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Risk Factors of Response to Neoadjuvant Chemotherapy in Patients with Luminal (HER2 Negative) Breast Cancer: Roc Curve and Logistic Regression Model Results

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ABSTRACT

Background: Neoadjuvant chemotherapy (NAC) is less effective for luminal human epidermal growth factor receptor 2 (HER2) negative breast cancer (BC) patients and generally shows a low pathological complete response (pCR) after NAC compared to HER2 positive and triple negative breast cancer (TNBC). This study aimed to determine the factors associated with histopathologic response following NAC in luminal (HER2 negative) BC.

Methods: This is a cross-sectional study conducted on 255 estrogen (ER) positive and HER2 negative BC patients after NAC between January 2018 and July 2023. Demographic and clinicopathological characteristics of the patients were collected for the statistical analysis. Chi-Square tests were used in the qualitative comparisons between study groups. Receiver Operating Characteristic (ROC) analysis was used for the diagnostic performance of Ki-67 expression and ER in determining the pCR rates. Using the Youden index, optimum cut points were determined. Also, multivariate logistic regression analysis was applied to determine the independent variables associated with the dependent variable (pCR).

Results: After NAC, pCR was achieved in the breast in 35 (14%) patients, in the axilla in 44 (17%) patients, and in both the breast and axilla in 18 (7%) patients. Ki-67 expression was the only common variable associated with the breast, axilla and both the breast and axilla pCR. The most appropriate Ki-67 expression cut-off value for determining the breast and axilla complete response was found to be 40%. ER positivity level was only associated with pCR in the breast and the cut-off value was found to be 85%.

Conclusion: The results of this study raise the possibility of patients with luminal (HER2 negative) BC with Ki-67 expression higher than 40% benefiting from chemotherapy, as they showed increased pCR rates.

INTRODUCTION

Luminal breast cancers are estrogen receptor (ER) positive and/or progesterone reseptor (PR) positive molecular subtypes that represent the most common subtype of breast cancer (BC).[1] Luminal subtypes of BC are less aggressive compared to human epidermal growth factor receptor 2 (HER2) positive and triple

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negative BC (TNBC) and respond well to the hormone therapy.[2,3] Luminal subtypes of BC are divided into luminal A and luminal B; Luminal A is characterized by the expression of ER and PR, low proliferation (measured by Ki67 expression) and a better prognosis, while luminal B is characterized by the expression of ER and/or PR, HER2 expression, high proliferation and a poorer prognosis compared to luminal A.[4]

In general, luminal HER2-negative patients are advised to receive adjuvant hormone therapy alone. However, there is a subpopulation showing poorer outcomes with the hormone therapy alone. Thus, these patients may benefit from chemotherapy. The efficacy of chemotherapy for patients with luminal tumors is still controversial. Therefore, it is difficult to determine if these patients should be recommended with neoadjuvant chemotherapy or not.[5]

Neoadjuvant chemotherapy (NAC) is the standard treatment for patients with locally advanced breast cancer (LABC) or inoperable BC. NAC is used to minimize the size of breast tumor, thus enabling the performance of breast conserving surgery (BCS) in patients that would have required mastectomy. Also, it is used to remove the metastatic axillary lymph nodes (ALNs) with an increasing need for sentinel lumph node biopsy (ALNB) vs axillary lymph node dissection (ALND) following NAC in both node negative and node positive patients, leading to the avoidance of ALND after a complete response in the axilla.[6-10]

Pathologic complete response (pCR) has been considered as the most important predictor of NAC outcomes and has emerged as an alternative prognostic marker in many clinical trials.[7]

Patients achieving pCR show improved disease-free survival.[6,11,12] The rates of pCR differ according to BC subtype (13). ER negativity, high Ki-67 proliferation index, high histologic grade, and low T stage have been associated with pCR.[14] Despite the better overall prognosis in luminal BC, the pCR rate is lower after NAC.[11,15,16] Patients with luminal BC showed a pCR rate between 6% to 11%. Therefore, NAC is less effective in luminal BC than in other subtypes; thus, the decision to use NAC treatment for these patients still remains a challenge.[7]

