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Receptor Conversion in Invasive Breast Carcinoma Following Neoadjuvant Chemotherapy and Its Prognostic Significance

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ABSTRACT

Testing for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) is carried out on pre-neoadjuvant chemotherapy (NAC) core biopsies of invasive breast carcinoma (IBC). Yet, these assays are not standard practice on post-NAC IBC specimens that harbor residual malignancy. This research contributes to understanding how shifts in ER, PR, and HER2 expression between pre- and post-NAC IBC with persistent disease correlate with prognostic endpoints, namely disease-free survival (DFS) and overall survival (OS). The investigation followed a cohort framework, integrating both prospective and retrospective arms. Consequently, newly identified IBC patients who received surgical resection after NAC, whose pre-NAC biopsy material was accessible, and who had residual tumor within the breast, were recruited between January 2017 and January 2020 (n = 174) and observed longitudinally until July 2022. The analysis encompassed 174 subjects. Out of these 174, 77 (44%) cases initially classified as ER-positive switched to negative, 10 ER-positive cases retained positivity, and 87 (50%) cases originally ER-negative remained so. For PR, 48 (27%) PR-positive cases became negative, 10 PR-positive cases stayed positive, and 116 (67%) cases persisted as negative. Concerning HER2, 64 (36%) HER2-positive cases converted to negative, 4 (2%) HER2-positive cases maintained their positive status, and 103 (59%) cases remained negative. Individuals who transitioned from ER/HER2-positive to negative status achieved significantly longer DFS and OS. Discordance in hormone receptor (HR) and HER2 status occurs in IBC with residual disease following NAC, and subjects with post-NAC receptor profile changes have more favorable OS and DFS than those with stable receptor expression.

Keywords: Invasive breast carcinoma, Neoadjuvant chemotherapy (NAC), Immunohistochemistry (IHC), Hormonal receptor, Receptor conversion, Biomarkers

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Introduction

Breast carcinoma stands as the most prevalent malignancy and a foremost contributor to oncological death among women across the globe. Presently, neoadjuvant chemotherapy (NAC) serves as the upfront strategy for all individuals presenting with locally advanced disease, later succeeded by operative procedures including modified radical mastectomy or breast-preserving surgery [1]. The present work aimed to determine the effects of variations in estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression on prognostic parameters in patients with persistent invasive ductal carcinoma following NAC at a tertiary referral institution in southern India.

Immunohistochemical markers ER, PR, and HER2 are key tools for molecular classification, therapeutic decision-making, and the personalization of chemotherapeutic protocols for breast cancer patients. The estrogen receptor is a nuclear protein detectable in 65% to 75% of breast carcinomas. ER status represents a pivotal element in breast cancer care [2] since ER-positive tumors typically manifest superior differentiation, a more indolent course, and sensitivity to hormonal agents. The progesterone receptor is a transcription factor identifiable in roughly 55%

to 65% of breast cancers. Cases with PR absence display a more aggressive phenotype and often prove refractory to endocrine manipulation. Human epidermal growth factor receptor 2 constitutes a transmembrane tyrosine kinase receptor that activates an intracellular cascade promoting cell division. Although a mere 12% to 20% of breast cancers demonstrate either HER2 protein excess or gene amplification, HER2+ tumors correlate with aggressive clinicopathological features, unfavorable prognosis, and reduced endocrine responsiveness [3]. Only tumors expressing hormone receptors receive adjuvant endocrine therapy postoperatively. However, there exists no definitive protocol concerning adjuvant hormonal therapy for subjects whose ER and PR expression convert following NAC. The prognostic significance of discordance between hormone receptor and HER2 status in these patients remains poorly defined [4-6].

This research contributes to understanding how shifts in ER, PR, and HER2 expression between pre- and post-NAC IBC with persistent disease correlate with prognostic endpoints, namely disease-free survival (DFS) and overall survival (OS).

Materials and Methods

This investigation was conducted as an intradepartmental effort within the pathology division, working jointly with the medical oncology and general surgery teams at a tertiary referral center. It employed a cohort design comprising both retrospective and prospective data collection. Subjects enrolled consisted of all individuals newly presenting with invasive ductal carcinoma from January 2017 through January 2020 who proceeded to modified radical mastectomy or breast-conserving excision following NAC, exhibited residual disease in the breast or lymph nodes, and possessed an accessible pre-NAC biopsy. Those attaining a pathological complete response were not included. Further exclusion criteria included instances in which tissue blocks could not be recovered from the pathology repository or in which the tissue was entirely consumed.

The aggregate count of cases arriving at our tertiary care facility, with matched pre-NAC and post-NAC biopsies obtainable, averaged 32 cases per 6-month period. The required sample size of 174 was determined using the formula for comparing two dependent proportions (at a 5% level of significance with 80% power). The projected conversion rate in immunohistochemistry from positive to negative was 0.09, whereas the shift from negative to positive was 0.02.

