Clinicopathologic Characteristics of Breast Cancer Patients Who Had a Pathologic Complete Response after Neoadjuvant Treatment

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AIM: Breast cancer is the most common cancer in women and is a leading cause of cancer-related mortality. The role of neoadjuvant therapy (NAT) in conjunction with surgical intervention is becoming increasingly prominent in the field of oncology. NAT enhance the probability of breast-conserving surgery in cases of locally advanced breast cancer and in patients with metastatic or inoperable disease.
METHODS: The study included patients who underwent surgery following neoadjuvant chemotherapy for breast cancer between 2012 and 2022. Their files were retrospectively analyzed. The following parameters were examined and statistically analyzed for patients with and without pathological complete response: age, gender, tumor size, location, stage, pathological type, grade, hormone receptor status, molecular type, and the type of surgery performed.
RESULTS: The study cohort comprised 329 patients who received NAT for breast cancer. Of the patients included in the study, 243 underwent mastectomy and 86 underwent breast-conserving surgery. A postoperative histopathologic examination revealed pathologic complete response (pCR) in 89 patients. The results of the statistical analysis indicated that certain parameters, including high grade, negative hormone receptor status, human epidermal growth factor receptor 2 (HER2) positivity, Ki-67 $\geq$30, and early tumor stage, were associated with higher rates of pCR following NAT.
CONCLUSIONS: The biomarkers identified in this study, including hormone receptor negativity, anatomical Tumour, Node, Metastasis (TNM) Stages 1–2 tumors, positive HER2 amplification, Ki-67 proliferation $\geq$30%, luminal B/HER2 (+) and HER2 (+) molecular subtypes, are crucial in predicting the likelihood of a complete response to NAT in breast cancer. The presence of these clinicopathologic biomarkers facilitates the process of therapeutic decision-making by identifying patients who are likely to achieve a complete response.

Keywords: breast; neoadjuvant; treatment; complete; response

Introduction

Breast cancer is one of the most prevalent forms of cancer globally, accounting for the majority of cancer-related mortalities among women [1]. It is classified into histologic, molecular, and genomic subtypes, each of which exhibits distinct diagnostic and therapeutic characteristics. In recent years, at least four distinct molecular subtypes have been identified through the examination of tumor biology. The classification of these subtypes was based on the consideration of several key factors, including hormone receptor (HR), human epidermal growth factor receptor 2 (HER2), and Ki-67 index. These categories are designated as luminal A, luminal B, HER2-enriched, and estrogen receptor (ER), progesterone receptor (PR), and HER2-negative (triple-negative) breast cancer [2,3].

The treatment of breast cancer depends on the stage of the disease and may include chemotherapy, hormonal therapy, radiotherapy, and surgery. While surgical treatment remains the primary option for early-stage cancers, neoadjuvant therapy (NAT) has become the standard approach for locally advanced breast cancers [4]. The objective of NAT is to diminish the dimensions of sizable tumors, thereby facilitating conservative breast surgery. Additionally, it can facilitate the resectability of unresectable tumors and serve as a means of assessing their sensitivity to adjuvant therapies [5].

The most significant predictor of neoadjuvant treatment efficacy is the absence of invasive tumor cells in the breast or axilla, which is defined as a pathologic complete response (pCR) [6]. Demonstration of a pathologic complete response is crucial for the planning of optimal surgical treatment, the selection of less invasive procedures,

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and the prediction of prognosis. Consequently, there are predictive factors that can be used to identify patients who may benefit from NAT. pCR can be estimated based on a number of criteria, including histopathological diagnosis, molecular subtype, tumor grade and classification, multicentricity, and neoadjuvant treatment regimen [7]. Furthermore, these markers facilitate the identification of patients in whom pCR is unattainable.

The objective of our study was to ascertain the predictive factors associated with a response in patients with pCR following NAT for breast cancer, and to elucidate the impact of these factors on the subsequent surgical procedure.

