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Research Article

Breast Cancer Patients Receiving Neoadjuvant Chemotherapy: Clinical, Pathological and Survival Characteristics and Factors Predicting Complete Response

Mukaddes Yılmaz,[1] Eda Erdiş,[2] Mahmut Uçar,[1] Birsen Yücel[2]

[1]Department of Medical Oncology, Cumhuriyet University Faculty of Medicine, Sivas, Türkiye
[2]Department of Radiation Oncology, Cumhuriyet University Faculty of Medicine, Sivas, Türkiye

Abstract

Objectives: To investigate the clinical, pathological, and survival characteristics of locoregional breast cancer patients receiving neoadjuvant chemotherapy (NACT).

Methods: Breast cancer patients at Cumhuriyet University Oncology Center between January 2010 and December 2022 were evaluated retrospectively.

Results: The study included 177 patients. After NACT, 43 (24%) of the patients achieved pCR. Pre-NACT clinicopathological data, including age (p=0.045), cN stage (p=0.038), ER status (p=0.004), PR status (p=0.019), HER2 status (p<0.001), Ki-67 percentage (p=0.001), molecular subtyping (p<0.001), axillary intervention (p<0.001), use of adjuvant hormone therapy (p=0.002), grade (p=0.044), distant metastasis (p<0.001), overall survival (OS, p=0.005), and disease-free survival (DFS, p=0.003), were significantly different between patients who achieved pCR and nonpCR patients. Menopausal status (p=0.044), HER2 status (p<0.001), Ki-67 status (p=0.001), molecular subtyping (p=0.031), and pertuzumab use (p=0.044) were identified as predictive factors for pCR.

Conclusion: Patients who achieved pCR were younger; had higher Ki-67 percentage; had lower ER and PR positivity; had higher HER2 positivity; had grade 3 disease; and had better OS and DFS. Being premenopausal, having HER2 positivity, having a Ki-67 percentage greater than 25, being in the HER2-positive molecular subtype, and receiving pertuzumab were favorable predictive factors for pCR.

Keywords: Breast cancer, clinical features, discordance, immunohistochemical characteristics, neoadjuvant treatment, pathological complete response, survival

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Neoadjuvant chemotherapy (NACT) is a systemic chemotherapy treatment performed before curative surgery. It is increasingly used to treat early-stage, high-risk breast cancer patients who are eligible for surgery.[1,2] The purpose of this treatment is to downstage the tumor, control early microscopic disease, and offer more patients the option of breast-conserving surgery (BCS) instead of mastectomy. Studies have shown that NACT increases the success rate of BCS by reducing the tumor stage.[2,3] Additionally, NACT aims to enable less extensive surgery, thereby improving cosmetic outcomes, which are a significant concern for women, and reducing postoperative complications such as lymphedema. It also allows for early patient-based assessment of the effectiveness of the systemic treatment provided. In ad-

Address for correspondence: Mukaddes Yılmaz, MD. Department of Medical Oncology, Cumhuriyet University Faculty of Medicine, Sivas, Türkiye
Phone: +90 506 356 66 17 **E-mail:** ylmzmukaddes@gmail.com

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dition to these clinical benefits, identifying tumor characteristics that may indicate treatment response or resistance is also possible through changes in the immunohistochemical (IHC) pattern of the tumor before and after treatment.

Patient treatments were planned based on the tumor IHC results from the core needle biopsy (CNB) of the breast mass taken before NACT. After NACT, the residual invasive tumor characteristics in the surgical specimen (SS) were evaluated. The correlation between tumor characteristics and both specimens and between the presence of these characteristics and the pattern of tumor response and survival continue to be of interest. Changes in hormone receptor (HR) expression following chemotherapy are important in breast cancer treatment because they play a significant role in this disease. The shift from negative to positive receptor status becomes more meaningful in terms of planning adjuvant treatment. Studies have detected more progesterone receptor (PR) than estrogen receptor (ER) expression in patients with CNB and SS, and this difference mostly manifests as a shift from HR positivity to negativity.[4-7] Changes in human epidermal growth factor receptor 2 (HER2) staining characteristics have also been evaluated. Studies suggest that changes in HER2 status between CNB and SS occur less frequently than HR changes and that HER2 status may be less sensitive to the effects of NACT (8,9). Additionally, it has been reported that a positive transformation in HER2 staining characteristics is more common than a negative transformation.[8,9] In nonpCR patients, residual disease allows for the development of new treatment strategies related to adjuvant therapy. Thus, in high-risk HER2-positive and triple-negative breast cancer (TNBC) patients, it is possible to anticipate additional benefits from NACT in patients whose HR negativity becomes positive.

