Original Article

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Factors Affecting the Complete Response in Breast and Axillary Regions Following Neoadjuvant Chemotherapy for Breast Cancer

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Abstract

Aim: Neoadjuvant chemotherapy (NAC) has transitioned from a treatment modality used solely for inoperable and locally advanced breast cancer to a therapeutic approach for early-stage breast cancer. High-risk patients, such as those with HER2-positive and triple-negative breast cancer, particularly benefit from NAC. This study aimed to evaluate the factors affecting pathological complete response (pCR) in primary breast tumors and axillary lymph nodes in patients with breast cancer.

Methods: The study included female patients with breast cancer who received NAC at a training and research hospital between 2020 and 2024. Patients were categorized based on age, tumor stage, and tumor biology: luminal A, HER2-positive luminal B, HER2-negative luminal B, HER2-positive alone, or triple-negative. The presence or absence of E-cadherin in tumor cells and Ki-67 levels were also examined. Data were obtained from medical records to assess the impact of these factors on complete response in patients with breast cancer and axillary metastatic lymph nodes following NAC.

Results: Univariate analysis revealed that histopathological subtypes, estrogen receptor and progesterone receptor (PR) status, HER2 status, perineural invasion, lymphovascular invasion (LVI), Ki-67 index, and carcinoma *in situ* (CIS) component significantly influenced pCR. Multivariate analysis confirmed that PR status [Odds ratio (OR): 3.33, 95% confidence interval (CI): 1.57-7.08, p=0.002], HER2 status (OR: 3.56, 95% CI: 1.71-7.44, p=0.001), LVI (OR: 3.91, 95% CI: 1.84-8.30, p<0.001), Ki-67 index (OR: 1.03, 95% CI: 1.01-1.05, p<0.001), and CIS component (OR: 7.01, 95% CI: 2.44-20.11, p<0.001) were independent predictors of complete response.

Conclusion: Our findings underscore the multifaceted nature of NAC response in breast cancer, which is influenced by histopathological and molecular characteristics.

Keywords: Neoadjuvant chemotherapy, pathological complete response, breast cancer, axillary lymph nodes

Introduction

Breast cancer is the most prevalent malignant tumor among women and a leading cause of cancer-related morbidity and mortality worldwide (1). One in eight women will develop breast cancer during their lifetimes (2). Neoadjuvant chemotherapy (NAC) is the standard therapeutic approach for patients with locally advanced breast cancer. It is particularly indicated in patients with large tumor volumes, the presence of lymph node metastases, HER2-positive breast cancer, or triple-negative breast cancer (TNBC) (3). The primary clinical benefit of NAC is reduced tumor staging, which increases the likelihood of breast-conserving surgery (4,5). Breast cancer is currently classified into distinct molecular subtypes based on the presence or absence of immunohistochemical markers.

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These subtypes have different risk profiles and therapeutic strategies (6). Human epidermal growth factor receptor 2 (HER2 or HER2/neu) is a critical molecular target, and it is characterized by a transmembrane receptor with tyrosine kinase activity. HER2 is overexpressed or amplified in approximately 20% of breast cancers, contributing to aggressive tumor behavior and poor clinical outcomes (7).

We hypothesized that specific demographic, clinical, and molecular factors may predict the likelihood of achieving pathological complete response (pCR) in patients undergoing NAC for breast cancer. Post-NAC pathological response data reflect tumor chemosensitivity (8). Several studies have demonstrated specific correlations between morphological changes and the use of chemotherapeutic agents using pCR (9,10). Trastuzumab and pertuzumab, humanized monoclonal antibodies targeting different epitopes of HER2, have been reported to significantly improve pCR rates with dual anti-HER2 blockade in HER2-positive subtypes (11). However, previous studies on the predictive factors of NAC in breast cancer suggested that no single factor adequately predicted pCR (12).

Therefore, the current study aimed to evaluate the factors affecting pCR in primary breast tumors and axillary lymph nodes in patients with breast cancer receiving NAC. These predictive factors. Despite these factors, this study aimed to contribute to clinical decision-making and potentially improve treatment personalization. This may improve patient outcomes by optimizing NAC regimens and surgical planning, ultimately contributing to effective and personalized approaches.

Methods

Ethical Standards

This study received approval from the Institutional Review Board (IRB) of University of Health Sciences Turkey, Antalya Training and Research Hospital (IRB number: 5/15) on April 25, 2024. Informed consent was obtained from all participants.

