Original Article

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Prognostic Value of Receptor Change After Neoadjuvant Chemotherapy in Breast Cancer Patients

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ABSTRACT

Objective: The aim of this study was to investigate the relationship between hormone receptors (HR) and human epidermal growth factor receptor 2 (HER-2) discordance with prognosis, before and after neoadjuvant chemotherapy (NAC) in breast cancer patients.

Materials and Methods: Histopathological data of 142 breast cancer patients attending a single center between 2001 and 2018 and were operated after NAC were evaluated retrospectively.

Results: The median (range) age of patients was 58 (32–69) years**.** In patients who underwent Tru-cut biopsy before NAC, 77 patients were ER+, 30 were ER (-), 73 were PR (+), 33 were PR-, 14 were HER-2 (+), and 94 patients were HER-2 (-). In terms of ER change, five patients were found to have changed status and 85 had no receptor change. The mean overall survival of patients with receptor changes was 31 months against 60 months in patients with no receptor changes, which was not significant (p = 0.351). In sub-group analysis of patients undergoing receptor change, the ER (+) → (–) group had significantly shorter survival (p = 0.003). For PR change, mean survival was 38 months in seven patients with a receptor change and 59 months in 87 patients without a receptor change, which was not significant (p = 0.603). Sub-group analysis of PR status change showed that survival was significantly shorter in the PR (+) → (–) group (p = 0.012).

Conclusion: These results suggest there is a need for reassessment of HR and HER-2 status in surgical samples from patients following NAC, and that NAC-induced changes in the HR state may be used as a prognostic factor.

Keywords: Breast cancer; neoadjuvant chemotherapy; estrogen receptor; progesterone receptor; receptor change

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Key Points

- Neoadjuvant chemotherapy might change the status of breast cancer biomarkers, including estrogen receptor (ER), progesterone receptor (PR), and HER-2.
- Receptor status change, the ER (+) → (–) and PR (+) → (–) patients had significantly shorter overall survival.
- There was no statistical relationship between the change of Ki-67 level and survival.

Introduction

The advantages of neoadjuvant treatment, such as the treatment of distant micrometastases, regression in tumor stage, increased operability, and increased chances of breast-conserving surgery, has meant it has become a standard for locally advanced breast cancer (1-3). Although neoadjuvant chemotherapy (NAC) treatment in local or locally advanced breast cancer does not have a disease-free survival (DFS) or overall survival (OS) superiority over adjuvant treatment, the achievement of a pathological complete response (pCR) is associated with prolonged survival (4, 5). In many studies investigating NAC treatment response, estrogen receptor (ER) status has been considered a determinant marker of chemosensitivity, and it has been shown that ER negativity can predict treatment response (6, 7). In a retrospective study of 1,731 patients,

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the pCR rate for ER-negative patients was 24%. However, ER-positive patients responded at a rate of 8%. In terms of pCR, despite the different chemotherapy regimens administered, ER negativity has been highlighted as a predictive factor, independent of treatment (8). National Surgical Adjuvant Breast and Bowel Project (NSABP) B27 and NSABP B18 studies also showed higher pCR rates in hormone receptor (HR) negative patients compared to HR-positive patients (9, 10). The effectiveness of anthracycline-based and taxane-based treatments as neoadjuvant treatment is known in breast cancer. Since triple-negative breast cancer and human epidermal growth factor receptor 2 (HER-2) positive breast cancer are more chemosensitive, they benefit from the neoadjuvant treatment to a higher extent and pCR is reported to occur at higher rates. However, the fact remains that only a small proportion of patients following NAC treatment achieve pCR, while most patients treated with NAC still have residual disease (11). Recent studies have reported levels of discordance between HR and HER-2, before and after NAC treatment (12-14). It is debatable whether post-NAC changes in breast cancer biomarkers, such as HRs and HER-2 affect patient prognosis. The aim of this study was to evaluate the prognostic value of pre- and post-NAC ER, Progesterone Receptor (PR) and HER-2 receptor changes and assess these in respect of clinical outcome.