Ki-67 is a nuclear protein that is expressed during all phases of the cell cycle, except the G0 phase, and is a marker for tumor proliferation.[17] The potential usefulness of Ki-67 in predicting the likely response and long-term outcome has been explored by assessing pre- and post-treatment levels of Ki-67 expression in NAC studies.[5,18-22] Proliferation biomarkers can predict responsiveness to systemic therapy, with highly proliferative tumors being more responsive to chemotherapy. Thus, Ki-67 might have a valuable role in predicting potential benefits from specific treatments in certain subtypes of BC.

Herein, we investigated some factors including Ki-67 expression, tumor stage and histological grade to predict the response to NAC in patients with luminal (HER2 negative) BC, in order to identify a subpopulation potentially benefiting from chemotherapy.

METHODS

Two hundred fifty-five ER positive and HER2 negative BC patients who were followed up at Istanbul University, Istanbul Faculty of Medicine Breast Surgery Service for surgical treatment after NAC between January 2018 and July 2023 were included in this cross-sectional study. In order to reach this number of patients, a detailed search was performed in the Istanbul Medical Faculty Breast Surgery patient database between September 04, 2023 and September 08, 2023. We used the following inclusion criteria for patient selection: (I) female; (II) Clinical axilla positive (cN1-3), ER(+) HER2-negative invasive breast cancer; and (III) complete data. The exclusion criteria were as follows: (I) infammatory breast cancer; (II) metastatic disease; (III) bilateral breast cancer; and (V) ER(+), HER2-positive breast cancer. The entire patient population within this peroid was included in the study. Therefore, no sample calculation was made in the study. Demographic (age and menopausal status) and clinicopathological characteristics of the patients [cTNM stage, tumor type, clinical tumor size (cT), axillary staging (cN), histological grade, hormone receptor (estrogen, progesterone) status, HER2 status and Ki-67 proliferation index] were collected for the statistical analyses. TNM staging was done according to the American Joint Committee on Cancer (AJCC) 7 version, and molecular subtype identification was made according to the recommendations of the St. Gallen 2013 consensus (3). The clinical research ethics committee of Istanbul University, Istanbul Faculty of Medicine approved the use of patients' medical records and reports in this study (No. 2022/755422).

Pathological Evaluation

The pathological tumor stage was assessed according to the American Joint Committee on Cancer's 7th Staging System.[23] All pathological results were collected from digital records and pathology reports of Istanbul Faculty of Medicine Hospital. Paraffin-embedded tissue obtained from excision specimen was microcut and stained with hematoxylin and eosin (H&E). Ki-67 (clone SP6, 1:100 dilution; Biocare Concord, CA, USA) and hormone reseptors ER (clone SP1, 1:100 dilution;

Biocare Concord, CA, USA) and PR (clone SP2, 1:400 dilution; Spring Pleasanton, CA, USA), HER2 (clone SP3, 1:200 dilution; Thermo Waltham, MA, USA) were evaluated by reviewing the archived glass slides. By tru cut biopsy, hormone receptor determination was performed and all patients were diagnosed with invasive BC. In this study, 1% and more positive nuclear staining in ER or PR was considered positive. HER2 status was determined by immunohistochemical analysis. Patients with HER2 negative and 1+ were considered HER2 negative.

Neoadjuvant chemotherapy

The majority of the patients (n=243, 95.3%) received 4 cycles of adriamycin (60mg/m^2) and cyclophosphamide (500 mg/m^2) plus 12 cycles of weekly paclitaxel (80mg/m^2). Also, 12 patients (4.7%) were treated with 4 cycles of docetaxel in combination with of AC (adriamycin and cyclophosphamide). pCR after NAC was defined as the absence of residual invasive cancer in both breasts and ALNs. The presence of ductal carcinoma in situ in the breast only was also considered as pCR (23).

