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The Effect of Progesterone Receptor Level on Treatment Response in Breast Cancer Patients Receiving Neoadjuvant Therapy

Neoadjuvan Kemoterapi Alan Meme Kanseri Hastalarında Progesteron Reseptör Düzeyinin Tedavi Yanıtına Etkisi

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Abstract: Clinicians face challenges in deciding on the use of neoadjuvant chemotherapy(NACT) for patients with estrogen receptor(ER)-positive breast cancer due to the potential for low efficacy. Progesterone receptor(PR) is a biomarker routinely evaluated in breast cancer patients prior to NACT, but there is a lack of sufficient clinical data and guideline recommendations regarding its role in treatment decision-making. This study aimed to evaluate the impact of PR status on pathological complete response in ER-positive breast cancer patients receiving NACT. Our study examined 52 ER-positive patients who received NACT. Participants were grouped into three cohorts based on PR levels: less than 1%, 1-9%, and 10% and above. The pathological complete response rate, an important indicator of overall survival, was compared across these three groups. The results of our study showed a statistically significant higher pathological complete response rate in patients with PR levels below 1%. These findings suggest that NACT may be more effective in this patient subgroup. The study findings indicate that PR status may play a role in the decision-making process for NACT in ER-positive breast cancer patients.

Keywords: Breast Cancer, Progesterone Receptor, Estrogen Receptor

Özet: Östrojen reseptörü(ER) pozitif meme kanseri hastalarında neoadjuvan kemoterapi(NACT) kullanımına karar vermede, klinisyenler olası düşük etkinlik nedeniyle zorlanmaktadır. Progesteron reseptörü(PR), meme kanserli hastalarda NACT öncesi rutin olarak değerlendirilen bir biyobelirteç olmasına rağmen, tedavi kararındaki rolüyle ilgili yeterli klinik veri ve kılavuz önerileri bulunmamaktadır. Bu çalışma, NACT alan ER-pozitif meme kanseri hastalarında PR durumunun patolojik tam yanıt üzerindeki etkisini değerlendirmeyi amaçlamıştır. Çalışmamız, NACT alan 52 ER-pozitif hastayı incelemiştir. Katılımcılar, PR düzeylerine göre üç kohort halinde gruplandırılmıştır: %1'den az, %1-9 ve %10 ve üzeri. Genel sağkalımın önemli bir göstergesi olan patolojik tam yanıt oranı, bu üç grup arasında karşılaştırılmıştır. Çalışmamızın sonuçları, PR düzeyleri %1'in altında olan hastalarda istatistiksel olarak anlamlı derecede daha yüksek patolojik tam yanıt oranı olduğunu göstermiştir. Bu bulgular, bu hasta grubunda NACT etkinliğinin daha yüksek olabileceğini düşündürmektedir. Çalışmanın bulguları, ER-pozitif meme kanseri hastalarında PR durumunun NACT kararında rol oynayabileceğini göstermektedir.
Anahtar Kelimeler: meme kanseri, progesteron reseptörü, östrojen reseptörü

Ethics Committee Approval: This study was conducted with the approval of the Non-Interventional Research Ethics Committee of Kütahya Health Sciences University, as per the decision number 2024/03-39 taken at the meeting held on 05.03.2024 with the number 2024/03.

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Authors' Contributions: ME: Study conception, data collection, designed data analysis, wrote first draft of the manuscript, approved final version to be published, ANY: Data collection, approved final version to be published.

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1. Introductions

While all systemic therapy for non-metastatic, invasive breast cancer aims to reduce the risk of distant recurrence, administering treatment prior to surgery can potentially eradicate micrometastases earlier. Additionally, neoadjuvant chemotherapy(NACT) is used to downstage the extent of disease in the breast and/or regional lymph nodes, and provide information about treatment response to guide subsequent adjuvant therapies(1-3). Downstaging can enable less extensive surgery on the breast and/or axilla, including avoiding the risks associated with breast reconstruction in patients who can undergo breast-conserving surgery instead of mastectomy, thereby improving cosmetic outcomes and reducing postoperative complications such as lymphedema(4). NACT allows for the assessment of the efficacy of systemic treatment, which is becoming more common in guiding adjuvant therapy recommendations(5). The presence, extent, or lack of residual invasive disease after neoadjuvant therapy is a powerful prognostic factor for the risk of recurrence and overall survival. As a result, biomarkers linked to pathological complete response(pCR) following neoadjuvant treatment are of critical importance in guiding treatment decisions(6).