Materials and Methods

Histopathological data of breast cancer patients who attended our clinic between 2001 and 2018 and were operated after NAC were evaluated retrospectively. The majority of patients (more than 90%) were referred from 2010 onwards, and about a quarter of the Tru-cut biopsies were taken by external centers. The study included only the patients whose Tru-cut biopsies were performed and histopathology examined in our hospital. We identified 142 patients diagnosed with primary breast cancer who had any residual disease in the breast and/or lymph nodes after receiving NAC, and pathology reports containing the ER, PR, and HER-2 status of pretreatment core needle biopsy (CNB) and residual tumor. We reviewed these patient's medical records for clinicopathological data. All pathological specimens, including the immunohistochemistry (IHC) slides from outside the institution, were reviewed by dedicated breast cancer pathologists. Patients with pCR were excluded.

Data items collected included demographic data (gender, age, and contact information), surgical procedure, histopathological and immunohistochemical characteristics, systemic adjuvant/neoadjuvant therapy and follow-up duration. The American Joint Committee on Cancer (AJCC) TNM grading system was used for staging. Immunohistochemical analysis of ER, PR, HER-2, Ki-67 proliferation index was performed. At least 1% of tumor cells being stained were considered ER and PR positive, and immunohistochemical staining 3+ was considered HER-2 (+). However, in cases with immunohistochemical HER-2 +2, fluorescent *in situ* hybridization (FISH) was performed. For cases in the study, the threshold value for Ki-67 immunochemical staining was taken as 14% (15). Changes in HR and HER-2/neu status were evaluated in terms of response to survival. This study followed the Declaration of Helsinki in terms of medical protocol and ethics and the regional Ethical Review Board approved the study. Before the study, approval was obtained from the clinical research ethics committee of our hospital.

Statistical Analysis

In statistical analysis, SPSS for Windows, version 11.5 was used (IBM Inc., Armonk, NY, US). The categorical measurements were summarized as number and percentage, and the continuous measurements were summarized as mean and standard deviation. Categorical variables were compared using the chi-square test or Fisher's exact test. The Kruskal–Wallis test was used on the parameters that were not normally distributed, followed by paired comparisons of the groups with Mann–Whitney U test. Pre- and post-chemotherapy comparisons were made using the Wilcoxon test. Overall survival (OS) was 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

The average age of patients was 58 at the time of diagnosis (min: 32, max: 69). The average follow-up time was 29±17 (range: 5–97) months. Table 1 shows the number of patients tested, and the number of patients positive or negative for ER, PR, HER-2 and their Ki-67 status.

The post-NAC receptor and Ki-67 changes of the patients are shown in Table 2. The mean overall survival of patients with receptor changes was 31 months against 60 months in patients with no receptor changes. However, this difference was statistically insignificant ($p = 0.351$).

The receptor status of five patients changed in terms of ER, while 90 patients underwent no change in ER receptor status. In sub-group analysis of the ER receptor change, the ER(+) → (-) patients had a significantly shorter survival ($p = 0.003$). Similarly, PR status changed in seven patients while 87 maintained their pre-NAC receptor status. Mean overall survival (mOS) was 38 months in these seven patients

Table 1. Receptor distribution in pre-NAC Tru-cut biopsy sample

ER		PR		HER-2		Ki-67	
107		106		108		104	
(+)	(-)	(+)	(-)	(+)	(-)	≥15	<15
77	30	73	33	14	94	83	21
72%	28%	69%	31%	13%	87%	80%	20%

ER: estrogen receptor; PR, progesterone receptor; HER-2: human epithelial growth factor 2 receptor; NAC: neoadjuvant chemotherapy

Table 2. Receptor distribution in post-NAC operation material

ER		PR		HER-2		Ki-67	
112		112		111		100	
(+)	(-)	(+)	(-)	(+)	(-)	≥ 15	< 15
87	25	77	35	20	91	60	40
78%	22%	69%	31%	18%	82%	60%	40%