Statistical Analysis

Descriptive, graphical and statistical methods were used to examine whether the scores obtained from each continuous variable were normally distributed or not. The Kolmogorov-Smirnov test was used to test the normality of the scores obtained from the continuous variable with the statistical method. Categorical variables were presented as frequency (n, %), continuous variables were presented as median and inter quantile range (25th percentile-75th percentile). Chi-Square tests (Pearson chi-square test, Yates' chi-square test and Fisher's exact test) were used in the qualitative comparisons between study groups. Receiver Operating Characteristic (ROC) analysis was used for the diagnostic performance of Ki-67 expression and ER in determining the pCR rates. Using the Youden index, the optimum cut points were determined. Multivariate logistic regression analysis was applied to determine the independent variables associated with the dependent variable (pCR). The strength of the association between dependent and independent variables and The Hosmer-Lemeshow test and Nagelkerke R Square were used to check the goodness of fit of a regression model. The level of significance within the 95% confidence interval was evaluated below P<0.05. All statistical analyses were performed with SPSS (Statistical Package for the Social Sciences) software version 26 (IBM Corp., Armonk, NY, USA).

RESULTS

Patients' characteristics

The study included 255 ER positive, HER2 negative BC patients who received NAC. The median age of the patients was 47 (P_{25}-$P_{75,}$ 39-55) years, and 149 (58%) patients were premenopausal. The tumor type was invasive ductal carcinoma in 217 (85%) patients. Tumor histological grade I/II cancers were observed in 83 (33%), and grade III in 59 (23%) patients, wherase histological grade of 113 (44%) patients was not examined pathologically before NAC. Ki-67 expression level was calculated as median 25% (P_{25}-$P_{75,}$ 20-40). ER was positive in all patients, and PR was positive in 221 (87%) patients. ER positivity was determined as median 90% (P_{25}-$P_{75,}$ 80-95). Based on the results, 43 (17%) patients were luminal A and 212 (83%) were luminal B (Table 1).

In the clinical examination before NAC, 22 (8.6%) patients were cT1, 163 (63.9%) were cT2, 28 (11%) were cT3 and 42 (16.5%) were cT4. 225 (88%) patients were cN1, 18 (7%) were cN2 and 12 (5%) were cN3 (Table 1).

Pathological response rates after NAC

After NAC, pCR was achieved in the breast in 35 (14%) patients, in the axilla in 44 (17%) patients, and in both the breast and axilla in 18 (7%) patients. cT1 and cT2 tumor (17% vs 4%; p=0.013), high histological grade (grade I/II, III and unknown, 6%, 24% and 14%; p=0.010), high Ki-67 expression (40% vs 25%; p=0.031) and low ER positivity (80% vs 90%; p=0.011) were statistically significantly associated with breast pCR.

High Ki-67 expression (35% vs 25%; p=0.002) was statistically significantly associated with axilla pCR. Additionally, high histological grade (grade I/II, III and unknown, 1.2%, 15% and 7%; p=0.006) and high Ki-67 expression (43% vs 25%; p=0.001) were statistically significant with both the breast and axilla pCR (Table 1).

ROC analysis results

Ki-67 expression was the only common independent variable associated with the breast, axilla and both the breast and axilla pCR. Ki-67 expression diagnostic performance was higher in determining pCR in both the breast and axilla (AUC, 0.74, CI, 0.62 to 0.87)

The most appropriate Ki-67 expression cut-off value for determining breast and axilla pCR was found to be 40%. For the detected 40% cut-off value, sensitivity, specificity and accuracy were found to be 78%, 70% and 71%, respectively. ER positivity level was only associated with pCR in the breast.