Patient Selection

This cross-sectional observational study included 222 female patients with breast cancer who received NAC at a training and research hospital between 2020 and 2024. Patients were categorized into five groups based on age, tumor stage, and tumor biology: luminal A, HER2-positive luminal B, HER2-negative luminal B, HER2-positive alone, and triple-negative. The presence or absence of E-cadherin in tumor cells and Ki-67 levels were analyzed. Data were obtained from medical records. The effects of these factors on complete response in malignant breast masses and metastatic axillary lymph nodes following NAC were evaluated. Patients exhibiting complete response in both regions were considered to have achieved pCR (Figure 1).

Neoadjuvant chemotherapy was performed based on the molecular subtypes and biomarkers of breast cancer. For patients with TNBC, we selected chemotherapy regimens that included platinum-based therapies. Specifically, the most frequently used regimens were cisplatin combined with gemcitabine or carboplatin. In cases in which the tumor expressed PD-L1 positivity or exhibited high microsatellite instability (MSI), pembrolizumab was added to these regimens, forming a triple-combination therapy. If PD-L1 or MSI was not detected, a dual regimen was used without immunotherapy. For HER2-positive tumors, treatment was consistent with the current guidelines, involving a three-drug regimen of pertuzumab, trastuzumab, and docetaxel.

Patients with hormone receptor-positive (HR+) and HER2-negative tumors were divided into luminal A and luminal B subtypes based on Ki-67 expression levels. For luminal B tumors (Ki-67 >14%), a more aggressive approach was used, typically involving four cycles of dose-dense doxorubicin and cyclophosphamide (AC), followed by four cycles of dose-dense paclitaxel. This regimen was selected based on the updated ESMO guidelines and was particularly beneficial for younger patients and those with high-risk clinical features.

Exclusion Criteria

Patients who did not complete NAC, had incomplete records, and had distant metastasis were excluded from the study.

Statistical Analysis

All analyses were performed using the IBM SPSS Statistics Version 22.0 statistical software package. Categorical variables were expressed as numbers

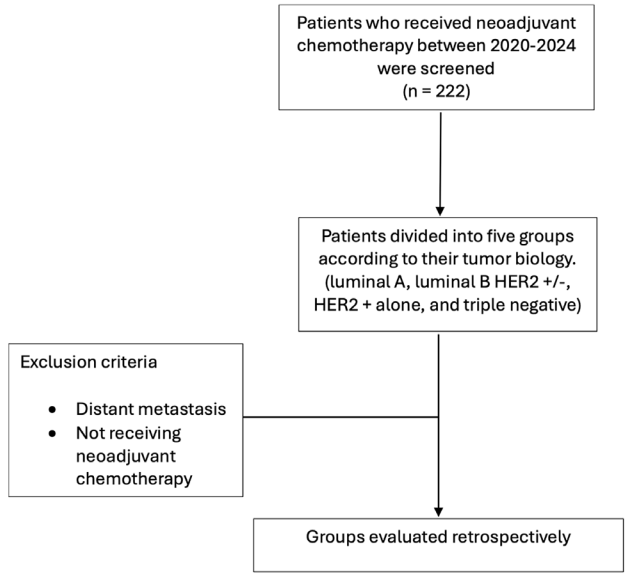

Figure 1. Flow chart of patient selection

and percentages, whereas continuous variables were summarized as mean and standard deviation or median (minimum-maximum) values, where appropriate. The normality of data distribution for continuous variables was confirmed using the Kolmogorov-Smirnov test. For the comparison of continuous variables between the two groups, Student's t-test or the Mann-Whitney U test was used, depending on whether the statistical hypotheses were fulfilled. Univariate and multiple logistic regression analyses were performed to identify factors predictive of complete response following NAC. Each variable was modeled as a univariate without considering other variables, and the common effect was revealed by multiple logistic regression. Odds ratios (ORs) and confidence intervals (CIs) were reported for variables with statistically significant effects on response.