Steroid hormone receptors, the estrogen receptor(ER) and progesterone receptor(PR), are critical biomarkers in breast cancer. According to guidelines from the American Society of Clinical Oncology and the College of American Pathologists, a tumor specimen can be classified as hormone receptor positive even if as few as 1% of the neoplastic cell nuclei exhibit positive immunohistochemical staining (7). A significant majority, over 70%, of breast cancer cases demonstrate positivity for these hormone receptors (8). Breast cancer patients with ER-negative tumors demonstrate a higher probability of achieving a pCR to neoadjuvant chemotherapy, relative to those with ER-positive tumors, which constitute the majority of the patient population (9). The advent of novel agents such as abemaciclib has enabled prolonged disease-free and overall survival in high-risk ER-positive breast cancer patients without the need for adjuvant chemotherapy(10). However, in this patient population with low rates of pathological complete response to NACT and available adjuvant treatment options without chemotherapy, clinicians may face challenges when deciding on the use of NACT.

While the transcriptional activity of the ER can modulate the expression of the PR, the expression profiles of these two steroid hormone receptors are typically aligned. Nonetheless, discordant ER and PR expression does occur in a subset of patients. Some ER-positive breast tumors exhibit a partial or complete loss of PR expression (11, 12). Existing evidence indicates that ER-positive/PR-negative breast tumors exhibit more aggressive biological and clinical features in comparison to ER-positive/PR-positive tumors (11). The loss of PR expression can identify subgroups of luminal B breast cancer patients who are at an elevated risk of disease recurrence and mortality, irrespective of c-erbB2 receptor status (13).

In our study, we aimed to investigate the impact of PR levels, which are routinely assessed in all patients receiving NACT, on pathological complete response in ER-positive patients where the effect of NACT is relatively lower.

2. Materials and Methods

2.1.Study participants

The medical records of breast cancer patients aged 18 and above who received neoadjuvant chemotherapy(NACT) and were seen at the Medical Oncology Clinic of Kütahya Evliya Çelebi Training and Research Hospital between 2017 and 2023 were retrospectively reviewed. A total of 52 patients were included in the study. The patients' demographic data, such as birth dates and gender information from their identification documents, were determined. The Eastern Cooperative Oncology Group performance status(ECOG-PS) was obtained from the file notes at the time of presentation. For the main hypothesis of the study, which examined the relationship between the percentage of PR and pCR, only patients who underwent surgery were included.

2.2.Pathological assessment

Tumor grade, ER, PR, c-erbB2, and Ki-67 ratio were obtained from preoperative biopsy results. Tumor grade was classified as well, moderately, and poorly differentiated. ER and PR were divided into three groups based on the staining percentages in the pathology report: less than 1%, 1-9%, and 10% and above. Patients with IHC+3 or IHC+2 positive and FISH positive were considered positive for c-erbB2, while the rest were negative. Ki-67 was grouped into five categories: 0-2.7%, 2.8-7.3%, 7.4-19.7%, 19.8-53.1%, and 53.2% and above. pCR was defined as

the absence of viable tumor cells in the surgical specimen.

2.3.Radiological assessment

The patients' preoperative clinical staging was based on physical examination and breast ultrasound, with some patients undergoing additional imaging such as thoracic and abdominal CT, whole-body bone scintigraphy, and positron emission tomography/computed tomography(PET-CT). Preoperative treatment response assessment was conducted for all patients through physical examination and comparative breast ultrasonography, with some also undergoing PET-CT scanning. Patients were divided into four groups based on the imaging results: complete response, partial response, stable disease, and progressive disease. The maximum diameter of the tumor on ultrasound was used as the basis for the response assessment.

2.4.Chemotherapy regimen

Patients received one of four different NACT regimens based on their clinical suitability. The first regimen was the doxorubicin/cyclophosphamide protocol followed by paclitaxel or docetaxel (AC+T). The second regimen was the docetaxel + cyclophosphamide(TC) protocol. The third regimen was the doxorubicin/cyclophosphamide + docetaxel/trastuzumab/pertuzumab protocol(AC+THP). The fourth regimen was the trastuzumab + paclitaxel (TH) protocol.