Data collection

Demographic and clinical details (such as age, disease stage, locations of metastasis, chemotherapy protocols, and respective dates of diagnosis, latest follow-up, recurrence, and death, when applicable) were abstracted from patient medical files. Fluorescence in situ hybridization (FISH) evaluation reports were obtained when available for HER2 borderline cases scored 2 or higher. Histopathological parameters were gathered from the pathology department archives and the hospital's electronic information system. Pathological TNM staging was assigned following the American Joint Committee on Cancer standards. Histological categorization of tumors adhered to the World Health Organization (WHO) blueprint for breast tumors. Histological grading performed on Tru-cut biopsy specimens employing the Modified Bloom Richardson Scoring System was likewise recorded. As the study was conducted in a fully anonymized manner, the Institutional Ethics Committee granted a consent waiver. Immunohistochemical staining was carried out manually in the laboratory on tissue sections containing residual malignancy. The molecular classes defined by immunohistochemistry were as follows: ER (+), HER2Neu (±), Ki67 (luminal); ER (–), HER2Neu (+), HER2-enriched; and ER (–) HER2Neu (triple negative). Surgical resections were appraised for pathological response to NAC in line with the 2018 ASCO-College of American Pathologists recommendations ("yp" T and N designations). The post-NAC modified radical mastectomy or breast-conserving surgery tissue blocks were sourced from the pathology stores.

Estrogen receptor and PR were scored using Allred scoring (score = % (0 to 5) + intensity (0 to)), with scores $\geqslant$ 3 considered positive. HER2 status was tiered as: a score of 0 implied absent staining or incomplete, faint/barely appreciable membrane reactivity in $\leqslant$ 10% of tumor cells; a score of 1+ reflected incomplete, faint/barely appreciable membrane reactivity in > 10% of invasive tumor cells; 2+ denoted weak to moderate circumferential membrane staining in > 10% of tumor cells; and 3+ signified strong, complete circumferential membrane staining in $\geqslant$ 10% of invasive tumor cells. For HER2 classification, scores of 0, 1+, and 2+ with negative FISH findings were designated HER2 (–). A score of 3+ or 2+, coupled with a positive FISH finding, was considered HER2 (+).

In situations where FISH testing was not performed, a HER2 score of 2+ was treated as positive for post-NAC specimens.

Differences in ER, PR, and HER2 expression between pre-NAC biopsy material and post-NAC surgical tissue from January 2017 to January 2020 were assessed retrospectively and subsequently related to disease prognosis metrics, incorporating disease-free survival (DFS) and overall survival (OS) rates over a 24- to 48-month observation window. The outcome parameters studied comprised DFS, measured from the date of diagnosis until documented relapse or final follow-up, and OS, determined from the date of diagnosis until death from any cause or last follow-up.

Statistical analysis

All categorical variables—covering age, pathological stage, clinical stage, grade, molecular subtype, ER status, PR status, and HER2 status—are reported as frequencies and proportions. All continuous variables are summarized as mean (SD) and median (IQR). These include age, tumor dimensions, and survival estimates, such as DFS and OS rates. Relationships between ER status, PR status, and HER2 status with the aforementioned categorical factors were examined via the chi-square test or Fisher's exact test. In contrast, the statistical significance of conversion in ER, PR, and HER2 status was evaluated using McNemar's test. Survival distributions were estimated using the Kaplan-Meier product-limit method, and contrasts in survival experiences relative to shifts in ER, PR, and HER2 status were assessed using the log-rank test. All statistical tests were two-sided and conducted at the 5% significance level; P-values < 0.05 were considered significant. Statistical Package for the Social Sciences (SPSS) version 20 served as the analytical software.

Results and Discussion

From January 2017 to January 2020, a total of 174 women with a confirmed diagnosis of invasive ductal carcinoma, who had been treated with NAC and found to have residual breast tumor, and who subsequently proceeded to either modified radical mastectomy or breast-conserving surgery, were entered into the study. Surveillance extended from January 2020 until July 2022. Accessible for every subject were the corresponding tissue blocks stored within the pathology laboratory, along with medical case files obtainable through the medical oncology unit and the institutional hospital information system. What this work reveals should motivate practicing oncologists to reevaluate ER, PR, and HER2 biomarker expression in post-NAC residual malignancy, supporting recognition of tumor adaptation or the emergence of treatment-refractory clones. Employing this knowledge permits the formulation of a bespoke therapeutic regimen, consequently bolstering the individual's survival probability.

Baseline clinicopathological parameters

Breast carcinoma diagnoses were grouped into molecular categories based on immunohistochemical detection of ER, PR, HER2, and Ki-67 proliferative index. Out of the 174 participants, 101 (58.2%) were classified as hormone receptor-expressing (luminal phenotype) tumors; however, finer segregation into luminal A versus luminal B subtypes was precluded because Ki-67 assessment had not been finalized for 80 (45.9%) subjects. Triple negative breast carcinoma accounted for 63 (36.1%) women, and HER2-enriched tumors were observed in 10 (5.7%) individuals. A compiled synopsis of these findings, supplemented with particulars of the adjuvant hormonal regimens delivered to the enrolled women, appears in **Table 1**. Endocrine treatment selection was guided by the HR profile documented before NAC administration.

Table 1. Details of baseline clinicopathological parameters.

Variable	Category	Percentage (%)	Frequency (n)
Age at diagnosis (median range 24–76 years)	< 35 years	6.0	10
	35–50 years	51.0	89
	> 50 years	43.0	75
Laterality	Right breast	56.9	99
	Left breast	43.1	75
Clinical T stage	T1	2.9	5