Studies have shown no difference in overall survival (OS) or disease-free survival (DFS) between patients receiving adjuvant or neoadjuvant treatments.[1,2] The most significant prognostic factor for better survival outcomes is pathological complete response (pCR), although most patients in clinical practice do not achieve pCR.[10-12] Among the breast cancer subtypes, pCR is most common in TNBC and HER2-positive breast cancer.[11-13] Furthermore, the characteristics of tumors that can achieve pCR, the most effective treatment combinations, and factors predicting treatment efficacy and clinical outcomes continue to be examined. In patients without a pCR, the prognosis is worse, and identifying potential biomarkers to distinguish these patients with different survival outcomes is crucial.

Our study aimed to investigate the clinical, pathological, and survival characteristics of locoregional breast cancer patients receiving NACT and to identify factors that can predict pCR.

Methods

This retrospective study was conducted with 177 patients diagnosed with clinical stage II-III breast cancer who received NACT and subsequently underwent surgery at Cumhuriyet University Medical Faculty Oncology Center between January 2010 and December 2022. The study received ethical approval from the Ethics Committee of Cumhuriyet University Faculty of Medicine (Date 18.04.2024/No. 2024/04-38). Written informed consent could not be obtained due to the retrospective nature and unanimous nature of the data.

Patient Selection

This study included women aged 18 and older, diagnosed with stage II-III breast cancer, who completed NACT and subsequently underwent surgery. Clinicopathological information was obtained from medical records, biopsies of the breast and/or axillary lymph nodes, and postsurgical pathological reports. Patients aged less than 18 years, at the metastatic stage, without clinical-radiological staging, who did not complete NACT or who did not undergo surgery, or who had untreated breast cancer were excluded. Patients receiving neoadjuvant hormonal therapy were also excluded from the study. Patients with a history of secondary malignancy, including breast cancer, were excluded due to potential influence on the outcomes. At diagnosis, age, menopausal status, treatment during follow-up, region at which breast cancer recurred, and vital status (whether the patient was alive or deceased) were collected from medical records. Patients who had been amenorrheic for more than six months before the diagnosis of breast cancer, who received hormone replacement therapy, or who were at least 50 years old without menopausal status noted in medical records were considered postmenopausal.

The performance status of the patients was based on the Eastern Cooperative Oncology Group (ECOG) scoring system. At the time of diagnosis, all patients were staged according to the Eighth Edition American Joint Committee on Cancer (AJCC) staging manual. Presurgical clinical T (cT) and clinical N (cN) stages and postoperative pathological T (pT) and pathological N (pN) stages were defined. pCR was assessed as no invasive cancer in the breast or axillary lymph nodes following neoadjuvant systemic treatment (as defined in the American Joint Committee on Cancer (AJCC) staging system ypT0/Tis (in situ tumor) ypN0).[14]

All patients were diagnosed via CNB from the breast mass and/or axillary lymph node prior to NACT. ER, PR, HER2, and Ki-67 levels were determined via IHC staining. The HR test (ER and PR) was performed using the method specified in the American Society of California and Prevention (ASCO)/CAP HR testing guidelines.[15] Cells expressing 1-100% ER or PR were considered HR-positive.

HER2 testing was conducted using IHC or single- or dual-probe in situ hybridization (ISH) tests. IHC 3+ patients were considered HER2-positive. However, IHC 2+ cases were determined based on concurrent IHC and in situ hybridization (ISH) results.[16] The molecular subgroup definitions of the patients were based on the St. Gallen International Expert Consensus on the Primary Treatment of Early Breast Cancer 2011.[17]

The time from the date of diagnosis to the date of last follow-up or death was evaluated as overall survival (OS), the time from the date of diagnosis to the date of relapse/distant metastasis, the date of death, and the date of last follow-up in those who did not develop relapse/metastasis were evaluated as disease-free survival (DFS).

Treatment

For HER2-negative patients, neoadjuvant chemotherapy included 4 cycles of anthracycline and cyclophosphamide (AC, 60 mg/m^2 adriamycin and 600 mg/m^2 cyclophosphamide, administered every 3 weeks or dose-dense every 2 weeks), followed by 4 cycles of paclitaxel (175 mg/m^2 every 3 weeks or 80 mg/m^2 weekly for 12 weeks) or 4 cycles of docetaxel and cyclophosphamide (TC, docetaxel 75 mg/m^2 every 3 weeks and cyclophosphamide 600 mg/m^2 every 3 weeks).