2.5.Data analysis

The statistical analyses were performed using *IBM SPSS Statistics for Windows, Version 25.0*. Descriptive statistics were presented, with categorical variables reported as frequency and percentage, and continuous variables reported as mean ± standard deviation and median. Comparisons of categorical variables were conducted using the chi-square test (Pearson or Fisher's Exact test, as appropriate). Baseline clinicopathological characteristics were additionally compared across PR groups to assess homogeneity. The associations between PR, ER, c-erbB2 status and treatment response (radiological and pathological complete response) were analyzed using chi-square and Fisher's Exact tests. To evaluate the independent effect of PR status on pathological complete response, a multivariate logistic regression analysis was performed, adjusting for ER, c-erbB2, menopausal status, ECOG performance status, tumor grade, and Ki-67 index. A p-value of less than 0.05 was considered statistically significant.

3. Results

The study included a total of 52 patients, with 50 female and 2 male participants. The mean age of the patients was 53.4 years, and the average body mass index was 27.5 kg/m². Baseline clinicopathological characteristics of the patients according to PR status are summarized in Table 1. No statistically significant differences were observed across PR groups in terms of menopausal status, ECOG performance, tumor grade, Ki-67, clinical stage, ER, c-erbB2, or treatment regimens (all $p > 0.05$), indicating that the groups were homogeneous

Table 1 .Baseline Characteristics of Patients According to Progesterone Receptor (PR) Status

Variable	PR <1% (n=17)	PR 1–9% (n=7)	PR ≥10% (n=28)	p-value
Menopausal status (Pre/Post)	11 / 6	4 / 3	5 / 23	0.312
ECOG PS (0/1)	17 / 0	6 / 1	20 / 8	0.284
Grade (1/2/3)	0 / 10 / 7	2 / 4 / 1	7 / 13 / 8	0.447
Ki-67 (<20% / ≥20%)	3 / 14	4 / 3	5 / 23	0.523
Clinical T stage (T2/T3/T4)	12 / 4 / 1	7 / 0 / 0	10 / 16 / 2	0.476
Clinical N stage (N0/N1/N2/N3)	2 / 4 / 8 / 3	0 / 3 / 4 / 0	2 / 9 / 17 / 0	0.391
ER (1–9% / ≥10%)	12 / 5	3 / 4	0 / 28	0.228
c-erbB2 (Neg / Pos)	8 / 9	4 / 3	24 / 4	0.336
NACT regimen (AC+T / TC / AC+THP / TH)	8 / 0 / 8 / 1	4 / 0 / 2 / 1	17 / 7 / 3 / 1	0.417

Data are presented as number of patients. p values were calculated using Pearson's χ^2 or Fisher's Exact test, as appropriate. All p values >0.05, indicating no significant differences across PR groups.

The study found a statistically significant relationship between radiological response and PR status. Specifically, the number of patients with a complete radiological response was higher than

expected among those with PR-negative or 1-9% PR positivity, while the number of patients with stable disease was higher than expected among those with 10% or greater PR positivity. No statistically significant relationship was observed between radiological response and ER or c-erbB2 status. The findings described were presented in Table 2.

Table 2. Relationship Between Radiological Response and Relevant Variables (N = 52)

Variable	Complete Response (n)	Partial Response (n)	Stable Disease (n)	p-value
ER				0.115*
1–9%	5	10	0	
≥10%	6	24	7	
PR				**0.016***
<1%	7	10	0	
1–9%	2	5	0	
≥10%	2	19	7	
c-erbB2				0.128*
Negative	5	25	6	
Positive	6	9	1	

*χ^2 test (*Pearson Chi-Square). Statistically significant at $p < 0.05$.*

The study found a statistically significant relationship between pCR and PR status. Specifically, the number of patients who achieved pCR was higher than expected among those with PR-negative tumors, while the number of patients without pCR was higher than expected among those with 1-9% and 10% or greater PR positivity.

A statistically significant relationship was also observed between pCR and ER status. The number of patients with pCR was higher than expected among those with 1-9% ER positivity, while the number of patients without pCR was higher than expected among those with 10% or greater ER positivity.