	T2	29.3	51
	T3	27.6	48
	T4a	3.4	6
	T4b	34.5	60
	T4c	2.3	4
Clinical N stage	N0	37.2	65
	N1	38.3	66
	N2	18.4	31
	N3	7.1	12
Nodal involvement	Positive	62.6	109
	Negative	37.4	65
AJCC stage grouping at diagnosis	Early stage (I–II)	39.7	69
	Locally advanced (stage III)	60.3	105
Tumor grade	Grade 1	4.0	7
	Grade 2	52.3	91
	Grade 3	43.7	76
Estrogen receptor (ER) status	Positive	48.3	84
	Negative	51.7	90
Progesterone receptor (PR) status	Positive	33.3	58
	Negative	66.7	116
HER2 status	Positive	40.8	71
	Negative	59.2	103
Ki-67 index	Low	4.6	8
	High	48.3	84
	Indeterminate / not assessed	47.1	82
Molecular subtype	Hormone receptor-positive (luminal type)	58.2	101
	Triple-negative	36.1	63
	HER2-enriched	5.7	10
Type of surgery	Modified radical mastectomy	88.6	155
	Breast-conserving surgery	10.9	19
Chemotherapy regimen	3FEC + 4DOCE	85.1	148
	3FEC + TZ + 4DOCE + TZ	9.8	17
	3FEC + 4DOCE + ZA	2.3	4
	6FDC	1.1	2
	6FEC	1.7	3

Abbreviations: D = doxorubicin; DOCE = docetaxel; FEC = F-5 fluorouracil, epirubicin, and cyclophosphamide; TZ = trastuzumab; ZA = zoledronic acid.

Clinicopathological parameters after neoadjuvant chemotherapy

After completing NAC, 84 (48.3%) of the persisting tumors were ypT2, with 38 (21.8%) assigned to ypT1, 37 (21.3%) to ypT3, and 15 (8.6%) to ypT4. The mean length of observation reached 22 months (spanning 4 to 59 months); throughout this period, 81 women (46.6%) stayed relapse-free; follow-up contact was severed for 50 (28.7%); documented disease recurrence occurred in 7 (4%); and fatal outcomes were recorded for 36 (20.7%) women during the investigation's timeline. These observations are collated in **Table 2.**

Table 2. Details of clinicopathological characteristics after neoadjuvant chemotherapy.

Clinical–pathological feature	Percentage (%)	Frequency (n = 174)
Tumor stage		
ypT1	1.8	38
ypT2	48.3	84
ypT3	21.3	37
ypT4	8.6	15
Nodal stage		
N0	50.0	87

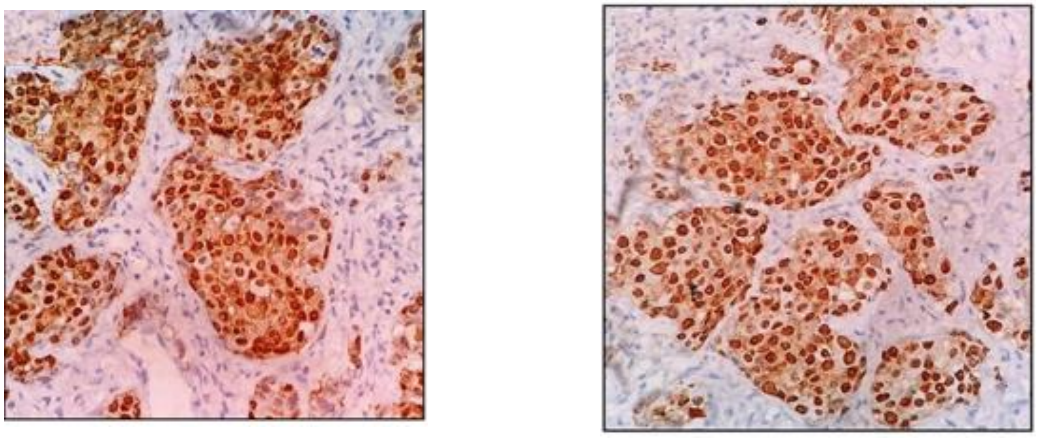
N1	28.7	50
N2	16.1	28
N3	5.2	9
Nodal involvement status		
Positive	50.0	87
Negative	50.0	87
Estrogen receptor (ER) status		
Positive	6.2	10
Negative	93.8	164
Progesterone receptor (PR) status		
Positive	6.2	10
Negative	93.8	164
HER2 status		
Positive	2.3	4
Negative	97.7	170
Current clinical status		
Under follow-up	46.6	81
Lost to follow-up	28.7	50
Relapse	4.0	7
Death	20.7	36

In 36.1% of the 174 evaluated cases, conversion of at least one of the three receptor markers was identifiable. **Table 3** lays out the pattern of these conversions.

Table 3. Changes in estrogen-receptor (ER), progesterone-receptor (PR), and HER2 expression after neoadjuvant chemotherapy.

Receptor	Negative to positive	Negative to negative	Positive to positive	Positive to negative
ER	0	87 (50%)	10 (6%)	77 (44%)
PR	0	116 (67%)	10 (6%)	48 (27%)
HER2	0	106 (61%)	4 (2%)	64 (36%)

Figures 1 and 2 provide the control illustrations. **Figure 3** demonstrates Invasive Ductal Carcinoma before systemic treatment, together with its immunohistochemical signature. **Figure 4** shows a post-NAC residual tumor with ER, PR, and HER2 positivity maintained. **Figure 5** presents another post-NAC residual tumor example, demonstrating loss of ER, PR, and HER2 staining.



a) b)

Figure 1. (a) and (b) Diffuse and strong nuclear expression of ER and PR (×400).