Materials and Methods

Study Design

A retrospective analysis was conducted on all patients admitted to Izmir Katip Çelebi University Atatürk Education and Research Hospital between 2012 and 2022 who were diagnosed with breast cancer and underwent surgical treatment. The primary cohort consisted of 329 female patients for whom data were available and who underwent the entirety of their treatment process in Izmir Katip Çelebi University Atatürk Education and Research Hospital. The demographic data, including age, gender, menopausal status, clinical features, imaging studies, and pathology results, were subjected to analysis.

Inclusion Criteria

- Female gender;
- Patients whose diagnosis was confirmed histopathologically;
- Patients who received NAT before surgery and were operated on after treatment;
- Those whose data were accessed from the hospital information system.

Exclusion Criteria

- Age less than 18 years;
- Male gender;
- Inoperable patients after NAT;
- Patients with inflammatory breast cancer;
- Patients with hereditary breast cancer;
- Those operated for palliative purposes;
- Patients with malignancies other than breast cancer.

Neoadjuvant Therapy

The nature of the NAT regimen was determined on an individual basis, taking into account the specific characteristics of the patient and the decisions reached by the multidisciplinary council. In the selection of NAT regimens, those containing anthracycline and taxane were the most commonly utilized. Such agents as fluorouracil and cyclophosphamide were combined with these. In addition, patients with HER2-positive disease received dual blockade with a combination of trastuzumab and pertuzumab.

Clinicopathologic Assessment

Tumor diameter, side, multifocality and multicentricity, lymph node involvement and distant metastasis status were determined through the use of ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) or positron emission scintigraphy (PET). A core biopsy was performed prior to neoadjuvant therapy in order to determine the histopathological diagnosis, molecular subtype, nuclear grade, receptor status, and Ki-67 proliferation index.

The determination of ER and PR status was conducted in accordance with standard immunohistochemical methods. The evaluation of hormone receptor (HR) expression was conducted in accordance with the updated guidelines set forth by the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) in 2020 [8]. For ER and PR staining, a result of less than 1% was classified as negative, a result of 1–10% was classified as low positive, and a result of greater than 10% was classified as positive. A HER2 amplification score of 0 or 1 was classified as HER2 negative, while a score of 3 was considered HER2 positive. A fluorescence *in situ* hybridization (FISH) test was conducted on individuals with a score of 2 positive following an immunohistochemical (IHC) examination. The results of the FISH test were used to define those samples as HER2 positive. In regard to Ki-67, the 2019 European Society of Medical Oncology guideline was utilized as a reference point, with values exceeding 30% classified as elevated [9]. Clinical staging of each patient was conducted in accordance with the aforementioned data. The new Tumour, Node, Metastasis (TNM) staging system, which includes the biological biomarkers in the 8th edition of American Joint Committee on Cancer (AJCC), was used to perform the staging [10].

The specific surgical technique and method of accessing the axilla were documented in the operative notes. In the histopathologic evaluation of the postoperative specimen, the absence of invasive cancer in the breast and axillary lymph nodes (ypT0/is ypN0), irrespective of ductal carcinoma *in situ*, was accepted as a pathological complete response.

Statistical Analysis

The data were analyzed using the IBM SPSS Statistics 26.0 software (IBM Corp., Armonk, NY, USA), with a p-value of less than 0.05 deemed statistically significant. Descriptive statistics are presented as frequencies and percentages for categorical variables. To compare categorical variables according to pathologic complete response status, both Pearson chi-square and Fisher exact tests were employed. Risk factors that affect the status of pathologic complete response were analyzed by binary logistic regression analysis. In the comparisons made according to pathologic complete response status, variables with $p < 0.200$ were included in the model and Backward Wald method was used.

Table 1. Comparisons based on pathologic complete response (n: 329).