Furthermore, a statistically significant relationship was found between pCR and c-erbB2 status. The number of patients with pCR was higher than expected among those with c-erbB2-positive tumors, whereas the number of patients without pCR was higher than expected among those with c-erbB2-negative tumors. These data were presented in Table 3.

Table 3. Relationship Between Pathological Complete Response (pCR) and Variables (N = 52)

Variable	No pCR (n)	pCR Present (n)	p-value
ER			**0.024***
1–9%	9	6	
≥10%	33	4	
PR			**0.002#**
<1%	9	8	
1–9%	7	0	
≥10%	26	2	
c-erbB2			**0.036***
Negative	32	4	
Positive	10	6	

*χ^2 test (*Pearson Chi-Square, #Fisher's Exact Test). Statistically significant at $p < 0.05$.*

In the multivariate logistic regression model adjusted for ER, c-erbB2, menopausal status, ECOG performance status, tumor grade, and Ki-67 (Table 4), PR negativity (<1%) was associated with a markedly higher likelihood of achieving pCR compared with PR ≥10% (OR: 12.1). Although this result did not reach statistical significance (p = 0.198), likely due to the limited sample size, the effect size suggests that PR negativity may independently predict pCR. Patients with low PR expression (1–9%) did not show a significant association with pCR (p = 0.999).

Table 4. Multivariate Logistic Regression Analysis of Progesterone Receptor (PR) Status and Pathological Complete Response

PR status	OR (Exp(B))	95% CI	p-value
<1% vs ≥10%	12.1	NE	0.198
1–9% vs ≥10%	0.00	NE	0.999

NE = Not estimable due to sparse data. Model adjusted for ER, c-erbB2, menopausal status, ECOG, tumor grade, and Ki-67 index.

4. Discussion

The study findings indicate that among patients assessed to have achieved a complete clinical response based on physical examination and ultrasonographic evaluation, a statistically significant difference was observed solely in the subgroup with negative PR status or PR positivity in the range of 1-9%. Interestingly, the ER expression level and c-erbB2 positivity, which were hypothesized to be influential factors in the response to NACT, did not demonstrate a significant effect. This suggests that in the context of chemotherapy response, negative PR status or low PR positivity may be of even greater importance than other key criteria such as ER and c-erbB2 status.

It is well-established that radiological complete response exhibits a strong correlation with pathological complete response(14). However, in this study, routine response assessment of the patients was performed solely through physical examination and ultrasonography, with PET-CT, CT, or whole-body bone scintigraphy requested only in cases of suspected systemic metastasis. Routine mammography and breast MRI were not included in the response evaluation protocol. Despite this limited assessment approach, a significant proportion of patients who were considered to have achieved a preoperative complete response were subsequently found to have a pCR. pCR was not observed in only 3 patients who were clinically assessed as having a complete response, and pCR was observed in 2 patients who were not clinically assessed as having a complete response. Additionally, no local progression or development of new systemic metastases was detected in any of the patients receiving NACT. Considering these results, it may be reasonable to conclude that cost-effective and readily available modalities such as physical examination and ultrasonography can be sufficient for response assessment in the neoadjuvant setting.

