

Original Article

Tumor Biology is More Strongly Associated with Pathological Complete Response Than Clinical Stage in Breast Cancer Treated with Neoadjuvant Systemic Therapy

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ABSTRACT

Aim: This study aimed to determine the pathological complete response (pCR) rate and identify independent clinicopathological predictors of pCR in patients with invasive breast cancer treated with neoadjuvant systemic therapy (NST).

Methods: In this multicenter retrospective cohort study, 360 patients with invasive breast cancer who underwent surgery following NST at Manisa Celal Bayar University Hospital between January 2015 and December 2025 were included. Demographic characteristics, tumor features, molecular subtypes, treatment regimens, and pathological responses were evaluated. Factors associated with pCR were assessed using univariate analyses; variables with $p < 0.20$ were entered into a multivariable logistic regression model.

Results: The overall pCR rate was 32.5%. In univariate analyses, Ki-67 proliferation index, ER and PR expression, clinical T stage, histological subtype, tumor grade, human epidermal growth factor receptor 2 (HER2) positivity, and anti-HER2 therapy were significantly associated with pCR (all $p < 0.05$). Multivariable logistic regression identified HER2-positive molecular subtype [odds ratios (OR)=9.82, 95% confidence intervals (CI): 4.46-21.58; $p < 0.001$], triple-negative breast cancer (TNBC) (OR=6.36, 95% CI: 2.23-18.11; $p < 0.001$), and grade 3 tumors (OR=4.36, 95% CI: 2.06-9.23; $p < 0.001$) as independent predictors of pCR; whereas clinical T3 stage was independently associated with a lower likelihood of achieving pCR (OR=0.24, 95% CI: 0.07-0.84; $p = 0.025$). The prediction model demonstrated excellent discriminative ability (area under the curve =0.869).

Conclusion: Molecular subtype and tumor grade are the strongest independent predictors of pCR following NST in invasive breast cancer. HER2-positive and TNBC subtypes are substantially more likely to achieve pCR. These findings emphasize the importance of tumor biology in treatment planning and response prediction.

Keywords: Breast cancer, neoadjuvant chemotherapy, pathological complete response, HER2-positive breast cancer, triple-negative breast cancer, predictive factors

Introduction

As the leading malignancy among women globally, breast cancer constitutes a substantial public health challenge owing to its high incidence and persistent contribution to cancer-related mortality. Although therapeutic advances have improved clinical outcomes, the disease continues to account for a significant proportion of the worldwide cancer burden [1].

Despite substantial advances in early detection strategies and systemic treatment modalities, locally advanced breast cancer continues to represent a major clinical challenge. The implementation of multidisciplinary treatment approaches integrating surgery, systemic therapy, and radiotherapy has significantly improved survival outcomes in recent years [2].

Neoadjuvant systemic therapy (NST) has evolved into an integral component of the treatment strategy for patients

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with operable stage II-III breast cancer. It was initially developed to reduce tumor burden before surgery and is now routinely incorporated into contemporary multidisciplinary management [2]. In addition to increasing breast-conserving surgery rates, NST provides a unique opportunity to assess tumor sensitivity to systemic treatment in vivo. In addition, the extent of residual disease after completion of NST has become a key factor in guiding postoperative systemic treatment, particularly for patients with human epidermal growth factor receptor 2 (HER2)-positive or triple-negative breast cancer (TNBC) [3,4]. During the 2015-2025 study period, neoadjuvant systemic treatment strategies evolved with increasing incorporation of subtype-directed therapies. Standard chemotherapy backbones include anthracycline- and taxane-based regimens or non-anthracycline taxane-based combinations, with carboplatin frequently incorporated for TNBC. In HER2-positive disease, trastuzumab-based treatment was routinely used, while dual HER2 blockade with trastuzumab and pertuzumab was increasingly incorporated into treatment for patients with higher-risk disease. These treatment approaches reflect the evolution of contemporary neoadjuvant management and the increasing importance of tumor biology in treatment selection and pathological response.