Results

Table 1 presents the descriptive statistics of the 222 patients included in the study according to their demographic and histopathologic characteristics. The median age of the patients was 53.4 years (range, 29-85 years), and the mean body mass index (BMI) was 26.03±1.68. Among the included patients, 201 (90.5%) had ductal carcinoma histopathology. Estrogen receptor (ER) positivity was observed in 164 patients (73.9%), progesterone receptor (PR) positivity in 139 (62.6%), and HER2 positivity in 79 (35.6%). A total of 140 patients (63.1%) were negative for E-cadherin, 198 patients (89.2%) were negative for perineural invasion (PNI), and 121 patients (54.5%) were negative for lymphovascular invasion (LVI). The mean Ki-67 index was calculated at 35.76±25.68. Regarding the pathological response to NAC, 21 patients (9.5%) exhibited no response, 115 patients (51.8%) had a partial response, and 86 patients (38.7%) achieved a complete response.

The descriptive statistics and p-values related to variables affecting pCR following NAC are presented in Table 2. Accordingly, the mean age and BMI distributions were comparable between patients with partial or no response and those with complete response (p=0.564 and 0.725, respectively). Concerning histopathological subtypes, mixed carcinoma (n=4, 2.90%), mucinous carcinoma (n=7, 5.10%), and micropapillary carcinoma (n=4 cases, 2.90%) were more common in patients with partial or no response compared with those with a complete response (p=0.010). Among patients with partial or no response, 117 (86.0%) were ER-positive and 107 (78.70%) were PR-positive. Among patients with a complete response, 47 (54.70%) were ER-positive and 32 (37.20%) were PR-positive, indicating a significant effect of the ER and PR status on the pathological response (p<0.001 for both). Furthermore, the number of PNI-positive patients was

Table 1. Demographic and histopathological characteristics of the patients

		n (%)
Age (years)		53.4 (29-85)
BMI (kg/m^2)		26.03±1.68
Localization	Right	115 (51.8)
	Left	107 (48.2)
Histopathology	Ductal carcinoma	201 (90.5)
	Lobular carcinoma	4 (1.8)
	Medullary	1 (0.5)
	Mix carcinoma	4 (1.8)
	Mucinous carcinoma	7 (3.2)
	Micropapillary	4 (0.5)
ER	Negative	58 (26.1)
	Positive	164 (73.9)
PR	Negative	83 (37.4)
	Positive	139 (62.6)
HER2	Negative	143 (64.4)
	Positive	79 (35.6)
E-cadherin	Negative	140 (63.1)
	Positive	82 (36.9)
PNI	Negative	198 (89.2)
	Positive	24 (10.8)
LVI	Negative	121 (54.5)
	Positive	101 (45.5)
Ki-67 index (%)		35.76
CIS component	Negative	166 (74.8)
	Positive	56 (25.2)
Molecular classification	Luminal A	43 (19.4)
	Luminal B (Ki-67+)	70 (31.5)
	Luminal B (HER2+)	51 (23.0)
	Tripple-	32 (14.4)
	HER2	26 (11.7)
Neoadjuvant chemotherapy protocol	PTD	52 (23.4)
	PT	26 (11.7)
	AC	103 (46.4)
	CISG	27 (12.2)
	DC	7 (3.2)
	DAC	2 (0.9)
	CARPAK	5 (2.3)
cN stage	cN0	4 (1.8)
	cN1	130 (58.6)
	cN2	88 (39.6)
Menopause	No	84 (37.8)
	Yes	138 (62.2)
Pathological response to NAC	No response	21 (9.5)
	Partial	115 (51.8)
	Complete	86 (38.7)

PNI: Perineural invasion, LVI: Lymphovascular invasion, CIS: Carcinoma *in situ*, NAC: Neoadjuvant chemotherapy