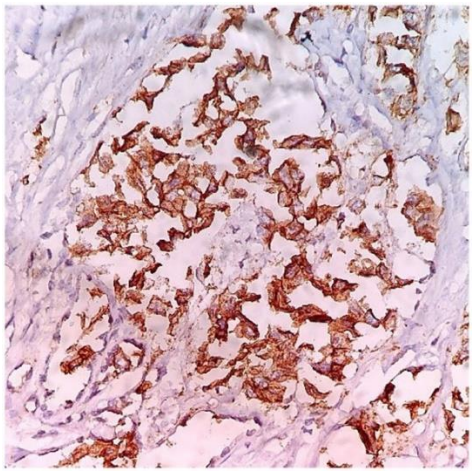
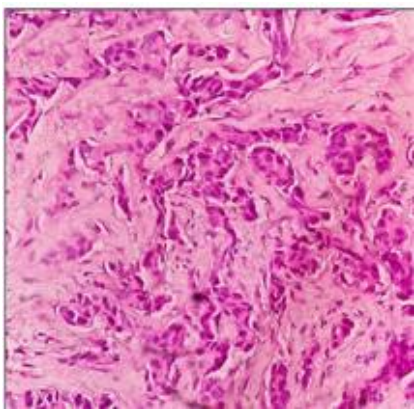
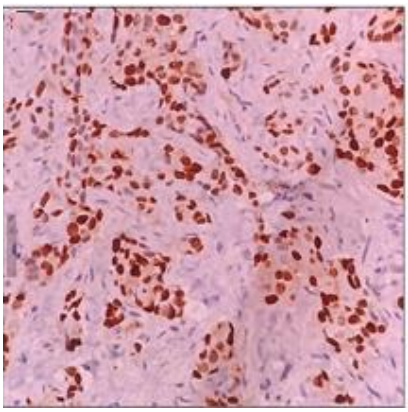


Figure 2. Circumferential complete intense membrane staining of HER2 (×400).



a)



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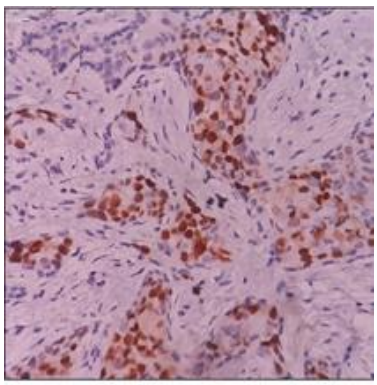
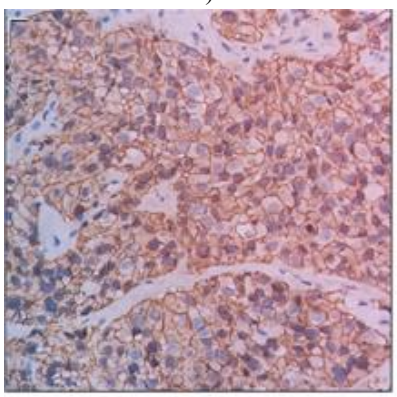
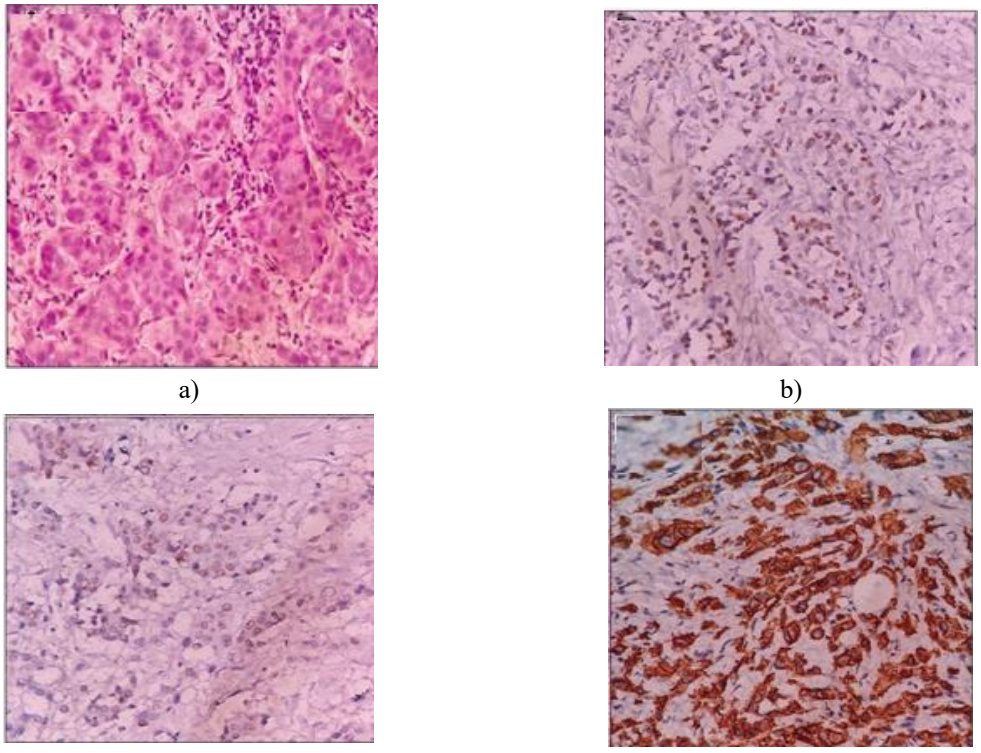


c)



d)