Table 1. Characteristics of the patients and pathological complete response rates

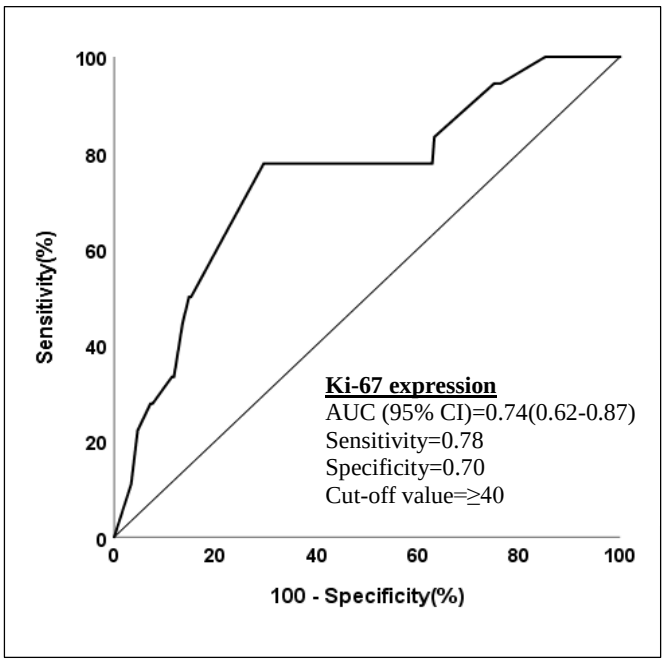
		Pathological Complete Response (pCR)					
		Breast		Axilla		Breast+Axilla	
Variables	All	Yes	No	Yes	No	Yes	No
All, n(%)	255(100)	35(13.7)	220(86.3)	44(17.3)	211(82.7)	18(7.1)	237(92.9)
Age, year[#]	47(39-55)	47(38-53)	47(39-56)	48(38-55)	47(39-55)	51(44-55)	47(39-55)
Test/*P*-value		Z=-0.343/p=0.731		Z=-0.066/p=0.947		Z=-1.045/p=0.296	
Menopausal status, n(%)							
Premenopausal	149(58.4)	21(14.1)	128(85.9)	23(15.4)	126(84.6)	8(5.4)	141(94.6)
Postmenopausal	106(41.6)	14(13.2)	92(86.8)	21(19.8)	85(80.2)	10(9.4)	96(90.6)
Test/*P*-value		$\chi2=0.000^{b}$/p=0.986		$\chi2=0.552^{b}$/p=0.457		$\chi2=1.002^{b}$/p=0.317	
Tumor type, n(%)							
IDC	217(85.1)	33(15.2)	184(84.8)	36(16.6)	181(83.4)	17(7.8)	200(92.2)
ILC	19(7.5)	2(10.5)	17(89.5)	4(21.1)	15(78.9)	1(5.3)	18(94.7)
Mixed (IDC+ILC)	12(4.7)	0(0)	12(100)	2(16.7)	10(83.3)	0(0)	12(100)
Other	7(2.7)	0(0)	7(100)	2(28.6)	5(71.4)	0(0)	7(100)
Test/*P*-value		$\chi2=2.278^{c}$/p=0.452		$\chi2=1.472^{c}$/p=0.699		$\chi2=0.402^{c}$/p=0.915	
Histological grade, n(%)							
I/II	83(32.5)	5(6)	78(94)	13(15.7)	70(84.3)	1(1.2)	82(98.8)
III	59(23.1)	14(23.7)	45(76.3)	15(25.4)	44(74.6)	9(15.3)	50(84.7)
Unknown	113(44.3)	16(14.2)	97(85.8)	16(14.2)	97(85.8)	8(7.1)	105(92.9)
Test/*P*-value		$\chi2=9.161^{a}$/p=0.010*		$\chi2=3.663^{a}$/p=0.160		$\chi2=10.376^{a}$/p=0.006*	
cT stage, n(%)							
I-II	185(72.5)	32(17.3)	153(82.7)	36(19.5)	149(80.5)	15(8.1)	170(91.9)
III-IV	70(27.5)	3(4.3)	67(95.7)	8(11.4)	62(88.6)	3(4.3)	67(95.7)
Test/*P*-value		$\chi2=6.203^{b}$/p=0.013*		$\chi2=1.766^{b}$/p=0.184		$\chi2=N/A^{c}$/p=0.413	
cN stage, n(%)							
I	225(88.2)	30(13.3)	195(86.7)	40(17.8)	185(82.2)	15(6.7)	210(93.3)
II-III	30(11.8)	5(16.7)	25(83.3)	4(13.3)	26(86.7)	3(10)	27(90)
Test/*P*-value		$\chi2=N/A^{c}$/p=0.578		$\chi2=N/A^{c}$/p=0.797		$\chi2=N/A^{c}$/p=0.453	
ER(%)[#]	90(80-95)	80(75-90)	90(80-95)	90(71-95)	90(80-95)	85(71-90)	90(80-95)
Test/*P*-value		Z=-2.536/p=0.011*		Z=-0.850/p=0.395		Z=-1.699/p=0.089	
PR							
Positive	221(86.7)	30(13.6)	191(86.4)	37(16.7)	184(83.3)	14(6.3)	207(93.7)
Negative	34(13.3)	5(14.7)	29(85.3)	7(20.6)	27(79.4)	4(11.8)	30(88.2)
Test/*P*-value		$\chi2=N/A^{c}$/p=0.793		$\chi2=0.095^{b}$/p=0.757		$\chi2=N/A^{c}$/p=0.275	
Ki-67 expression(%)[#]	25(20-40)	40(20-50)	25(20-40)	35(25-58)	25(15-40)	43(35-71)	25(20-40)
Test/*P*-value		Z=-2.158/p=0.031*		Z=-3.164/p=0.002*		Z=-3.471/p=0.001*	
Molecular subtypes, n(%)							
Luminal A	43(16.9)	5(11.6)	38(88.4)	4(9.3)	39(90.7)	1(2.3)	42(97.7)
Luminal B	212(83.1)	30(14.2)	182(85.8)	40(18.9)	172(81.1)	17(8)	195(92)
Test/*P*-value		$\chi2=0.038^{b}$/p=0.845		$\chi2=1.670^{b}$/p=0.196		$\chi2=N/A^{c}$/p=0.324	