Achieving pathological complete response (pCR) after neoadjuvant systemic therapy is widely recognized as a favorable early treatment endpoint and has been consistently linked to improved long-term disease-free and overall survival, particularly among patients with HER2-positive and TNBC [3,5]. Nevertheless, the likelihood of achieving pCR differs markedly according to breast cancer subtype, with the highest response rates consistently reported in HER2-positive and TNBC, whereas hormone receptor-positive/HER2-negative cancers generally exhibit lower responsiveness to neoadjuvant therapy [5]. A wide range of clinicopathological characteristics has been evaluated for its ability to predict pCR, including patient age, tumor grade, proliferative activity, hormone receptor expression, HER2 status, and clinical stage. However, published findings remain heterogeneous, and no single predictor has demonstrated consistent performance across different patient cohorts [6].

Identification of independent clinicopathological predictors of pCR is of considerable clinical importance for optimizing neoadjuvant treatment strategies, improving patient selection, and facilitating individualized therapeutic decision-making. The objective of this study was to evaluate the frequency of pCR following neoadjuvant systemic therapy and to identify the clinicopathological characteristics that independently predict pCR in patients with invasive breast cancer. In addition, multivariable logistic regression analysis was performed to identify independent predictors of pCR among variables that were significant in univariate analyses.

Methods

Study Design and Patient Population

This multicenter, retrospective cohort study included patients with histopathologically confirmed invasive breast cancer who received NST followed by definitive surgical resection at the Medical Oncology Clinics of Manisa Celal Bayar University Hospital between January 2015 and December 2025. Only patients with complete baseline clinicopathological data before the initiation of NST and with available pathological response assessments following surgery were included. Demographic characteristics, clinical and pathological features, treatment regimens, and postoperative pathological findings were retrospectively retrieved from electronic medical records and pathology reports. Due to the retrospective design of the study, complete information for all clinicopathological variables was not available for every patient. Therefore, the denominators varied across variables. Each analysis was performed using data from patients with available measurements for the respective variable. Missing data primarily resulted from the absence of relevant information in clinical records or pathology reports; no imputation was performed. Accordingly, the number of patients included in individual analyses may differ from the overall study population, and the corresponding denominators are indicated in the tables whenever applicable. The baseline demographic and clinicopathological characteristics of the study population are summarized in Table 1.

Table 1. Baseline demographic, clinical, and pathological characteristics of the patients

Variables	N
Age (year), mean±SD	51.12±10.74
Age groups	
<50 years, n (%)	177 (49.2)
≥50 years, n (%)	183 (50.8)
Menopausal status	
Premenopausal, n (%)	149 (41.4)
Postmenopausal, n (%)	211 (58.6)
Tumor laterality	
Left, n (%)	191 (53.1)
Right, n (%)	162 (45)
Bilateral, n (%)	7 (1.9)
Clinical T stage	
T0/Tis, n (%)	11 (3.1)
T1, n (%)	92 (26.1)
T2, n (%)	160 (45.3)
T3, n (%)	52 (14.7)
T4, n (%)	38 (10.8)