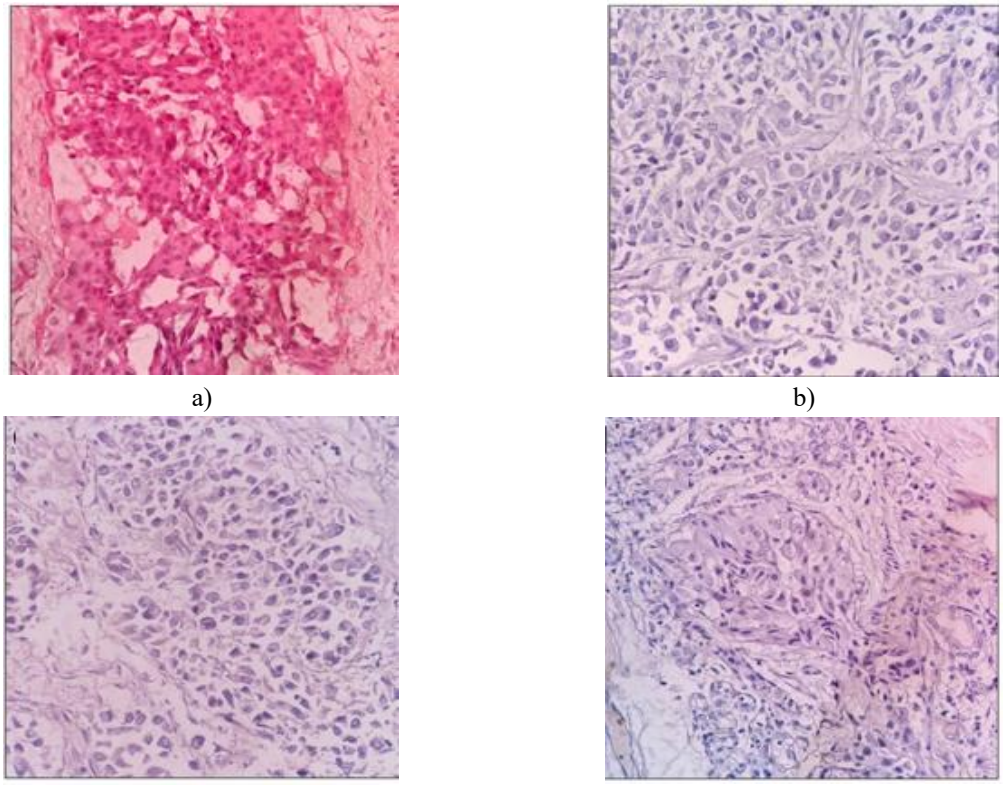
Figure 3. Invasive ductal carcinoma before neoadjuvant chemotherapy: (a) Tumor cells arranged in nests and cords: grade 2, score 7 (H&E ×400); (b) and (c) Tumor cells showing strong and diffuse nuclear expression of ER and PR (immunohistochemistry ×400); and (d) Circumferential complete intense membrane staining of HER2 (immunohistochemistry ×400).



a) b)

c) d)

Figure 4. Invasive ductal carcinoma after neoadjuvant chemotherapy: (a) Residual tumor cells in nests (H&E ×400); (b)–(d) Tumor cells showing retained ER, PR & HER2 expression (immunohistochemistry ×400).



a) b)

c) d)

Figure 5. Invasive ductal carcinoma after neoadjuvant chemotherapy: (a) Residual tumor cells in cords and nests (H&E ×400). (b)–(d) Tumor cells showing loss of estrogen receptor, progesterone receptor, and HER2 expression (immunohistochemistry ×400).

Association of changes in ER, PR, and HER2 expression after NAC with baseline clinicopathological characteristics

Discrepancies between pre- and post-treatment ER, PR, and HER2 designations were systematically reviewed and juxtaposed with a range of other baseline clinicopathological attributes, using either the chi-square or Fisher's exact test. No statistically significant associations were found between the examined baseline clinical and pathological variables and the observed switches in ER, PR, or HER2 status. Neither the presenting clinical stage nor the intrinsic molecular subtype showed a meaningful association with receptor conversion events. **Tables 4-6** present the statistical output of these association analyses along with the corresponding p-values.

Table 4. Association of estrogen receptor (ER) expression with other baseline characteristics.

Baseline clinicopathological characteristics	P-value	Changed ER expression n = 77	Unchanged ER expression n = 97
Age (years)		N (%)	N (%)
< 35	0.939[a]	5 (50.0)	5 (50.0)
35-50		39 (43.8)	50 (56.2)
> 50		33 (44.0)	42 (56.0)
Clinical Stage		N (%)	N (%)
Early breast cancer	0.270[b]	27 (39.1)	42 (60.9)
Locally advanced breast cancer		50 (47.6)	55 (52.4)
Nodal Status		N (%)	N (%)
Node positive	0.879[b]	38 (43.7)	49 (56.3)
Node negative		39 (44.8)	48 (55.2)
Grade		N (%)	N (%)
1	0.083[a]	6 (7.1)	1 (1.1)
2		40 (44.0)	51 (56)
3		31 (40.8)	45 (59.2)
Molecular Subtype		N (%)	N (%)
Hormone positive	0.259[b]	50 (49.5)	51 (50.5)
Triple negative		22 (37.3)	37 (62.7)
HER2 enriched		5 (35.7)	9 (64.3)

a Data shown as frequencies with percentages; p-values calculated using Fisher's exact test.
b Data shown as frequencies with percentages; p-values calculated using the chi-square test.

Table 5. Association of progesterone receptor (PR) expression with other baseline characteristics.