ER: estrogen receptor; PR, progesterone receptor; HER-2: human epithelial growth factor 2 receptor; NAC: neoadjuvant chemotherapy

with a receptor status change but 59 months in 87 patients without a receptor change, which was statistically insignificant (p = 0.603). Sub-group analysis of patients experiencing a PR status change showed that survival was significantly shorter in the PR (+) → (-) group (p = 0.012) (Table 3). The total rate of change in the post-NAC treatment of ER (+) patients was (5/95) ≅ 5%, and the total rate of PR change was (7/94) ≅ 7%. In terms of HER-2 change, mean survival was 66 months in 14 patients with HER-2 change and was 57 months in patients with no change (p = 0.442). Finally, 25% of the patients with pre-NAC Ki-67 ≥15% presented post-NAC Ki-67 as ≤14% and 33% of the patients with pre-NAC Ki-67 level ≤14% were found to be ≥15% after treatment but no relationship was detected between these changes and survival (Table 4).

Discussion and Conclusion

In this study, the pre- and post-NAC receptor status change rates were ~5% for ER, ~7% for PR, and ~17% for HER-2. In sub-group analysis of patients undergoing receptor status change, the ER (+) → (-) and PR (+) → (-) patients had significantly shorter overall survival. The results of various studies concerning the prognostic value of such post-NAC changes in these receptor levels are controversial. In the compilation published by van de Ven et al. (16), they reported

Table 3. Receptor change rate after NAC

	ER (+)[a]		ER (-)[b]		PR (+)[c]		PR (-)[d]		HER-2 (+)[e]		HER-2 (-)[f]		Ki-67 (≥15)[g]		Ki-67 (<15)[h]	
n	69		26		64		30		12		84		64		15	
	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	≥15	<15	≥15	<15
	68	1	4	22	60	4	3	27	8	4	12	72	48	16	5	10

[a] ER (+) patients; Post NAC ~ 1.4% NEGATIVE

→ TOTAL ER CHANGE RATE (5/95) ≅ 5.3%

[b] ER (-) patients; Post NAC ~ 15.4% POSITIVE

[c] PR (+) patients; Post NAC ~ 6% NEGATIVE

→ TOTAL PR CHANGE RATE (7/94) ≅ 7.4%

[d] PR (-) patients; Post NAC 10% POSITIVE

[e] HER-2 (+) patients; Post NAC 33% NEGATIVE

→ TOTAL HER-2 CHANGE RATE (16/96) ≅16.7%

[f] HER-2 (-) patients; Post NAC 14% POSITIVE

[g] Ki-67 ≥ 15 ; Post NAC 25% < 15

→ TOTAL Ki-67 CHANGE RATE WAS 26%

[h] Ki-67 <15 ; Post NAC 33% ≥ 15

ER: estrogen receptor; PR, progesterone receptor; HER-2: human epithelial growth factor 2 receptor; NAC: neoadjuvant chemotherapy

Table 4. The effect of receptor change before and after NAC on prognosis

	ER	PR	HER-2
Total number of patients	95	94	96
Patient with changed receptor, n (%)	5 (5.3)	7 (7.4)	16 (16.7)
Change to negative	1	4	4
Change to positive	4	3	12
mOS receptor status change (months)	31	38	57
mOS receptor status unchanged (months)	60	59	77
	p = 0.351	p = 0.603	p = 0.447

Survival was shorter in the subgroup that became ER negative after NAC when they had been ER positive prior to NAC (p = 0.003).
Survival was shorter in the subgroup that became PR negative after NAC when they had been PR positive prior to NAC (p = 0.012).
ER: estrogen receptor; PR: progesterone receptor; HER-2: human epithelial growth factor 2 receptor; NAC: neoadjuvant chemotherapy; mOS: mean overall survival; n: number

discordance rates of ER, PR and HER-2 status of 2.5%–17%, 5.9%–51.7% and 2.3%–35%, respectively. Another meta-analysis indicated ER and PR changes during NAC (17). Finally, a large-scale retrospective study showed that approximately 21.4% of HER-2 (+) patients have become HER-2 (-) in the metastatic region (18). The results of various studies related to the prognostic value of post-NAC changes in the status of these receptors are controversial. Most studies concluded that HR (+) → (-) patients have a worse prognosis in terms of both OS and DFS (19). However, Tacca et al. (20) observed no significant change in DFS or OS between HR (-) → (+) and HR (-) → (-) patients.