Table 1. Continued

Variables	N
Clinical N stage	
N0, n (%)	13 (3.6)
N1, n (%)	149 (41.7)
N2, n (%)	175 (49)
N3, n (%)	20 (5.6)
Clinical M stage	
cM0, n (%)	350 (97.2)
Oligometastatic disease, n (%)	6 (1.7)
cM1, n (%)	4 (1.1)
Tumor focality	
Unifocal, n (%)	194 (54)
Multifocal, n (%)	104 (29)
Multicentric, n (%)	24 (6.7)
Multifocal and multicentric, n (%)	37 (10.3)
Histological subtype	
IDC, n (%)	214 (59.8)
Mixed (IDC+ILC), n (%)	58 (16.2)
ILC, n (%)	51 (14.2)
Other/NOS, n (%)	35 (9.8)
Tumor grade	
Grade 1, n (%)	17 (5.9)
Grade 2, n (%)	149 (51.7)
Grade 3, n (%)	122 (42.4)
ER-positive, n (%)	254 (75.6)
PR-positive, n (%)	183 (57.9)
HER2-positive, n (%)	101 (30.7)
Ki-67 (%), mean±SD	40.13±24.09
Molecular subtype	
HR-positive/HER2-negative, n (%)	182 (55.5)
HER2-positive, n (%)	101 (30.8)
TNBC, n (%)	45 (13.7)
Clinical/radiological response after neoadjuvant therapy	
Radiological complete response, n (%)	24 (6.7)
Partial response, n (%)	231 (64.5)
Stable disease, n (%)	79 (22.1)
Progressive disease, n (%)	5 (1.4)
Not evaluable, n (%)	19 (5.3)
Surgery type	
Breast-conserving surgery, n (%)	131 (40.2)
Modified radical mastectomy, n (%)	116 (35.6)
Simple mastectomy, n (%)	65 (19.9)
Bilateral simple mastectomy, n (%)	14 (4.3)

Table 1. Continued

Variables	N
Axillary surgery	
SLNB, n (%)	126 (38.7)
ALND, n (%)	189 (58)
SLNB+ALND, n (%)	4 (1.2)
Bilateral SLNB, n (%)	3 (0.9)
Bilateral ALND, n (%)	2 (0.6)
No axillary surgery, n (%)	2 (0.6)
Extracapsular extension present, n (%)	95 (31.9)
pCR, n (%)	100 (32.5)
RCB classification (non-pCR)	
RCB-1, n (%)	17 (9.6)
RCB-2, n (%)	105 (59)
RCB-3, n (%)	56 (31.5)
ypN status	
ypN0, n (%)	152 (50.7)
ypN+, n (%)	148 (49.3)
Number of lymph nodes removed, median (range)	9.00 (1.00-57.00)
Number of positive lymph nodes, median (range)	1.00 (0.00-22.00)
Adjuvant radiotherapy, n (%)	289 (96.7)
Recurrence, n (%)	47 (14.5)
Metastasis, n (%)	40 (13.3)
Continuous variables are presented as mean±standard deviation (SD) or median (minimum-maximum), whereas categorical variables are presented as number (n) and percentage (%). ALND: Axillary lymph node dissection, ER: Estrogen receptor, HER2: Human epidermal growth factor receptor 2, HR: Hormone receptor, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, Ki-67: Ki-67 proliferation index, MRM: Modified radical mastectomy, NAT: Neoadjuvant therapy, NOS: Not otherwise specified, OS: Overall survival, pCR: Pathological complete response, PR: Progesterone receptor, RCB: Residual cancer burden, RT: Radiotherapy, SLNB: Sentinel lymph node biopsy, SS: Standard deviation, TNBC: Triple-negative breast cancer	

Treatment and Pathological Assessment

Neoadjuvant systemic treatment was planned by a multidisciplinary breast cancer team in accordance with contemporary national and international clinical practice guidelines. Neoadjuvant treatment consisted of anthracycline- and taxane-containing chemotherapy protocols selected according to contemporary institutional practice. Patients with HER2-positive tumors received anti-HER2 therapy when clinically indicated. Following completion of systemic treatment, all surgical specimens were independently reviewed by dedicated breast pathologists. The primary outcome of the study was pCR, defined as complete eradication of invasive cancer from both the breast and the axillary lymph nodes after neoadjuvant therapy (ypT0/is ypN0).

Clinicopathological Variables

Demographic, clinical, pathological, and treatment-related characteristics were collected for analysis. These included patient age; menopausal status; Eastern Cooperative Oncology Group (ECOG) performance status; comorbid conditions; tumor laterality; clinical T and N stages; tumor focality; histological subtype; histological grade; estrogen receptor (ER), progesterone receptor (PR), and HER2 status; Ki-67 proliferation index; molecular subtype; neoadjuvant chemotherapy regimen; use of anti-HER2 therapy; radiological response to NST; type of breast surgery; and the axillary surgical approach. Tumors were categorized into three molecular subtypes according to pretreatment immunohistochemical profiles: HR-positive/HER2-negative, HER2-positive, and TNBC. HR positivity was defined as the expression of ER, PR, or both. A comprehensive summary of the baseline clinicopathological characteristics of the study cohort is provided in Table 1.