For the 67 HER2-positive patients, 34 received 4 cycles of neoadjuvant anthracycline and cyclophosphamide (AC, 60 mg/m^2 adriamycin and 600 mg/m^2 cyclophosphamide, administered every 3 weeks or dose-dense every 2 weeks), followed by 4 cycles of paclitaxel (175 mg/m^2 every 3 weeks or 80 mg/m^2 weekly for 12 weeks), trastuzumab (6 mg/kg every 3 weeks or 2 mg/kg weekly), or 4 cycles of AC followed by 4 cycles of docetaxel (75 mg/m^2) + trastuzumab (6 mg/kg every 3 weeks).

Especially after 2019, of the 67 HER2-positive patients, 33 received neoadjuvant therapy after AC (4 cycles of pertuzumab (420 mg/kg every 3 weeks) + trastuzumab (6 mg/kg every 3 weeks or 2 mg/kg weekly) + paclitaxel (175 mg/m^2 every 3 weeks or 80 mg/m^2 weekly for 12 weeks) or docetaxel (75 mg/m^2 every 3 weeks). All patients received at least 4 cycles of NACT. For HER2-positive patients, adjuvant trastuzumab treatment was completed for 1 year.

HR-positive patients were given hormonotherapy (for at least 5 years in relapsed/metastasis-free patients or until relapse/metastasis). Premenopausal patients were started on tamoxifen, postmenopausal patients were started on aromatase inhibitors, and patients with lymph node involvement were treated for up to 10 years. In premenopausal patients with lymph node involvement, ovarian suppression therapy with an Luteinizing Hormone Releasing Hormone (LHRH) analog was combined with hormonotherapy for 3 years. Post-NACT, patients with residual TNBC received adjuvant treatment with capecitabine for 1 year.

Adjuvant radiotherapy (RT) was indicated according to the clinical stage. Adjuvant RT was used in all patients who underwent breast-conserving surgery, and those who underwent modified radical mastectomy and had tumors larger than 5 cm and positive surgical margins underwent whole-breast and chest wall irradiation. In patients with positive lymph nodes, axillary and supraclavicular lymph nodes were added to the radiotherapy field. RT was given at 1.8-2 Gy daily for a total dose of 50 Gy to the whole breast, chest wall and lymphatic areas, while a 10-16 Gy boost was added to the tumor bed during breast-conserving surgery.

Statistics

SPSS version 23 (IBM Corp., Armonk, New York, USA) was used for statistical analysis. Descriptive statistics (frequencies, percentages, medians) are presented in Table 1 to determine the clinicopathological characteristics before and after NACT. The McNemar test was used in Table 2 to calculate the changes in ER, PR, HER2, and molecular subtypes in nonpCR patients post-NACT, and the Wilcoxon test was used to determine changes in the median percentages of ER, PR, and Ki67. In Table 3, the chi-square test (for categorical variables such as menopausal status, clinical stage, ER and PR status, HER2 status, grade, etc.), Student's t test (for non-categorical variables such as age and Ki67 expression), and Kaplan–Meier test were used to compare the clinicopathological and survival outcomes between pCR patients and non–pCR patients. A multivariable logistic regression model was used to determine the factors predicting pCR. P values <0.05 were considered to indicate statistical significance.

Results

This study retrospectively evaluated 177 patients diagnosed with invasive breast carcinoma who underwent surgery post-NACT. The median follow-up period was 46 months (8-155 months). The median age of the patients was 49 years (25-82), with 92 (52%) premenopausal and 85 (48%) postmenopausal patients. All included patients had ECOG PS 0 and 1 (PS 0; 118 (67%) and PS 1; 59 (33%) patients, respectively). Regarding tumor histopathology, 161 (91%) patients had invasive ductal carcinoma, 4 (2%) had invasive lobular carcinoma, 3 (2%) had mixed tumors, and 9 (5%) had other histological subtypes. All patients underwent surgery; 128 (72%) underwent mastectomy, and 49 (28%) underwent BCS. For axillary intervention, 54 (30%) patients underwent sentinel lymph node biopsy (SLNB), and 123 (70%) patients underwent ALND. Adjuvant RT was administered to 176 (99%) patients; 1 patient declined RT.