Table 2. Predictors affecting pathological response to NAC

		Response to NAC		p value
		Partial and no response n (%)	Complete response n (%)	
Age		53.2±11.1	53.8±11.3	0.564
BMI		26.0±1.7	26.1±1.6	0.725
Localization	Right	65 (47.80)	50 (58.10)	0.168
	Left	71 (52.20)	36 (41.90)	
Histopathology	Ductal carcinoma	116 (85.30)	85 (98.80)	**0.010**
	Lobular carcinoma	4 (2.90)	0	
	Medullary	0	1 (1.2)	
	Mix carcinoma	4 (2.90)	0	
	Mucinous carcinoma	7 (5.10)	0	
	Micropapillary	4 (2.90)	0	
ER	Negative	19 (14.0)	39 (45.30)	**<0.001**
	Positive	117 (86.0)	47 (54.70)	
PR	Negative	29 (21.30)	54 (62.80)	**<0.001**
	Positive	107 (78.70)	32 (37.20)	
HER2	Negative	103 (75.70)	40 (46.50)	**<0.001**
	Positive	33 (24.30)	46 (53.50)	
E-Cadherin	Negative	65 (47.80)	50 (58.10)	0.345
	Positive	71 (52.20)	36 (41.90)	
PNI	Negative	114 (83.80)	84 (97.70)	**0.001**
	Positive	22 (16.20)	2 (2.30)	
LVI	Negative	61 (44.90)	60 (69.80)	**<0.001**
	Positive	71 (55.10)	26 (30.20)	
Ki-67 index		26.9±21.8	49.8±25.2	**<0.001**
CIS component	Negative	88 (64.70)	78 (90.70)	**<0.001**
	Positive	48 (35.30)	8 (9.30)	
Molecular classification	Luminal A	41 (30.10)	2 (2.30)	**<0.001**
	Luminal B (Ki-67+)	51 (37.50)	19 (22.10)	
	Luminal B (HER2+)	25 (18.40)	26 (30.20)	
	Triple-	13 (9.60)	19 (22.10)	
	HER2	6 (4.40)	20 (23.30)	
NAC protocol	PTD	26 (19.10)	26 (30.2)	**0.005**
	PT	6 (4.40)	20 (23.30)	
	AC	82 (60.30)	21 (24.40)	
	CISG	10 (7.40)	17 (19.80)	
	DC	7 (5.10)	0	
	DAC	2 (1.50)	0	
	CARPAK	3 (1.40)	2 (2.30)	
cN stage	cN0	1 (0.70)	3 (3.50)	**0.684**
	cN1	81 (59.60)	49 (57.0)	
	cN2	54 (39.70)	34 (39.50)	
Menopause	No	52 (38.20)	32 (37.20)	**0.888**
	Yes	84 (61.80)	36 (62.80)	

Bold values indicate statistical significance at p<0.05
Statistics: χ^2 or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables
NAC: Neoadjuvant chemotherapy, BMI: Body mass index, ER: estrogen receptor, PR: Progesterone receptor, PNI: Perineural invasion, LVI: Lymphovascular invasion, CIS: Carcinoma in situ

higher in the partial or no response group (n=22, 16.20%) than in the complete response group (n=2, 2.30%) (p=0.001). Similarly, LVI positivity was more common in the partial or no response group (n=71, 55.10%) than in the complete response group (n=26, 30.20%) (p<0.001). The mean Ki-67 index was significantly higher in patients with complete response (49.8±25.2) than in those with partial or no response (p<0.001). There was a higher number of patients with luminal A and luminal B (Ki-67+) subtypes in the partial or no response group, whereas luminal B (HER2+), triple-negative, and HER2-enriched subtypes were more prevalent in the complete response group (p<0.001). Upon evaluating the NAC protocols used, AC (n=82, 60.30%), DC (n=7, 5.10%), and DAC (n=2, 1.50%) were more common in the partial or no response group than in the complete response group (p=0.005).

Table 3 presents the results of univariate and multivariate regression analyses conducted to identify predictive factors for resistance to pCR following NAC. HER2-negative patients were 3.59 (95% CI: 2.02-6.39) times more likely to achieve a complete response than HER2-positive patients. The ORs for complete response in PNI-positive patients versus PNI-negative patients were 8.11 (95% CI: 1.86-35.42) and 2.84 (95% CI: 1.60-5.02), respectively. The OR for a complete response in patients with a positive carcinoma *in situ* (CIS) component compared with those without this component was 3.51 (95% CI: 2.37-11.93). Multivariate logistic regression revealed that PR status, HER2 status, LVI, Ki-67 index, and CIS component were significant predictors, with the positive CIS component having the highest effect on complete response (OR: 7.01, 95% CI: 2.44-20.11).

Discussion

This study evaluated the demographic and histopathological characteristics of 222 patients with breast cancer who received NAC and identified factors affecting pCR. The findings provide critical insights into the predictors of response, potentially guiding personalized treatment strategies and improving outcomes for patients with breast cancer. The mean ages and BMIs of our cohort were 53.4 years and 26.03 kg/m², respectively, with no significant differences observed between patients with partial or no response and those with complete response. This is consistent with previous studies showing that age and BMI are not primary determinants of NAC response in breast cancer, emphasizing the greater importance of other biological factors.