Categorical variables	P-value	Changed PR expression (n = 58)	Unchanged PR expression (n = 116)
Age (Years)		N (%)	N (%)
< 35	1.000[a]	3 (30.0)	7 (70.0)
35-50		30 (33.7)	59 (66.3)
> 50		25 (33.3)	50 (66.7)
Clinical stage		N (%)	N (%)
Early breast cancer	0.324[b]	20 (29.0)	49 (71.0)
Locally advanced breast cancer		38 (36.2)	67 (63.8)
Nodal status		N (%)	N (%)
Node positive	0.520[b]	27 (31.0)	60 (69.0)
Node negative		31 (35.6)	56 (64.4)
Grade		N (%)	N (%)
1	0.096[a]	5 (71.4)	2 (28.6)
2		28 (30.8)	63 (69.2)
3		25 (32.9)	51 (67.1)
Molecular subtype	0.162[a]	N (%)	N (%)

Hormone positive		39 (38.6)	62 (61.4)
Triple negative		14 (23.7)	45 (76.3)
HER2 enriched		5 (35.7)	9 (64.3)

[a] Data shown as frequencies with percentages; p-values calculated using Fisher's exact test.
[b] Data shown as frequencies with percentages; p-values calculated using the chi-square test.

Table 6. Association of HER2 expression with other baseline characteristics.

Baseline clinical pathological characteristic	P-value	Changed HER2 expression n = 64	Unchanged HER2 expression n = 110
Age (Years)	0.936[a]	N (%)	N (%)
< 35		3 (30.0)	7 (70)
35-50		33 (37.1)	56 (62.9)
> 50		28 (37.3)	47 (62.7)
Clinical Stage	0.400[b]	N (%)	N (%)
Early breast cancer		2 (40.6)	41 (59.4)
Locally advanced breast cancer		36 (34.3)	69 (65.7)
Nodal Status	0.028[b]	N (%)	N (%)
Node positive		25 (28.7)	62 (71.3)
Node negative		39 (44.8)	48 (55.2)
Grade	0.260[a]	N (%)	N (%)
1		3 (42.9)	4 (57.1)
2		38 (41.8)	53 (58.2)
3		23 (30.3)	53 (69.7)
Molecular subtype	0.763[b]	N (%)	N (%)
Hormone positive		35 (34.7)	66 (65.3)
Triple negative		23 (39.0)	36 (61.0)
HER2 enriched		6 (42.9)	8 (57.1)

[a] Data shown as frequencies with percentages; P values calculated using Fisher's exact test.
[b] Data shown as frequencies with percentages; P values calculated using the chi-square test.

Association of changes in ER, PR, and HER2 expression with OS and DFS rates

Overall survival was measured as the number of months from the date of initial diagnosis to either the final documented follow-up encounter or death, irrespective of cause. Disease-free survival was defined as the period, in months, from the commencement of therapy to the time of disease recurrence or death. The median OS duration stood at 42 months. Receptor status conversions in ER, PR, and HER2 were individually plotted against both OS and DFS through the construction of Kaplan-Meier survival plots. The analyses revealed a statistically robust association between ER conversion and HER2 conversion across both OS and DFS outcomes. By contrast, fluctuations in PR status had no significant effect on either OS or DFS. **Figures 6 and 7** graphically capture the meaningful association between ER and HER2 shifts and patient DFS, with their respective p-values annotated. Those individuals whose ER and HER2 status switched from positive to negative had markedly longer OS and DFS.

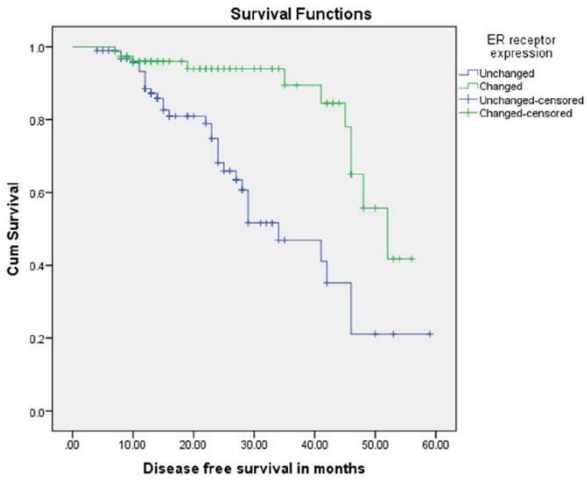


Figure 6. Survival curve showing changes in estrogen receptor (ER) status and disease-free survival in patients (P < 0.001).

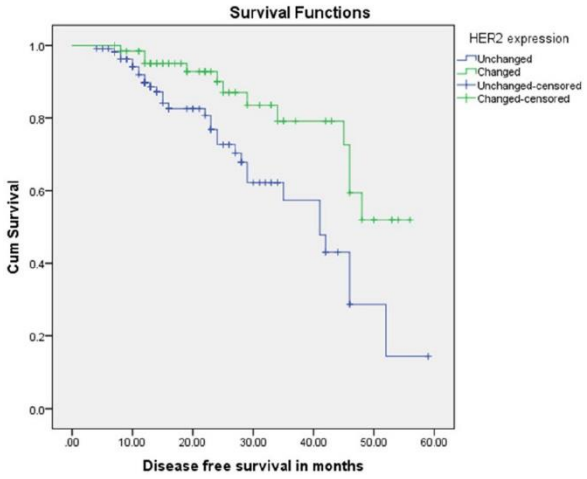


Figure 7. Survival curve showing changes in HER2 status and disease-free survival (P = 0.003).

In parallel, the p-values for the association between ER alterations and HER2 alterations and OS were P < 0.001 and P = 0.004, respectively.