*p<0.05, **a:** Pearson chi-square test, **b:** Yates' chi-square test, **c:** Fisher's exact test, **Z:** Mann-Whitney U test, **N/A:** Not Available, **IDC:** Invasive Ductal Carcinoma, **ILC:** Invasive Lobular Carcinoma, **ER:** Estrogen Receptor, **PR:** Progesterone Feceptor. [#]Median **(**25th percentile-75th percentile)

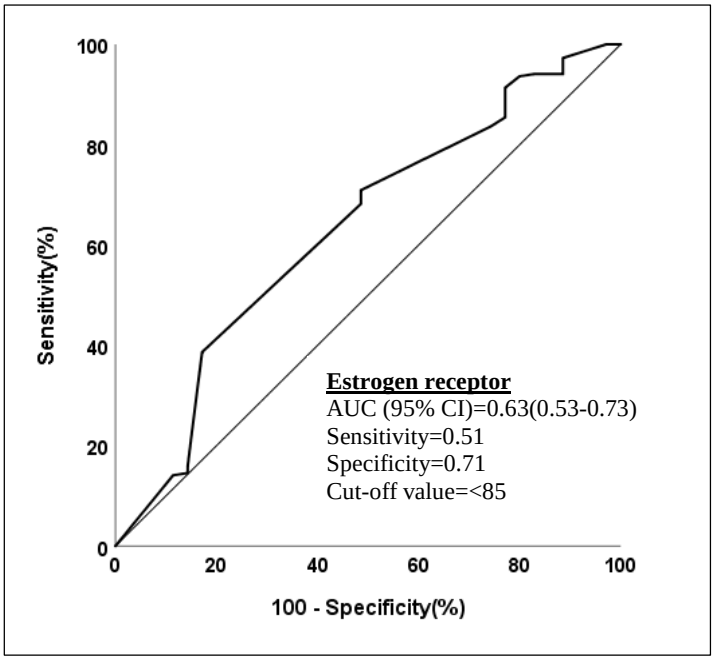
While the cut-off value for the ER positivity level in determining breast pCR was determined as 85% (AUC, 0.63, CI, 0.53 to 0.73; *p*=0.013), for the 85% cut-off value, sensitivity, specificity and accuracy were determined as 51%, 71% and 68%, respectively (Figure 1).