Ethical Approval

Ethical approval for the study was obtained from the Ethics Committee of Clinical Research, Manisa Celal Bayar University Faculty of Medicine (decision no: 20.478.486/4061, date: 15.04.2026).

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows (version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables were examined for normality based on skewness and kurtosis values, with coefficients between -3 and +3 considered acceptable. Variables showing a normal distribution were compared using the independent-samples t-test, whereas the Mann-Whitney U test was applied to variables that were not normally distributed. Associations between categorical variables were evaluated using Pearson's chi-square test or Fisher's exact test, depending on the expected cell frequencies.

To identify factors associated with pCR, each clinicopathological variable was first examined in a univariate analysis. Variables with $p < 0.20$ were subsequently entered into a multivariable logistic regression model to determine independent predictors of pCR. Because ER, PR, HER2 status, and anti-HER2 treatment were highly correlated, these variables were not analyzed simultaneously. Instead, molecular subtype was incorporated into the final regression model as a composite biological variable.

Effect estimates are reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Model calibration was evaluated using the Hosmer-Lemeshow goodness-of-fit test, while model discrimination was assessed by calculating the area under the receiver operating characteristic (ROC) curve area under the curve (AUC). Potential multicollinearity among predictor variables was examined using variance inflation factor values. All statistical tests were two-tailed, and statistical significance was defined as a p value below 0.05.

Results

Baseline Clinicopathological Characteristics

A total of 360 patients with invasive breast cancer who underwent surgical resection following NST were included in the study. The mean age was 51.1 ± 10.7 years, and 50.8% of the patients were aged ≥ 50 years. Overall, 58.6% of patients were postmenopausal and 41.4% were premenopausal; the majority (92.5%) had an ECOG performance status of 0. Regarding clinical stage, T2 tumors (45.3%) and N2 nodal disease (49.0%) were the most common presentations. Histologically, invasive ductal carcinoma was the predominant subtype (59.8%), and grade 3 tumors accounted for 42.4% of cases. Positivity for ER, PR, and HER2 was observed in 75.6%, 57.9%, and 30.7% of patients, respectively. According to molecular subtype, 55.5% of patients had HR-positive/HER2-negative disease, 30.8% had HER2-positive disease, and 13.7% had TNBC. The most frequently administered neoadjuvant regimen was dose-dense anthracycline/cyclophosphamide-based chemotherapy (60.3%). Most patients with HER2-positive tumors received anti-HER2 targeted therapy. Overall, pCR was achieved in 32.5% of patients following surgery (Table 1).

Factors Associated with Pathological Complete Response

In the univariate analysis of factors associated with pCR, the Ki-67 proliferation index was significantly higher in patients who achieved pCR than in those who did not (51.98 ± 23.24 vs. 35.60 ± 22.55 , $p < 0.001$). In contrast, ER and PR expression levels were significantly lower in patients who achieved pCR (both $p < 0.001$). Clinical T stage was significantly associated with pCR ($p = 0.014$), with higher pCR rates observed in patients with T1 and T2 tumors, whereas lower rates were observed in those with T3 and T4 disease. Histological subtype was also significantly associated with pCR, as patients with invasive lobular carcinoma or mixed histology had substantially lower pCR rates than those with invasive ductal carcinoma ($p < 0.001$). Grade 3 tumors demonstrated a significantly higher pCR rate (51.6%) than grade 1-2 tumors ($p < 0.001$). Furthermore, HER2 positivity and the use of anti-HER2 therapy were both significantly associated with higher pCR rates (both $p < 0.001$). No significant associations were observed between pCR and age, menopausal status, ECOG performance status, or clinical N stage (Table 2).