Prognosis is poor in cases with a high index of Ki-67 proliferation, which is one of the most important prognostic parameters in breast cancer. Available studies show that the Ki-67 score generally changes after NAC (21-23). A study conducted by Arens et al. (24) on a small sample (n = 25) reported an insignificant change in post-NAC Ki-67 expression, while Burcombe et al. (21) detected a significant relationship between post-NAC Ki67 decrease and the pathological response. In our study, the post-NAC Ki-67 change rate was 26% and there was no statistical relationship between the change of Ki-67 level and survival.

HER-2 overexpression or amplification is detected in 15%–25% of all breast cancers, and HER-2 positivity in breast cancer is associated with poor prognosis, resistance to standard treatments, early recurrence risk, shorter DFS and shorter OS (2, 3). In a recent study, Tiezzi et al. (25) reported a significant relationship between the overexpression of HER-2 protein and DFS and OS in breast cancer patients. On the other hand, they detected no change in HER-2/neu expression after NAC. Similarly, Zhao et al. (26) and Arens et al. (24) failed to report any changes in HER-2 status after NAC (24, 26, 27). A meta-analysis performed by Li et al. (27) showed that HR and HER-2 were lost or gained in a significant portion of the patients after receiving NAC. It was reported to be noteworthy that after NAC 13.8% and 2.6% of patients gained ER or HER-2 positivity, respectively (24). On the other hand, HR+ → – patients in the meta-analysis had both worse DFS and OS compared to HR (+) → (+) patients. These authors suggested that shorter DFS and OS and HR loss in HR (+) → (-) patients could suggest a more aggressive phenotype.

At present there is no consensus on whether adjuvant endocrine treatment is required for patients with HR changes following NAC treatment. Regarding the adjuvant endocrine therapy, there is a general approach for administering hormonal therapy whenever HR are positive. There was only one retrospective study (28) designed to investigate the value of adjuvant endocrine treatment in HR (+) → (-) patients (57 patients were treated for endocrine and 40 patients were not treated for endocrine). The DFS of the adjuvant endocrine treatment group was significantly higher than of the non-adjuvant endocrine treatment group. However, the 5-year OS rate was not different statistically. Therefore, further studies and future research are required to understand the role of adjuvant endocrine treatment for HR+ → – patients. In addition, HER-2 (+) → (-) patients had a poor DFS in the meta-analysis. However, there was no statistically significant difference in HER-2 (+) → (-) patients in terms of the OS. A retrospective analysis (11) involved 182 advanced breast cancer patients with HER-2 (+) → (-) at the metastatic site. There were significant differences between HER-2 (+)→ (-) and HER-2 (+) → (+) patients in terms of the OS, irrespective of whether patients were given trastuzumab or not. However, in the HER-2 (+) → (-) subgroup, the OS did not differ between those receiving trastuzumab and those who did not. These results suggest that patients with loss of HER-2 status may be less sensitive to trastuzumab. Previous research suggested that receptor changes were indicators of poor prognosis for both residual (29, 30) and metastatic sites (18, 31, 32). In our study, the survival analysis of patients showed no relationship between ER, PR, HER-2 receptor changes and survival. However on subgroup analysis of patients undergoing ER and PR status change those patients in the ER (+) → (-) and PR (+) → (-) patients had significantly shorter survival, which is consistent with earlier reports.

In conclusion, these results suggest there is a need for reassessment of ER, PR and HER-2 status in surgical samples from patients following NAC, and that NAC-induced changes in the HR state may be used as a prognostic factor.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of İzmir Bozyaka Training and Research Hospital (decision date and number: 24.11.2021-2021/191).

Informed Consent: It is a retrospective observational study and there is no informed consent form.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Z.; Concept: Ö.Ö.; Design: Ö.Ö., B.Z.; Data Collection and/or Processing: B.Z., D.K.Ç., C.Y.; Analysis and/or Interpretation: R.D., Literature Search: Ö.Ö., B.Z., D.K.Ç.; Writing: Ö.Ö., B.Z.

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