Variables	All patients	No pCR	pCR (+)	Test statistic	*p*
Age, *n* (%)					0.575**
<35	17 (5.2)	11 (4.6)	6 (6.7)	–	
≥35	312 (94.8)	229 (95.4)	83 (93.3)		
Menopause, *n* (%)					0.207**
Pre-menopause	144 (43.8)	100 (41.7)	44 (49.4)	1.593	
Post-menopause	185 (56.2)	140 (58.3)	45 (50.6)		
Location, *n* (%)					0.592**
Right breast	151 (45.9)	108 (45.0)	43 (48.3)	0.287	
Left breast	178 (54.1)	132 (55.0)	46 (51.7)		
Pathological diagnosis, *n* (%)					0.184**
Invasive ductal carcinoma	254 (77.2)	181 (75.4)	73 (82.0)		
Invasive lobular	20 (6.1)	18 (7.5)	2 (2.2)	3.385	
Other	55 (16.7)	41 (17.1)	14 (15.7)		
Nuclear grade, *n* (%)					0.018***
Grade 1	15 (4.6)	15 (6.3)[a]	0 (0.0)[b]		
Grade 2	186 (56.5)	139 (57.9)[a]	47 (52.8)[a]	–	
Grade 3	128 (38.9)	86 (35.8)[a]	42 (47.2)[a]		
ER staining, *n* (%)					<0.001**
Negative	96 (29.2)	54 (22.5)[a]	42 (47.2)[b]		
Weak positive	28 (8.5)	20 (8.3)[a]	8 (9.0)[a]	20.291	
Positive	205 (62.3)	166 (69.2)[a]	39 (43.8)[b]		
PR staining, *n* (%)					0.010**
Negative	113 (34.3)	72 (30.0)[a]	41 (46.1)[b]		
Weak positive	67 (20.4)	48 (20.0)[a]	19 (21.3)[a]	9.286	
Positive	149 (45.3)	120 (50.0)[a]	29 (32.6)[b]		
HER2, *n* (%)					<0.001**
Negative	226 (68.7)	192 (80.0)	34 (38.2)	52.742	
Positive	103 (31.3)	48 (20.0)	55 (61.8)		
Ki-67, *n* (%)					0.016**
<30	139 (42.2)	111 (46.3)	28 (31.5)	5.820	
≥30	190 (57.8)	129 (53.8)	61 (68.5)		
Molecular type, *n* (%)					<0.001**
Luminal A	102 (31.0)	94 (39.2)[a]	8 (9.0)[b]		
Luminal B, HER2 (–)	68 (20.7)	60 (25.0)[a]	8 (9.0)[b]	64.186	
Luminal B, HER2 (+)	50 (15.2)	24 (10.0)[a]	26 (29.2)[b]		
HER2 positive	53 (16.1)	24 (10.0)[a]	29 (32.6)[b]		
Triple negative	56 (17.0)	38 (15.8)[a]	18 (20.2)[a]		
T, *n* (%)					0.278***
Stage 0 (occult)	6 (1.8)	5 (2.1)	1 (1.1)		
Stages 1–2	163 (49.5)	111 (46.3)	52 (58.4)	–	
Stage 3	52 (15.8)	41 (17.1)	11 (12.4)		
Stage 4	108 (32.8)	83 (34.6)	25 (28.1)		
N, *n* (%)					0.572**
Stage 0	25 (7.6)	17 (7.1)	8 (9.0)	1.118	
Stages 1–2	257 (78.1)	191 (79.6)	66 (74.2)		
Stage 3	47 (14.3)	32 (13.3)	15 (16.9)		
TNM (anatomical), *n* (%)					0.027**
Stages 1–2	90 (27.4)	58 (24.2)[a]	32 (36.0)[b]	7.232	
Stage 3	223 (67.8)	167 (69.6)[a]	56 (62.9)[a]		
Stage 4	16 (4.9)	15 (6.3)[a]	1 (1.1)[a]		

Table 1. Continued.