Independent Predictors of Pathological Complete Response

Variables with a p value univariate analysis were entered into the multivariable logistic regression model. In the multivariable analysis, molecular subtype emerged as the strongest independent predictor of pCR. Compared with patients with the HR-positive/HER2-negative subtype, those with HER2-positive disease were approximately 9.8 times more likely to achieve pCR (OR=9.82, 95% CI: 4.46-21.58; $p < 0.001$). Similarly, patients with TNBC had a 6.4-fold higher likelihood of achieving pCR (OR=6.36, 95% CI: 2.23-18.11; $p < 0.001$).

Table 2. Univariate analysis of factors associated with pathological complete response

Variable/category	pCR yes	pCR no	p
Age (years), mean±SD	52.29±10.76 (n=208)	51.45±10.41 (n=100)	p=0.517
Ki-67 (%), mean±SD	35.60±22.55 (n=202)	51.98±23.24 (n=98)	p<0.001
ER expression (%), mean±SD	69.96±35.93 (n=207)	24.51±37.03 (n=97)	p<0.001
PR expression (%), mean±SD	32.28±37.20 (n=207)	7.60±18.71 (n=94)	p<0.001
Age group (<50/≥50 years)			
<50	93 (66%)	48 (34%)	p=0.588
≥50	115 (68.9%)	52 (31.1%)	
Menopausal status			
Postmenopausal	124 (66.3%)	63 (33.7%)	p=0.569
Premenopausal	84 (69.4%)	37 (30.6%)	
Clinical T stage			
T0/Tis	0 (0%)	3 (100%)	p=0.014
T1	29 (60.4%)	19 (39.6%)	
T2	105 (65.6%)	55 (34.4%)	
T3	42 (80.8%)	10 (19.2%)	
T4	28 (73.7%)	10 (26.3%)	
Clinical N stage			
N0	10 (83.3%)	2 (16.7%)	p=0.530
N1	72 (66.7%)	36 (33.3%)	
N2	108 (65.5%)	57 (34.5%)	
N3	15 (75%)	5 (25%)	
Histological subtype			
Other/NOS	18 (51.4%)	17 (48.6%)	p<0.001
IDC	99 (59.3%)	68 (40.7%)	
Mixed (IDC+ILC)	48 (82.8%)	10 (17.2%)	
ILC	43 (89.6%)	5 (10.4%)	
Tumor grade			
1	17 (100%)	0 (0%)	p<0.001
2	116 (85.3%)	20 (14.7%)	
3	59 (48.4%)	63 (51.6%)	
ER status			
Negative	27 (33.3%)	54 (66.7%)	p<0.001
Positive	180 (80.7%)	43 (19.3%)	
PR status			
Negative	65 (49.2%)	67 (50.8%)	p<0.001
Positive	142 (84%)	27 (16%)	
HER2 status			
Negative	167 (78%)	47 (22%)	p<0.001
Positive	37 (42%)	51 (58%)	
Anti-HER2 therapy			
Not administered	170 (77.3%)	50 (22.7%)	p<0.001
Administered	35 (41.7%)	49 (58.3%)	

Continuous variables were compared using the independent samples t-test or Mann-Whitney U test, as appropriate. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. P values <0.05 were considered statistically significant.

ER: Estrogen receptor, HER2: Human epidermal growth factor receptor 2, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, NAT: Neoadjuvant therapy, NOS: Not otherwise specified, pCR: Pathological complete response, PR: Progesterone receptor, SD: Standard deviation

A high histological grade remained an independent predictor of treatment response. Compared with grade 1-2 tumors, patients with grade 3 disease were more than four times as likely to achieve pCR (OR=4.36, 95% CI: 2.06-9.23; $p<0.001$). Regarding clinical tumor stage, only T3 tumors were associated with a significantly reduced probability of pCR relative to T1 tumors (OR=0.24, 95% CI: 0.07-0.84; $p=0.025$). In contrast, neither histological subtype nor the Ki-67 proliferation index retained statistical significance after adjustment for other covariates in the multivariable model. The multivariable logistic regression model demonstrated satisfactory agreement between observed and predicted outcomes, as indicated by a non-

significant Hosmer-Lemeshow goodness-of-fit test ($p=0.705$). Furthermore, the model showed excellent discrimination between patients who did and did not achieve pCR, with an area under the ROC curve of 0.869 (Figure 1, Table 3).