A significant proportion of our patients (90.5%) had ductal carcinoma, consistent with the overall prevalence of breast cancer. Our results indicated a higher probability of pCR in patients with ductal carcinoma than in other histopathological subtypes (p=0.010), supporting the

Table 3. Univariate and multivariate analyses of predictors of complete response following neoadjuvant chemotherapy

	Univariate analyses			Multivariate analyses		
	OR	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
ER	5.11	2.68-9.73	**<0.001**			
PR	6.23	3.42-11.34	**<0.001**	3.33	1.57-7.08	0.002
HER2	3.59	2.02-6.39	**<0.001**	3.56	1.71-7.44	**0.001**
PNI	8.11	1.86-35.42	**0.005**			
LVI	2.84	1.60-5.02	**<0.001**	3.91	1.84-8.30	**<0.001**
Ki67 (%)	1.039	1.026-1.052	**<0.001**	1.03	1.01-1.05	**<0.001**
CIS component	3.51	2.37-11.93	**<0.001**	7.01	2.44-20.11	**<0.001**
Molecular Classification						
HER2+	-	-				
Luminal A	68.33	12.64-369.31	**<0.001**			
Luminal B (HER2-)	29.96	6.14-146.19	**<0.001**			
Luminal B (HER2+)	21.32	4.66-97.65	**<0.001**			
Triple-	7.64	1.68-34.71	**0.008**			

Bold values indicate statistical significance at p<0.05
OR: Odds ratio, CI: Confidence interval, ER: Estrogen receptor, PR: Progesterone receptor, PNI: Perineural invasion, LVI: lymphovascular invasion, CIS: Carcinoma in situ
Statistics: Logistic regression analyses

existing evidence that ductal carcinoma may be more sensitive to NAC than lobular and mucinous carcinomas, which are often associated with weaker responses. Predicting pCR contributes to evaluating the benefits of NAC in patients with newly diagnosed breast cancer and assisting in selecting the optimal surgical approach preoperatively. However, there is no consensus on the imaging-based assessment of pCR following NAC, and it is not possible to reliably predict pCR (13,14). Over time, surgical trends have shifted toward the implementation of less-invasive procedures that minimize long-term morbidity without compromising oncological safety. The benefits of neoadjuvant therapies in facilitating breast conservation are well established (15).

In a study by Dou et al. (16), age, T stage, N stage, ER status, PR status, HER-2 status, Ki-67, histological grade, molecular subtype, clinical stage, and pathology type were strongly associated with pCR rates (p<0.05). However, no significant correlation was observed between pCR and chemotherapy regimen, surgical method, menopausal status, BMI, or lymphatic infiltration (p>0.05). A younger age, lower T and N stages, ER negativity, PR negativity, HER2-positivity, high Ki-67 expression, and lower histological grades were reported to be more likely to achieve pCR (16). Another study observed a higher frequency of pCR in patients with right breast cancer, with 63.5% of pCR occurring in the right breast and 36.5% occurring in the left breast (p=0.012) (17). It has also been suggested that the pre-NAC Ki-67 index reflects tumor cell proliferative capacity and is closely related to NAC sensitivity (18), thus being consistently recognized as an independent predictor of NAC response (19,20). Concerning HER2, the efficacy of NAC in HER2-positive patients has been significantly improved through the use of trastuzumab and/or pertuzumab. Consequently, HER2 status has emerged as an independent predictor of the efficacy of NAC (21,22). Another study highlighted that women with more advanced cancer stages and a Ki-67 index >20% were more likely to achieve pCR (23).

In a study conducted by Yan et al. (24), the group with a tumor size of 2 cm following NAC exhibited the highest rate of pCR. Patients with luminal A subtype had the lowest pCR rate, whereas those with TNBC had the highest pCR rate. Furthermore, the HER2-positive subtype showed a higher pCR percentage than the luminal B subtype (24). Qian et al. (25) categorized 325 patients into two groups based on whether they achieved pCR. Within this cohort, 126 patients achieved pCR (a rate of 38.8%). Overall, compared with the non-pCR group, patients in the pCR group had several significant characteristics: older age, smaller tumor size, lower stage, a higher Ki-67 index, a higher proportion of HER2-positive tumors, and a lower percentage of HR+ tumors (p<0.05) (25). Hormone receptor-positive breast cancer exhibits a better prognosis than HER2-positive breast cancer or TNBC. In contrast, HER2-positive breast cancer and TNBC exhibit better therapeutic response to chemotherapy. However, only a few studies have evaluated the oncological outcomes of NAC in patients with locally advanced HR-negative breast cancer (26,27).