Variables	All patients	No pCR	pCR (+)	Test statistic	*p*
TNM (clinical-prognostic), *n* (%)					0.130**
Stages 1–2	102 (31.0)	71 (29.6)	31 (34.8)	4.085	
Stage 3	211 (64.1)	154 (64.2)	57 (64.0)		
Stage 4	16 (4.9)	15 (6.3)	1 (1.1)		
Multi-centricity, *n* (%)					0.164**
Uni-centric	284 (87.9)	203 (86.4)	81 (92.0)	1.934	
Multi-centric	39 (12.1)	32 (13.6)	7 (8.0)		
Multi-focality, *n* (%)					0.240**
Unifocal	263 (81.4)	195 (83.0)	68 (77.3)	1.378	
Multifocal	60 (18.6)	40 (17.0)	20 (22.7)		

** Pearson chi-square test, *** Fisher Freeman Halton test. superscripts [a] and [b] indicate differences between groups. pCR, pathologic complete response; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNM, Tumour, Node, Metastasis; T, Tumour; N, Node.

Table 2. Investigation of factors affecting pathologic complete response by binary logistic regression (n: 329).

	β	S.E.	Wald statistics	*p*	OR	95% confidence interval for OR	
						Lower limit	Upper limit
Molecular type							
Luminal A	Reference						
Luminal B, HER2 (–)	0.446	0.531	0.707	0.400	1.563	0.552	4.422
Luminal B, HER2 (+)	2.656	0.479	30.788	<0.001	14.245	5.574	36.404
HER2 (+)	2.623	0.469	31.283	<0.001	13.782	5.496	34.560
Triple negative	1.704	0.472	13.022	<0.001	5.497	2.178	13.871
Anatomical TNM							
Stages 1–2	Reference						
Stage 3	–0.416	0.311	1.797	0.180	0.659	0.359	1.212
Stage 4	–2.311	1.110	4.335	0.037	0.099	0.011	0.873
Multi-centricity							
Uni-centric	Reference						
Multi-centric	–0.811	0.483	2.812	0.094	0.445	1.172	1.147

Variables included in the model: Breast bx diagnosis, Nuclear grade, ER positivity, PR positivity, HER2, Ki-67, Molecular type, Anatomic TNM, Clinical/Prognostic TNM, Multicentricity. Method: Backward Wald. Model significance $p < 0.001$. OR, Odds Ratio.

Results

The study cohort comprised 329 female patients. The median age of the patients was 50 years (minimum age: 26 years; maximum age: 84 years). A total of 185 patients (56.2%) were in the postmenopausal period. The characteristics of the patients and the tumors are presented in Table 1. Imaging methods revealed that the tumor was unifocal in 263 (81.4%) patients and multifocal in 60 (18.6%) patients. With regard to localization, the tumor was in the right breast in 151 (45.9) cases and in the left breast in 178 (54.1) cases.

In the histopathologic examination, 254 patients (77.2%) were diagnosed with invasive ductal carcinoma (IDCC), 20 patients (6.1%) with invasive lobular carcinoma (ILC), 11 patients (3.3%) with mixed invasive cancer, 9 patients (2.7%) with clear cell carcinoma, 8 patients (2.4%) with apocrine carcinoma, and 27 patients (8.2%) with other types of cancer. Of the patients, 15 (4.6%) were diagnosed as grade 1, 186 (56.5%) as grade 2, and 128 (38.9%) as grade 3. In terms of hormone receptor characteristics, 96 (29.2%) patients were ER negative, 28 (8.5%) patients were ER low positive, 205 (62.3%) patients were ER positive, 113 (34.3%) patients were PR negative, 67 (20.4%) patients were PR low positive, 149 (45.3%) patients were PR positive. In addition, 103 (31.3%) patients were HER2 positive. There were 139 (42.2%) patients with Ki-67 index below 30% and 190 (57.8%) patients with Ki-67 index above 30%. According to molecular classification; 102 (31%) patients were Luminal A, 68 (20.7%) patients were Luminal B/HER2 (–), 50 (15.2%) patients were Luminal B/HER2 (+), 56 (17%) patients were triple negative (TN) and 53 (16.1%) patients were HER2 positive.