Inspection of the forest plot derived from the multivariable logistic regression model demonstrated that the HER2-positive molecular subtype had the strongest independent association with pCR, followed by TNBC and grade 3 tumors. In contrast, the confidence intervals for histological subtype and the Ki-67 proliferation index crossed the null value (OR=1), indicating that these variables were not independent predictors of pCR (Figure 1).

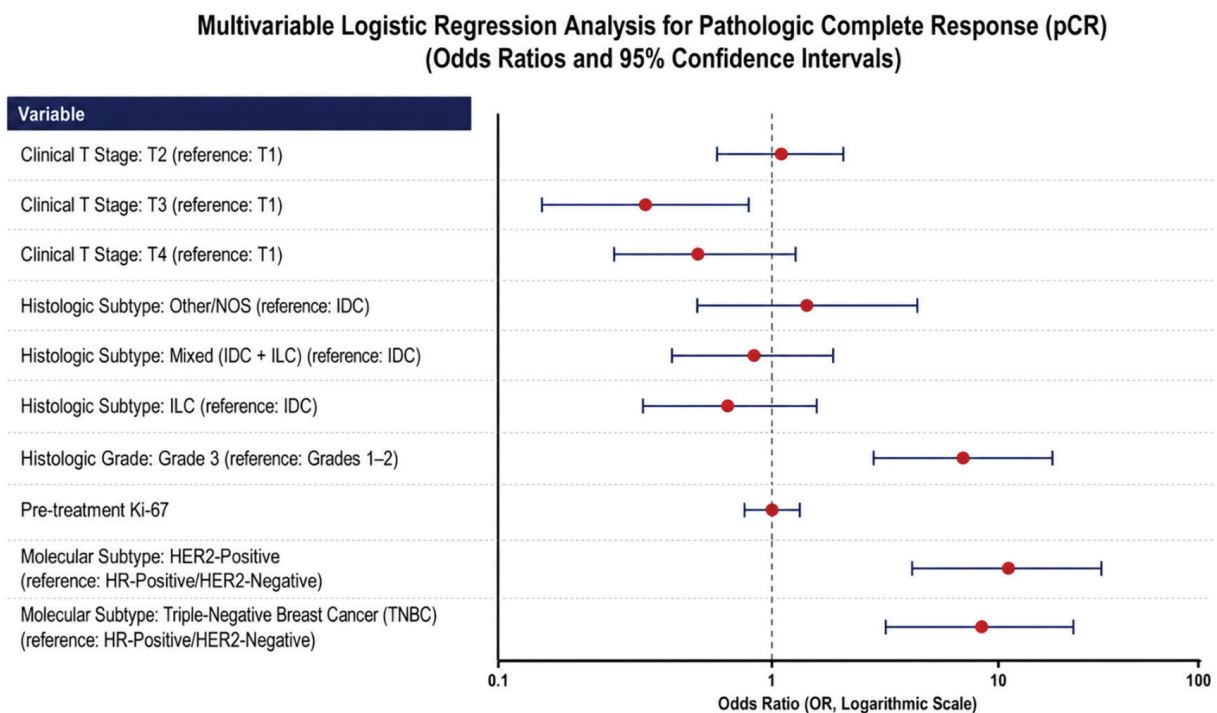


Figure 1. Forest plot of multivariable logistic regression analysis identifying factors associated with pathologic complete response. HER2: Human epidermal growth factor receptor 2, ILC: Invasive lobular carcinoma,

Table 3. Multivariable logistic regression model for predicting pathological complete response