Independent factors associated with pathologic complete response

To identify independent variables associated with the pathologic response in the breast (model, $\chi2=25.81$; P<0.001) and in both the breast and axilla (model, $\chi2=21.58$; P<0.001) after NAC, variables with a P-value of 0.1 or less were used in the analyses. These variables were included in multiple logistic regression using the enter method. The association between the independent variables of the model and the dependent variable was examined; Independent factors that increase breast pathological complete response were cT1 and cT2 (OR=4.2, CI=1.2 to 14.5; *p*=0.024), <85% ER positivity (OR=2.4, CI=1.1 to 5.1; P=0.024) and ≥40% Ki-67 expression (OR=2.7, CI=1.3 to 5.9; P=0.011). However, it was determined that the only independent factor increasing both the breast and axilla pCR was ≥40% Ki-67 expression (OR=6.9, CI=2.1 to 22.1; P=0.001).



A-) Ki-67 expression diagnostic performance in determining Breast+Axilla pathological complete response



B-) Estrogen receptor diagnostic performance in determining breast pathological complete response

Table 2. Independent factors associated with pathologic complete response

	Breast Pcr					
	Unadjusted OR	Adjusted OR				
Variables	OR(95% CI)	B	SE	OR(95% CI)	P-value	Model Summary
cT stage(I/II vs III/IV**)	4.671(1.382-15.786)	1.430	0.635	4.178(1.203-14.504)	0.024*	Method=Enter
Histological grade (III vs others**)	2.593(1.223-5.496)	0.668	0.412	1.950(0.869-4.373)	0.105	$\chi 2$=25.81
Estrogen receptor (<85% vs ≥85%**)	2.581(1.251-5.323)	0.875	0.387	2.399(1.124-5.121)	0.024*	p<0.001
Ki-67 expression (<40%** vs ≥40%)	3.250(1.566-6.744)	1.006	0.394	2.735(1.263-5.924)	0.011*	R^2_N=0.20
Constant	N/A	-3.994	0.670	0.018	<0.001	
	Breast+Axilla pCR					
	Unadjusted OR	Adjusted OR				
Variables	OR(95% CI)	B	SE	OR(95% CI)	P-value	Model Summary
Histological grade (III vs others**)	3.740(1.41-9.917)	0.918	0.526	2.504(0.894-7.013)	0.081	Method=Enter
Estrogen receptor (<85% vs ≥85%**)	2.247(0.857-5.892)	0.717	0.518	2.049(0.742-5.657)	0.166	$\chi 2$=21.58
Ki-67 expression (<40%** vs ≥40%)	8.350(2.655-26.258)	1.925	0.597	6.856(2.126-22.111)	0.001*	p<0.001
Constant	N/A	-4.228	0.586	0.015	<0.001	R^2_N=0.20

*P<0.05, Multivariate logistic regression, B=Regression coefficient , Dependent variable=pCR(1=yes, 0=no), SE:Standard error, OR:Odds ratio, CI:confidence interval, **:Reference level, R^2_N: Nagelkerke R Square, N/A: Not available

DISCUSSION

Treatment management according to the molecular subgroups in LABC is still being a challenge. Treatment management is more difficult and controversial in luminal subgroups compared to locally advanced stage TNBC and HER2 positive subtypes. Surgical treatment is an option in patients with non-metastatic locally advanced luminal subtype with ALNs involvement. NAC can be applied to this group to minimize the size of the tumor and make it suitable for BCS and to protect patients from unnecessary ALND.