A total of 243 patients (73.9%) underwent a mastectomy, while 86 patients (26.1%) underwent breast-conserving surgery (BCS). Two hundred fourteen patients (65.0%), 76 patients (23.1%), and 39 patients (11.9%) underwent axil-

lary dissection, Sentinel lymph node biopsy (SLNB), and SLNB + Axillary Dissection (AD), respectively. With regard to the postoperative pathologic responses, 112 patients (34%) exhibited a complete response in the breast, while 136 patients (41.3%) demonstrated a complete response in the axilla. Overall, 89 patients (27.1%) exhibited an overall complete response.

In terms of anatomical TNM staging, three patients (0.9%) were classified as Stage 1, 87 patients (26.4%) as Stage 2, 223 patients (67.8%) as Stage 3, and 16 patients (4.9%) as Stage 4. In accordance with the clinical-prognostic TNM staging system, 23 patients (7%) were classified as Stage 1, 79 (24%) as Stage 2, 211 (64.1%) as Stage 3, and 16 patients (4.9%) as Stage 4. With regard to tumor size, the distribution was as follows: 6 (1.8%) patients were at T0, 31 (9.4%) at T1, 132 (40.1%) at T2, 52 (15.8%) at T3, and 108 (32.8%) at T4. With regard to lymph node invasion, the distribution of patients was as follows: 25 (7.6%) were classified as N0, 169 (51.4%) as N1, 88 (26.7%) as N2, and 47 (14.3%) as N3.

The patients were divided into two groups based on whether they exhibited a complete response to neoadjuvant treatment or not. No statistically significant differences were identified between pCR and the following variables: age, menopausal status, direction, quadrant of mass location, multicentricity, multifocality, tumor histopathological subtype, Tumour (T) and Node (N) Stage, and clinical-prognostic TNM Stage (Table 1).

The rate of patients exhibiting a complete response was higher in those with ER-negative tumors (47.2%), whereas the rate of patients without a complete response was higher in those with ER-positive tumors (69.2%) ($p < 0.001$). The rate of patients exhibiting a pathological complete response (pCR) was higher in those with PR negativity (46.1%), while the rate of patients without pCR was higher in those with PR positivity (50.0%) ($p = 0.010$). It has been demonstrated that the incidence of pCR is significantly higher in patients with HER2-positive and Ki-67 levels of 30 or above ($p < 0.001$ and $p = 0.016$, respectively). While the proportion of patients with Luminal A and Luminal B/HER2 (–) is lower in patients with pCR, the proportion of patients with Luminal B/HER2 (+) and HER2 (+) is higher ($p < 0.001$). In patients with anatomical TNM Stages 1–2, the rate of complete responses (36.0%) was higher than the rate of incomplete responses (24.2%) ($p = 0.027$).

According to Binary Logistic Regression analysis; Luminal B/HER2 (+) patients have 14.245-fold higher chance of having pCR than Luminal A patients. Individuals with HER2 (+) have a 13.782-fold increased likelihood of achieving a complete response compared to those with Luminal A. Those with TN have a 5.497-fold increased likelihood of achieving a complete response (Table 2).

Discussion

Neoadjuvant therapies represent the standard treatment for locally advanced breast cancers, defined by the presence of large tumors in the breast and malignant lymphadenomegaly at the axilla. The objective of NAT is to diminish the tumor burden prior to surgical intervention in this patient population, thereby rendering them eligible for BCS or creating an opportunity for surgical intervention in cases where it would otherwise be inoperable [4]. In our study, the rate of mastectomy following neoadjuvant therapy was slightly elevated. This rate was attributable to the fact that, in accordance with the patients' requests, our clinic performs subcutaneous mastectomies and implants.