Variables	OR	95% CI	p
Clinical T stage =T2 (ref: T1)	0.95	0.36-2.52	$p=0.917$
Clinical T stage =T3 (ref: T1)	0.24	0.07-0.84	$p=0.025$
Clinical T stage =T4 (ref: T1)	0.47	0.13-1.66	$p=0.242$
Histological subtype =Other/NOS (ref: IDC)	1.20	0.45-3.19	$p=0.716$
Histological subtype =Mixed (IDC+ILC) (ref: IDC)	0.74	0.29-1.94	$p=0.545$
HISTOLO_GRP=ILC (ref: IDC)	0.59	0.17-2.06	$p=0.407$
Histological grade =Grade 3 (ref: Grade 1-2)	4.36	2.06-9.23	$p<0.001$
Pre-treatment Ki-67	1.01	0.99-1.03	$p=0.174$
Molecular subtype =HER2 positive (ref: HR positive/HER2 negative)	9.82	4.46-21.58	$p<0.001$
Molecular subtype =TNBC (ref: HR positive/HER2 negative)	6.36	2.23-18.11	$p<0.001$

Variables with $p<0.20$ in the univariate analysis were entered into the multivariable logistic regression model. ORs and 95% CIs are presented. Grades 1-2, T1 disease, invasive ductal carcinoma, and HR-positive/HER2-negative subtype were used as reference categories.
CI: Confidence interval, HER2: Human epidermal growth factor receptor 2, HR: Hormone receptor, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, OR: Odds ratio, pCR: Pathological complete response, TNBC: Triple-negative breast cancer

Discussion

Our analysis showed that nearly one-third of patients achieved a pCR after neoadjuvant systemic therapy. After adjustment for potential confounders, molecular subtype emerged as the strongest determinant of treatment response, with HER2-positive and TNBCs demonstrating significantly greater odds of achieving pCR than HR-positive/HER2-negative disease. In addition, high histological grade independently increased the likelihood of pCR, whereas clinical T3 stage was associated with a reduced treatment response. Neither histological subtype nor the Ki-67 proliferation index remained significant in the multivariable model. Collectively, these findings reinforce the concept that intrinsic tumor biology has a greater influence on response to neoadjuvant therapy than the anatomical extent of disease [7,8].

The frequency of pCR in our study was consistent with the range reported in previous clinical studies of neoadjuvant systemic therapy. Large cohorts of patients with early-stage and locally advanced breast cancer receiving NST have reported overall pCR rates ranging from approximately 20% to 40%. Differences among studies are largely attributable to variations in patient selection, molecular subtype distribution, chemotherapy regimens, and the use of anti-HER2 therapy [9,10]. Considering that the majority of patients in our cohort had HR-positive/HER2-negative disease, the observed pCR rate falls within the expected range.

Among all variables included in the multivariable model, molecular subtype demonstrated the greatest predictive value for achieving pCR. Relative to patients with HR-positive/HER2-negative tumors, those with HER2-positive disease had almost a tenfold increase in the odds of attaining pCR, while those with TNBC had an approximately sixfold increase. These findings further support the concept that intrinsic tumor biology is the principal determinant of responsiveness to neoadjuvant treatment. The favorable outcomes observed in HER2-positive disease largely reflect the introduction of dual HER2 blockade into neoadjuvant treatment protocols, which has substantially increased pCR rates in modern clinical trials, frequently exceeding 60% [11,12]. Similarly, the pronounced responsiveness of TNBC is thought to result from its aggressive biological profile, characterized by rapid cellular proliferation, marked genomic instability, and enhanced susceptibility to cytotoxic chemotherapy, all of which contribute to higher pCR rates than those achieved in HR-positive tumors [13].

High histological grade was another independent factor associated with an increased likelihood of achieving pCR. Although high-grade tumors generally exhibit more aggressive biological behavior, their increased proliferative activity renders them more susceptible to cytotoxic chemotherapy. Several previous studies have similarly demonstrated that high histological grade is associated with improved response to neoadjuvant chemotherapy, and our findings further support these observations [14].