PR is an important biomarker that can predict the prognosis and response to endocrine therapy in ER-positive breast cancers (15). Previous studies have demonstrated that progestogens can inhibit estrogen-stimulated growth of ER-positive/PR-positive patient-derived tumor models (16). Additionally, PR expression can limit estrogen-mediated proliferation and ER transcriptional activity in ER-positive breast cancer cells (17). Furthermore, higher PR levels in early-stage disease may partially suppress tumor metastasis, and administration of progesterone before surgery can provide improved clinical outcomes(18). These findings suggest that PR activation can have an anti-tumorigenic effect in the context of ER-positive breast cancer. The prognostic and predictive significance of PR expression has traditionally been attributed to its dependence on ER activity. The absence of PR has been associated with a dysfunctional ER and resistance to hormonal therapies. However, emerging evidence from experimental studies suggests alternative molecular mechanisms may explain the divergent clinical outcomes and selective ER modulator resistance observed in ER-positive/PR-negative tumors. These studies indicate that hyperactive crosstalk between ER and growth factor signaling pathways can reduce PR levels, even as they activate other ER-mediated functions. Thus, the lack of PR may reflect this complex interplay between ER and growth factor signaling, potentially contributing to the differential response patterns in these tumor subtypes. Additionally, the lack of PR expression may indicate heightened crosstalk between growth factor signaling pathways and the ER (19). Specifically, ER-positive/PR-negative breast tumors tend to exhibit elevated expression of epidermal growth factor receptor and c-erbB2 compared to ER-positive/PR-positive breast tumors(20). Comprehensive genomic analysis has revealed that ER-positive and PR-negative breast cancers exhibit an elevated number of DNA copy number variations and heightened activation of the PI3K/Akt/mTOR signaling pathway (21). Although limited research has been conducted to explore the relationship between PR status and chemosensitivity, one study reported that patients with low PR-expressing tumors may experience greater clinical benefit from chemotherapy. Conversely, for patients with high PR-expressing tumors, the prognostic significance of chemotherapy was relatively modest (11). Previous studies have demonstrated that the lack of PR expression is indicative of a dysfunctional ER signaling pathway, and is associated with reduced

responsiveness to selective estrogen receptor modulators like tamoxifen(19).

Studies have shown that patients with ER-positive tumors exhibiting 1-9% expression levels tend to have higher rates of pathological complete response following NACT compared to those with ER expression levels of 10% or greater (22). In our study, we similarly found that the pCR was higher in the group with low positive ER expression compared to the group with high ER expression. The presence of c-erbB2 positivity has also been identified as one of the factors that can enhance pathological complete response rates(23). Our study likewise demonstrated similar findings.

Existing studies have shown that ER-positive breast cancer patients with negative(<1%) or low PR levels(1-9%) demonstrate worse clinicopathological features compared to those with higher PR(≥10%) expression. In other words, patients with low positive PR status have been observed to exhibit similar clinicopathological and genetic characteristics as those with PR-negative disease(24). Interestingly, our study found that the pCR rate to NACT was lower than expected in the group with low positive PR expression, similar to the group with high PR expression. It is well-established that ER-positive, PR-negative breast cancer patients exhibit poor prognostic characteristics akin to those observed in triple-negative breast cancer (12). From this, it can be inferred that in ER-positive patients, even low-level expression of PR provides support for luminal characteristics. Additionally, these patients tend to exhibit a lower proliferation index compared to PR-negative cases. Consequently, the chemotherapy sensitivity of patients may be reduced even in the context of low positive PR status.

For ER-positive patients, genetic analysis is recommended to evaluate the options of adjuvant chemotherapy followed by hormonal therapy or hormonal therapy alone(25). For ER-positive patients, the need for chemotherapy is higher in those with PR negativity compared to those with PR positivity. This has been demonstrated through genomic assays such as Oncotype DX, MammaPrint, and BluePrint, which generally indicate a chemotherapy requirement(15, 26). Furthermore, for operable breast cancer patients who are ER-positive and PR-negative and are slated to undergo adjuvant chemotherapy, the administration of NACT can be considered. This approach may facilitate the earlier eradication of micrometastatic disease and provide an in vivo assessment of the tumor's response to chemotherapeutic intervention.

5. Study Limitations

While this study included only 52 patients, larger multi-center investigations with more participants may provide more definitive conclusions. Additionally, the patients did not routinely undergo genetic analyses such as Oncotype DX. For ER-positive, PR-negative patients, evaluating both the tumor biology and treatment responses through a combination of genetic analyses and clinical follow-up may offer more valuable insights.

6. Conclusion

PR is a crucial biomarker utilized in breast cancer classification, and its assessment is essential for patients being considered for NACT. However, there remain no clear-cut criteria for NACT decision-making based on PR levels, and the PR status can be a confounding factor for clinicians, particularly in ER-positive patients. The current study found that PR negativity in ER-positive patients appears to be a substantial supporting data point for pursuing NACT. Interestingly, low positive PR expression did not emerge as a predictive marker for pCR. For patients with ER-positive, PR-negative breast cancer, the unfavorable prognosis, enhanced sensitivity to chemotherapy, and potential resistance to hormonal therapy, combined with the increased rates of pCR demonstrated in our study findings, may warrant a more proactive approach to NACT.

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