The response of the tumor after NAT can be in four different ways. These include pCR, partial response, no response and progressive disease. The primary objective of an effective neoadjuvant therapy is a complete response to treatment. The CTNeoBC analysis examined the long-term clinical outcomes of pCR and identified a significant correlation between pCR and disease-free survival (DFS) and overall survival (OS) [11]. This correlation was particularly pronounced in the TN and HER2-positive patient cohorts. Nevertheless, the correlation between pCR and long-term outcomes was less pronounced in patients with hormone-positive tumors. A recent meta-analysis demonstrated that achieving a pathological complete response (pCR) in both the breast and axilla significantly improves disease-free survival (DFS) and overall survival (OS), and is associated with a lower recurrence rate [12]. The significance of pCR has grown in light of the anticipated enhanced survival prospects of patients, and it is regarded as the most optimal alternative to neoadjuvant therapy (NAT). In instances where pCR is unattainable following NAT and residual tumor burden persists, more radical surgical procedures may be advised.

Different studies have shown pCR rates of 27–37% for breast and 38–49% for axilla. General pCR rates vary between 25–30%, although there are differences according to subtypes [13,14,15]. Conversely, approximately 20% of patients do not respond to NAT [16]. In our study, the pCR rate was 34% and 44% for the breast and axilla, respectively, resulting in an overall pCR rate of 27%. The rate of patients exhibiting no response to NAT was 20%, which was comparable to the findings reported in the literature. It is of great importance to ascertain the tumor characteristics that will respond favorably to NAT. However, it is equally crucial to identify the patient group that will not respond well to the treatment in order to modify the treatment plan accordingly.

The incidence of breast cancer is highest among women in their 50s. The median age of the patients in our study was 50 years, with the youngest and oldest patients ranging from 26 to 84 years. This is consistent with the findings reported in the existing literature on the subject [17]. The relationship between age, menopause, and pCR has been the subject of

various studies in the literature. In the GeparTrio study, it was reported that higher pCR was achieved below the age of 40 years. Conversely, Huober J *et al*. [18] and Müller *et al*. [19] suggested that age was not an indicator for pCR. The present study did not identify a statistically significant correlation between age and menopausal status and the occurrence of pCR.

The existing literature on the relationship between the histological subtype of the tumor and NAT response does not provide definitive evidence of a correlation between pCR and the pathological type of the tumor [13,20]. In addition, the histologic subtype was not identified as a statistically significant factor influencing the probability of achieving a pCR in the present study. Nevertheless, the pCR rate was markedly inferior in the invasive lobular carcinoma cohort relative to the ductal carcinoma cohort. It is established that high-grade tumors in breast cancer exhibit greater aggressiveness due to their elevated proliferation rate. Similarly, it has been demonstrated that these tumors exhibit enhanced sensitivity to chemotherapeutic agents [21]. In three separate studies, it was demonstrated that a greater proportion of patients with high-grade breast tumors exhibited a pathological complete response (pCR) [18,19,22]. The present study revealed a statistically significant correlation between histologic grade and pCR. The incidence of PCR was observed to increase in correlation with the grade of the tumor.

The HR status is a significant variable in this context, as it is associated with a favorable response to endocrine therapy and more favorable prognostic outcomes. Nevertheless, in studies conducted on patients undergoing NAT, an inverse correlation was identified between pCR and HR positivity [23,24]. In the study conducted by Guarneri and colleagues [25], which included 1731 patients who had undergone treatment with various neoadjuvant regimens, the rates of pCR were significantly higher in patients with estrogen receptor (ER) negativity, irrespective of the specific treatment regimen. In our study, both ER and PR negativity were found to be statistically significant predictors of pCR. Likewise, luminal type cancers presenting with HR+/HER2 (–) similarly demonstrate an inadequate response to neoadjuvant chemotherapy (NAT). In the study conducted by Carey *et al*. [26], the rates of pCR in patients who received NAT were 6% in the Luminal A group and 8% in the Luminal B group, which were statistically significantly lower than those observed in the other subtypes.