In a study by Lan et al. (28), univariate analysis of predictive factors between the pCR and non-pCR groups revealed statistically significant differences in cT, cN, ER, PR, and Ki-67 status (p<0.05). However, there were no statistically significant differences between the two groups in terms of age, menopausal status, HER2 status,

or chemotherapy cycles (28). In another study, Guan et al. (29) reported that 57 patients (14.8%) achieved breast pCR. Univariate analysis indicated that tumor size, ER, PR, and Ki-67 were associated with breast pCR. Additionally, multivariate analysis identified tumor size, PR, and Ki-67 as statistically significant factors. Dou et al. (30) found that hormone receptor status was an independent predictor of the pCR rate in patients with breast cancer who received NAC. The authors reported that the ER+/PR and ER/PR phenotypes were more responsive to chemotherapy than the ER+/PR+ phenotypes (30).

In our study, the percentages of ER and PR positivity were significantly lower in patients achieving pCR (ER: 54.7% vs. 86.0%, $p<0.001$; PR: 37.2% vs. 78.7%, $p<0.001$), underscoring the known association between HR positivity and reduced chemotherapy sensitivity. HER2 positivity was also a significant determinant, with a higher prevalence in patients achieving pCR (HER2+: 34.9% vs. 38.5%, $p<0.001$). HER2-positive tumors, typically more aggressive, respond well to chemotherapy combined with HER2-targeted therapies, highlighting the importance of incorporating HER2-targeted agents into NAC regimens.

In this study, PNI and LVI were significantly associated with weaker NAC responses (PNI: $p=0.001$, LVI: $p<0.001$), indicating more aggressive tumor biology and higher metastatic potential, thus explaining the reduced chemotherapy efficacy. The Ki-67 proliferation index emerged as a critical determinant, with higher values significantly associated with pCR (49.8% vs. 26.9%, $p<0.001$). Ki-67 serves as a marker of cellular proliferation, with higher indices reflecting a larger fraction of actively dividing cells that are more susceptible to chemotherapy. The molecular classification revealed significant differences in pCR rates. Luminal A tumors, with an OR of 68.33 for treatment resistance, were most resistant to NAC ($p<0.001$). In contrast, HER2-positive and triple-negative subtypes exhibited better responses, reflecting their aggressive nature but higher chemosensitivity.

Lastly, multivariate analysis identified the presence of CIS, PR, HER2, LVI, and Ki-67 index as significant resistance determinants. In particular, CIS had the highest effect on treatment resistance (OR: 7.01, $p<0.001$), highlighting the complexity of treating these tumors.

Study Limitations

This study has several limitations. Its retrospective design may introduce selection bias, limiting the generalizability of the findings. Additionally, the single-center nature of the study may not fully capture the broader variability in treatment protocols and patient populations observed in multicenter studies. The relatively small sample size, particularly within certain molecular subtypes, may restrict the statistical power to detect subtle differences in response predictors. The reliance on pathologic assessment of pCR without standardized imaging protocols could have impacted the accuracy of response evaluation. Despite these limitations, this study provides valuable insights into the factors influencing pCR in breast cancer patients receiving NAC. The findings contribute to the growing body of evidence that can improve personalized treatment planning and optimize outcomes for breast cancer patients.

Conclusion

This study highlighted the multifaceted nature of NAC response in breast cancer, which is driven by histopathological and molecular characteristics. These findings demonstrate the need for personalized therapeutic approaches based on individual tumor biology to enhance treatment efficacy and patient outcomes. Further research should explore these predictive factors in larger, more diverse cohorts to validate and improve these insights.

Footnote

Ethics Committee Approval: This study received approval from the Institutional Review Board (IRB) of University of Health Sciences Turkey, Antalya Training and Research Hospital (IRB number: 5/15) on April 25, 2024.

Informed Consent: Informed consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: H.O., R.C.C., O.C., T.C.Y., E.A., B.D.H., A.L., Concept: H.O., Design: H.O., O.C., Data Collection or Processing: O.C., T.C.Y., E.A., Analysis or Interpretation: B.D.H., A.L., Literature Search: H.O., R.C.C., T.C.Y., Writing: H.O., R.C.C.

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