The predictive and prognostic markers embedded in the most recent WHO taxonomy for breast neoplasms include HR status, HER2 status, and the type of NAC protocol administered. Numerous studies have reported associations between these elements and patients' DFS and OS. There is a broad consensus that HR-positive individuals treated with NAC have better survival outcomes than their HR-negative counterparts. While a growing body of recent work has sought to decode the impact of post-NAC shifts in hormone receptor and HER2 expression on OS, explorations situated specifically within the Indian landscape remain sparse. In the present inquiry, we appraised 174 patients managed for invasive ductal carcinoma in southern India. For context, comparable investigations elsewhere have used cohort sizes ranging from 325 to 4596 participants. We have, moreover, attempted to pinpoint changes in ER, PR, and HER2 status after NAC and to identify any associations between these changes and DFS and OS metrics. Connections linking HR and HER2 conversions with salient clinicopathological characteristics were likewise scrutinized. Additional contributory variables may well have shaped OS and DFS. Future inquiries with expanded sample sizes promise sharper resolution.

Baseline clinicopathological parameters (pre-NAC)

Within the population of women harboring invasive ductal carcinoma examined here, the median age at presentation was 50 (35-50) years, a statistic that dovetails with the most recent breast cancer epidemiological indicators from India. The entire study group comprised female subjects. A sizable proportion (60.3%) came to clinical attention with locally advanced breast carcinoma, a pattern likely driven by gaps in public consciousness

and restricted penetration of early detection programs [7]. The histological grade most frequently encountered in our material was grade 2 (52.3%), closely reflecting earlier published frequencies of 59% [8] and 40.8% [9]. Within this series, HR-positive disease accounted for 58.2% of cases, triple-negative breast carcinoma for 36.2%, and HER2-enriched tumors for 5.7%, echoing the series by Parinyanitikul *et al*. [10], in which HR-positive tumors accounted for 49.1% of the cohort, triple-negative tumors for 32.6%, and HER2-enriched tumors for 18.3%.

Clinicopathological parameters post-NAC

In the current study cohort, modified radical mastectomy was performed on 88.6% of subjects, with the balance of 10.9% receiving breast-sparing surgery after NAC. These percentages resonate with the report from Ozmen *et al*. [11] in which mastectomy was undertaken in 87.8% and breast preservation surgery in 12.2%. A large majority (85.1%) of individuals in our cohort were exposed to taxane- and anthracycline-based chemotherapeutic combinations, similar to the 70.8% who received analogous regimens in the Parinyanitikul *et al*. [10] publication. Upon completion of NAC, 48.3% of patients in the present analysis were reclassified as ypT2, and nodal involvement was confirmed in 50%, matching the observations of Al-Saleh *et al*. [12], who reported nodal positivity in 54%. No further statistically significant linkage between HR or HER2 conversion and other clinicopathological attributes—including age, affected side, or clinical stage—was identified. Reports by Hirata *et al*. [6] and Enomoto *et al*. [13] equally failed to uncover any significant statistical interplay among these same variables.

HR receptor and HER2 status conversion rates post-NAC

Among the 174 subjects treated with NAC, 77 (44%) originally ER-positive tumors switched to a negative phenotype, whereas 10 held onto their positive designation; 87 (50%) ER-negative tumors stayed negative; 48 (27%) PR-positive tumors converted to negative, and 10 persisted as positive; 116 (67%) PR-negative tumors remained negative; 64 (36%) HER2-positive tumors became negative, and 4 (2%) maintained positivity; and 103 (59%) HER2-negative tumors continued to test negative. These figures for changes in receptor status exceed those reported in multiple other series. By way of illustration, Chen *et al*. [14] described conversion proportions of 16% for ER, 22.2% for PR, and 15.2% for HER2; Hirata *et al*. [6] documented rates of 14.9% for ER, 29.1% for PR, and 22.6% for HER2; and Yang *et al*. [15] reported 13% for ER, 19.5% for PR, and 22.6% for HER2.

A shift in at least one of the three assayed biomarkers occurred in 36.6% of the individuals we studied, a finding that aligns with the aggregate conversion rate of 40.7% reported by Parinyanitikul *et al*. [10] and 23.1% reported by Al-Saleh *et al*. [12]. Elsewhere in the literature, there are indications that HR and HER2 expression remain largely unaltered following NAC. Arens *et al*. [16], for example, detected no meaningful variation in any of the three hormonal indices after NAC, a result possibly attributable to the smaller patient number relative to investigations that did capture a change. Kasami *et al*. [17] likewise saw no appreciable shift in ER and HER2 expression, while PR expression changed in 36% of their cases; because their inquiry centered upon subjects with locally advanced disease accompanied by regional and distant metastatic deposits, their data may more accurately reflect response patterns to NAC in the setting of far-advanced illness.

In our series, among tumors that retained both ER and PR expression, 6 (60%) were histological grade 3, and the remaining 4 (40%) were grade 2. Of those tumors that retained HER2 positivity, 3 (75%) were grade 2, and just 1 (25%) was grade 3. We interpret these observations as a manifestation of tumor heterogeneity [17, 18]. The biological machinery responsible for switching HR and HER2 phenotypes after exposure to NAC is intricate. Heterogeneity within and across tumors enables the coexistence of multiple clonal subpopulations with diverse phenotypes within the same lesion. Some clones populating a given tumor mass are HR-positive, while neighboring clones are HR-negative. Correspondingly, HER2-expressing cells are irregularly distributed throughout individual neoplasms. Susceptibility to cytotoxic agents also varies across these clonal subsets: HR-negative tumor cells are more chemosensitive than their HR-positive counterparts, suggesting that HR-positive cells, often labeled as chemoresistant, persist through NAC and constitute the residual tumor burden. Wang *et al*. [18] and Thor *et al*. [19] have further shown that HER2-positive cell populations are preferentially targeted and eradicated by chemotherapy, resulting in therapeutic benefit for affected patients.