With regard to tumor size, only clinical T3 stage remained a significant negative predictor of pCR. Larger tumors may

exhibit greater intratumoral heterogeneity, more extensive hypoxic regions, and an increased prevalence of treatment-resistant clones, all of which may contribute to reduced treatment sensitivity. Nevertheless, previous studies have consistently suggested that the predictive effect of tumor size is less pronounced than that of molecular subtype, highlighting the dominant role of tumor biology in determining response to neoadjuvant therapy [15].

Although invasive lobular carcinoma and mixed histological tumors demonstrated lower pCR rates in univariate analysis, histological subtype was no longer a significant predictor after adjustment for other clinicopathological variables, indicating that its apparent effect was largely explained by other tumor characteristics. A similar pattern was observed for the Ki-67 proliferation index. Although higher Ki-67 values were associated with pCR in the univariate analysis, this relationship was no longer significant after adjustment for other clinicopathological factors. This finding is likely explained by the strong correlations among Ki-67, molecular subtype, and tumor grade. Recent studies have likewise suggested that Ki-67 provides greater prognostic and predictive value when interpreted in conjunction with intrinsic molecular subtype rather than as a standalone biomarker [16].

This study has several notable strengths. The relatively large patient cohort, together with the availability of detailed clinicopathological information, allowed a comprehensive evaluation of factors potentially associated with pCR. Multivariable logistic regression enabled adjustment for potential confounders, and the high discriminative ability of the final prediction model (AUC=0.869) further supports the reliability of the results.

Study Limitations

Nevertheless, certain limitations should be considered when interpreting these findings. The retrospective design carries an inherent risk of selection bias. Moreover, because the study population was derived from a limited geographic area, caution is warranted when extrapolating the results to other populations. Changes in neoadjuvant treatment strategies over the study period may also have influenced patient outcomes. Finally, several potentially informative biomarkers, including genomic profiling assays, tumor-infiltrating lymphocytes, and PD-L1 expression, were not routinely available and therefore could not be included in the present analysis.

Several limitations should be considered when interpreting the findings of this study. First, the retrospective design inherently carries a risk of selection and information biases, and the availability of clinicopathological variables varied among patients. Second, although the study included a relatively large, real-world cohort from two centers, both of which were located within the same geographic region, the findings may have limited generalizability to other populations and healthcare settings. Third, neoadjuvant treatment strategies evolved during the study period (2015-2025), particularly with the increasing use of HER2-directed therapies and contemporary systemic approaches. Therefore, treatment heterogeneity

over time may have influenced pathological response rates. Potentially informative biomarkers, including genomic profiling assays, tumor-infiltrating lymphocytes, and PD-L1 expression, were not routinely available and, consequently, could not be incorporated into the present analysis. Prospective multicenter studies incorporating standardized treatment protocols and comprehensive molecular and immunological biomarkers are warranted to further validate these findings.

Conclusion

In summary, our findings indicate that intrinsic tumor biology, particularly molecular subtype and histological grade, is a stronger determinant of pCR after NST than anatomical disease extent in invasive breast cancer. Compared with HR-positive/HER2-negative tumors, HER2-positive tumors and TNBC had substantially higher odds of achieving pCR, whereas molecular subtype and histological grade showed stronger independent associations with pCR than did clinical T stage. These findings highlight the importance of incorporating tumor biological characteristics into pretreatment assessment to improve patient stratification and support individualized therapeutic decision-making. Further prospective multicenter studies integrating molecular and immune-based biomarkers are warranted to validate these observations and refine predictive models of treatment response.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethics Committee of Clinical Research, Manisa Celal Bayar University Faculty of Medicine (decision no: 20.478.486/4061, date: 15.04.2026).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.G., Concept: M.U., Design: F.E., Data Collection or Processing: A.P.E., Analysis or Interpretation: E.Z.G., Literature Search: H.S.S., Writing: M.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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