Achieving pCR has become one of the most important factors determining patient survival in

studies conducted in LABC without subtypes distinction.[24,25] Many studies have examined response to treatment in LABC but almost all of them examined TNBC or HER2 positive subtypes that highly responded to treatment. Very few studies have examined luminal A and B subtypes.[26] It has been reported that the pCR rate in hormone-positive, HER2 negative LABC is approximately 10% or below. In the luminal A subtype group, this rate is lower and is below 5%.[27,28] In our study, consistent with the literature, pCR was determined as 2.3% in the luminal A group and 8% in the luminal B group, for a total of 7.1%.

It is known that cT and cN are insufficient to predict NAC response, since the clinical TNM classification before NAC does not fully reflect the pathological staging.[29] While some studies have reported an association between cT and cN and pCR[27,28], other studies have reported that there is no association between cT and cN stage and pCR (30). In this study, cN stage had no statistical association with pCR (P>0.05). However, cT stage had a statistically significant association only with breast pCR, and cT1 and cT2 tumors had a higher breast pCR compared to cT3 and cT4 tumors (17% vs 4%; P<0.05).

In many studies, it has been reported that the Ki-67 staining rate in hormone positive tumors determines the NAC response and is associated with the prognosis of patients.[18] In our study, the median of Ki-67 expression was determined as 25% (IQR, 20% and 40%) and the pCR rate was significantly higher in tumors with high Ki-67 expression (P<0.05). Furthermore, in univariate and multivariate analysis, Ki-67 expression was the only independent variable associated with pCR in the breast, axilla, and both breast and axilla. In Horimoto *et al.* study, they reported that the pCR rate was significantly higher in patients with luminal (HER2 negative) tumors with high Ki-67 expression, and that the Ki-67 cut-off value which separates patients with pCR from other cases was 35%.[5] In this study, we determined the Ki-67 cut-off value, which differentiates patients with pCR from other patients, at 40% (AUC, 74%). The diagnostic performance of the Ki-67 cut-off value we determined was high (sensitivity and specificity, 78% and 70%, respectively).

In a study by Kim *et al.*[7] which compared luminal (HER2 negative) and non-luminal (HER2 negative) tumors, it was reported that histologic grade had no association with pCR in the luminal group in both univariate and multivariate analyses. In a study by Collins *et al.*, where they examined only lumina A tumors, it was reported that pCR was statistically significantly higher in grade III tumors.[27] In our study, in the univariate analysis, the pCR rate of tumors with histologic grade III was higher (P<0.05); In multivariate analysis, histological tumor grade was not an independent risk factor for chemotherapy response (P>0.05).

It has been reported that ER and/or PR negative tumors have better treatment responses after NAC.[5,28,31] In a study by Boughey *et al.*, it was reported that ER positivity level ≤70% in the luminal group was an independent factor increasing breast pCR and axillary pCR.[35] In our study, it was observed that PR negativity did not contribute to the increase in pCR, but ER positivity <85% increased breast pCR.

The limitation of this study is that it is a single-center retrospective study and there is no survival analysis data to support the findings. In order to perform survival analysis, we need a median follow-up period of at least 3-5 years.

CONCLUSION

In our study, high tumor burden, ≥85% ER positivity and low Ki-67 expression level were found to be independent factors that increase the risk of partial breast response. We found that luminal (HER2 negative) subtype patients with Ki-67 protein expression of over 40% would benefit most from NAC. However, this Ki-67 limit needs to be supported by long-term survival analyses. The risk of not receiving a complete response to chemotherapy in the luminal B subtype was not lower than in the luminal A subtype. Additionaly, demographic variables (age and menopausal status), cN stage, PR negativity and molecular subtypes had no statistical effect on achieving NAC complete response.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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ETHICAL CONSIDERATIONS

The clinical research ethics committee of Istanbul University, Istanbul Faculty of Medicine approved the use of patients' medical records and reports in this study (No. 2022/755422).

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