A widely acknowledged pathway responsible for HR status reclassification is the dampened expression of estrogen receptor following NAC administration. Bines *et al*. [20], along with Rose and Davis [21], have advanced the view that cytotoxic drugs can impair ovarian and adrenal secretory activity, culminating in lowered circulating sex steroid titers. This hormonal deficit may prompt the HR phenotype of the residual neoplastic cells to flip from

HR-positive (+) to HR-negative (–) upon completion of NAC. The phenomenon is considered the predominant explanation for HR status discordance arising after systemic treatment. At the same time, spurious negative determinations of HR and HER2 on pre-NAC Tru-cut biopsy specimens have been reported, attributed to the confounding effect of intertumoral heterogeneity. The apparent switch from HR-negative to HR-positive and from HER2-negative to HER2-positive may be a consequence of the limited tumor material obtained via Tru-cut sampling, which risks capturing only a minor fraction of the lesion that expresses divergent phenotypic features. Other factors that may contribute to receptor discordance include somatic mutations, random statistical variation, and discrepancies in immunohistochemical staining techniques [4].

Our data strengthen the conclusions drawn by other groups who report a robust association between any receptor conversion event and both DFS and OS among breast cancer patients, as reflected in work such as that of Vemuru *et al*. [22] Departing from the pattern we observed, however, Tacca *et al*. [23], Yang *et al*. [15], Jin *et al*. [24], and van de Ven *et al*. [25] each maintain that OS and DFS are more favorable for patients whose HR status reverts from negative to positive, measured against those who exhibit no shift after NAC. In the present cohort, those subjects whose ER and HER2 expression converted from positive to negative registered superior OS and DFS outcomes. Given that no participants in our series transitioned from negative to positive for either HR or HER2, it was not feasible to estimate survival in this subgroup. Tacca *et al*. [23] nonetheless underscore that patients with HR-negative tumors that reverted to HR positivity after NAC had a survival advantage in terms of OS and DFS compared with counterparts whose cancers failed to convert to HR positivity after NAC.

The subset displaying a positive-to-negative switch in both ER and HER2 achieved prolonged DFS and OS, with these differences attaining statistical significance. ER conversion ($P < 0.001$) and HER2 conversion ($P < 0.003$) were meaningfully tied to OS. Similarly, ER conversion ($P < 0.001$) and HER2 conversion ($P < 0.004$) were meaningfully correlated with DFS. In stark contrast, no detectable link was uncovered between PR status shift and either OS ($P = 0.604$) or DFS ($P = 0.605$). These observations differ from those of Jin *et al*. [24], who found that PR status conversion, rather than ER status, was associated with both OS and DFS.

Among the 174 subjects in the present work, 7 (4%) suffered a recurrence of their breast carcinoma: 4 (57%) with the luminal subtype, 2 (29%) with HER2-enriched cancers, and 1 (14%) with triple-negative breast carcinoma. Of these 7 individuals, 4 (57%) were histological grade 3, while 3 (43%) were grade 2 at initial assessment. Receptor conversion was documented among the HR and HER2 profiles of luminal and HER2-enriched tumors; however, no such changes were apparent within the triple-negative breast cancer group.

During the study timeframe, 36 out of 174 enrolled subjects (20.7%) died. Stratifying these deaths by subtype, 21 (58%) were triple-negative breast cancers, 11 (31%) luminal-type tumors, and 4 (11%) HER2-enriched breast cancers. In terms of histological grade, 21 (58%) were grade 3, 14 (39%) were grade 2, and 1 (3%) was grade 1. A change involving at least one of the three immunohistochemical markers was observed in 23 (69%) of these 36 deceased individuals. Yet, as previously noted, no statistically significant association was observed between HR and HER2 conversion and either histological grade or molecular subtype, a result that aligns with comparable series published by Al-Saleh *et al*. [12], Yang *et al*. [15], and Uzun *et al*. [26].

Limitations of our study

The restrictions encountered in our investigation primarily originated from gaps in the available information. Among the 4 patients whose pre-NAC HER2 score was 2+ and lacked accompanying FISH documentation, all 4 tested positive and were ultimately categorized as HER2 (–) based on the post-NAC surgical specimen. As a result, other cancer subtypes could not be incorporated into our evaluation. Menopausal status likewise went unexamined owing to missing records. No participant in our series switched to positive status for any of the three biomarkers following NAC. As a direct result, survival within that particular subgroup remained unassessable.

Conclusion

The present inquiry set out to appraise the consequences of alterations in ER, PR, and HER2 expression on oncologic outcomes among South Indian patients with residual invasive ductal carcinoma who proceeded to modified radical mastectomy or breast-conserving resection after completing NAC. We discovered that HR and HER2 phenotypes do indeed shift in these individuals, with the predominant direction of change being from positive to negative across all three examined markers. Subjects manifesting a receptor status change post-NAC went on to have more favorable prognostic trajectories, reflected in superior OS and DFS, than did those whose

receptor status held constant. Accordingly, we conclude that a genuine reclassification of ER and HER2 status occurs after NAC. ER and HER2 expression may well represent useful prognostic biomarkers for the treatment planning of invasive ductal carcinoma patients who harbor residual disease following NAC.

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Consent for publication is obtained from all the co-authors and their respective departments.

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