DATA AVAILABILITY

The data is available from the corresponding author on request.

FUNDING

This study received no funding support.

CONFLICT OF INTEREST

The authors declare no confilict of interest for this article.

ACKNOWLEDGEMENTS

None.

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How to Cite This Article

G K, Khan AA, Zaheer S , Ahuja S, Zaheer S Evaluating Biomarker Dynamics in Breast Cancer Post-Neoadjuvant Chemotherapy: A Retrospective Cross-sectional Study. Arch Breast Cancer. 2024; 11(4):385-91.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/986