Approximately 30% of breast cancer cases exhibit positive *HER-2* gene expression. Among the various molecular subtypes, patients with HER2-positive tumors demonstrate the most favorable response to neoadjuvant treatment [24,26]. A meta-analysis of 14,000 cases revealed that patients with HER2-positive tumors exhibited the highest rate of pCR following NAT, with a pCR rate of 38.7% [27]. In a multivariate logistic regression analysis, the HER2 molecular subtype was identified as a significant predictor of pCR, independent of other factors. Similarly, in our study, the occurrence of pCR was higher in patients with Luminal B/HER2 (+) and HER2 (+) in the univariate analysis. In binary regression analysis, patients with Luminal B/HER2 (+) and HER2 (+) were approximately 15 times more likely to achieve pCR than patients with Luminal A. A substantial body of evidence indicates that the TN group exhibits high rates of pCR, despite the absence of HER2 positivity [19,27,28]. In a meta-analysis of 9460 patients, Wu *et al*. [29] observed that the pCR rate after NAT in TN patients was 28.9%. Additionally, they demonstrated that TN patients exhibited a higher complete response rate than non-TN patients. In our study, the frequency of pCR was higher in the TN patient group compared to the Luminal groups, and the results were consistent with those reported in the literature.

The nuclear antigen Ki-67 is detectable during the cell division process and exhibits a higher concentration in the S phase of cell proliferation. It has been demonstrated that agents that act on the S phase have a more pronounced effect on tumors with high Ki-67 values [20]. Two separate studies have demonstrated that a high level of Ki-67 is a predictor of pCR in univariate analysis, yet this is not a significant finding when multiple regression analysis is employed [21,30]. In the study conducted by Petit *et al*. [31], it was demonstrated that a Ki-67 level greater than 20% was a predictor of pCR in patients. In our study, the proportion of patients who achieved pCR was statistically significantly higher in those with a Ki-67 score of >30%.

Tumor size is a significant determinant of treatment response in patients undergoing NAT. In recent studies, a negative correlation has been observed between primary tumor size and axillary lymph node involvement and treatment response [24,32]. In the study conducted by Baron *et al*. [33], it was observed that tumors classified as T1 + T2 Stages demonstrated a higher response rate to NAT compared to those classified as T3 + T4 Stages. However, the observed difference was not found to be statistically significant. The data indicate a decline in pCR rates from cT1 to cT3, with a slight increase observed in cT4. No statistically significant difference was identified between T Stages in terms of pCR.

Despite the existence of numerous studies examining the predictive value of tumor size, axillary lymph involvement, and distant metastasis in pathological response to NAT, there is a paucity of research data concerning the role of TNM Stage in this context. The present study revealed that patients with early-stage (Stages 1–2) breast cancer exhibited significantly enhanced pCR rates in accordance with the anatomical TNM classification. Conversely, no statistically significant difference in pCR rates was observed between tumor stages according to clinical-prognostic TNM, which also incorporates molecular markers. This may be attributed to the fact that HR positivity is linked to a less favorable prognosis.

The limitations of the study include its retrospective and single-center design, the involvement of multiple surgical teams in the operations, and the use of different neoadjuvant treatment regimens. Despite its single-center design, the study has a large patient series and all patients undergo evaluation by a multidisciplinary team, which are key strengths of the study.

Conclusions

The present study offers compelling evidence for the identification of predictive factors associated with pCR in breast cancer patients undergoing NAT. The predictors of pCR were found to be high-grade, HR negativity, positive HER2 amplification, Ki-67 proliferation of 30% or greater, an anatomical TNM Stages 1–2 tumor, Luminal B/HER2 (+) and HER2 (+) molecular subtypes. Our data indicate that the NAT sensitivity of this patient group is high, thereby warranting the expectation of a high pCR rate. Consequently, surgeons will be more inclined to opt for breast-conserving surgery in patients with an anticipated pCR.

Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the first author if needed.

Author Contributions

FK was the designer of the study and revised the article critically for scientific content, collected the data and drafted this manuscript; YYB, MGB and MKA participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; MG and BBK collected and reported the patients' data. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Ethics committee approval for this study was obtained from the Izmir Kâtip Celebi University Ethics Committee (İKÇÜ-GOKAEK 2022/0296). Informed consent was obtained from the patients. This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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