Table 1 presents the clinicopathological characteristics of all patients before NACT (at CNB) and after surgery (at SS). Post-NACT, among the operated patients, 43 (24%) exhib-

Table 1. Comparison of clinicopathological features of all patients before and after NACT

	Pre-NACT (CNB)		Postop (SS)*	
	n	%	n	%
T stage				
T0/Tis	4	2**	53	30
T1	19	11	63	36
T2	101	57	46	26
T3	21	12	12	7
T4	32	18	3	2
N stage				
N0	17	10	75	42
N1	58	33	47	27
N2	54	30	33	19
N3	48	27	22	12
Stage				
I	-	-	24	14
II	76	43	52	29
III	101	57	58	33
pCR	-	-	43	24
ER				
Negative	48	27	29	22
positive	129	73	105	78
PR				
Negative	61	34	49	37
Positive	116	66	85	63
HER2				
Negative	110	62	104	78
Positive	67	38	30	22
Ki-67, median %	25 (1-98)		10 (0-90)	
Grade				
1	25	14	15	11
2	92	52	76	57
3	60	34	43	32
Molecular subtype				
ER+ and/or PR+, HER2-negative	86	49	86	64
HER2-positive	67	38	27	20
Triple Negative	24	13	21	16
NACT response				
pCR	-	-	43	24
Partial response	-	-	99	56
Stabile/progressive	-	-	35	20
Lymphovascular invasion	-	-	67	50
Perineural invasion	-	-	36	27
DCIS	-	-	86	64
Multi-centricity/focality	-	-	28	21
Tumor necrosis	-	-	26	19
Extracapsular invasion	-	-	66	49

*: In this column, ER, PR, HER2, Ki67, grade, molecular subtypes, lymphovascular invasion, perineural invasion, DCIS, multicentricity/multifocality, tumor necrosis, extracapsular invasion status were evaluated on SS in 134 patients with residual invasive tumors; **: Patients presenting with axillary involvement only. NACT: Neoadjuvant chemotherapy; CNB: Core needle biopsy; SS: Surgical specimen; T stage: Tumor stage; Tis: In situ tumor; N stage: Nodal stage; pCR: Pathologic complete response; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; DCIS: Ductal carcinoma in situ.

Table 2. Changes in the pathological characteristics of patients who did not achieve a pCR after NACT

	Pre-NACT (CNB)		Postop (SS)*		Discordances (%)	p
	n	%	n	%		
ER						
Negative	29	22	29	22	4	0.995
Positive	105	78	105	78		
ER, median %	90 (3-100)		85 (0-100)			0.161
PR						
Negative	40	30	49	37	10	0.022
Positive	94	70	85	63		
PR, median %	70 (2-100)		50 (0-100)			<0.001
HER2						
Negative	97	72	104	78	7	0.065
Positive	37	28	30	22		
Ki-67, median %	25 (1-98)		10 (0-90)			<0.001
Molecular subtype						
ER+ and/or PR+, HER2-negative	79	59	86	64	12	0.026
HER2-positive	37	28	27	20		
Triple Negative	18	13	21	16		

pCR: Pathologic complete response; NACT: Neoadjuvant chemotherapy; CNB: Core needle biopsy; SS: Surgical specimen; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2.

ited a pCR, and 35 (20%) showed stable/progressive responses. Only 6 pCR patients (11%) had ypTis. In nonpCR patients with residual invasive tumors postsurgery, 50% exhibited lymphovascular invasion (LVI), 27% had perineural invasion (PNI), and 49% had extracapsular invasion according to the SS evaluation.

Table 2 provides the pathological changes (discordance) identified based on the assessments of the CNB and SS for nonpCR patients. Discordance was found for 4% of the patients with ER, 10% of the patients with PR, 7% of the patients with HER2, and 12% of the patients with different histological subtypes. The results indicated statistically significant reductions in PR positivity (p=0.022), median PR percentage (p<0.001), Ki-67 percentage (p<0.001), and changes in molecular subtypes (p=0.001).

Table 3 compares the pre-NACT pathological features, treatments, and clinical outcomes between patients who achieved a pCR and patients who did not. Significant differences were found between the groups in terms of age (p=0.045, Ki-67 percentage (p=0.001), cN stage (p=0.038), ER status (p=0.004), PR status (p=0.019), HER2 status (p<0.001), molecular subtyping (p<0.001), axillary intervention (p<0.001), use of adjuvant hormone therapy (p=0.002), tumor grade (p=0.044), distant metastasis (p<0.001), overall survival (OS, p=0.005), and disease-free survival (DFS, p=0.003). Figures 1 and 2 display the curves for OS and DFS, respectively.

Table 4 shows the factors predicting pCR according to the multivariable logistic regression model. According to this model, menopausal status (p=0.044), HER2 status (p<0.001), Ki-67 status (p=0.001), HER2-positive subgroup (p=0.031), and the use of pertuzumab (p=0.044) were identified as predictors of pCR.

Discussion

In this study, evaluating the outcomes of breast cancer patients receiving neoadjuvant chemotherapy (NACT), a pathological complete response (pCR) was detected in 24% of patients, while 20% exhibited no response to NACT. significant discordance was observed in the PR status and molecular subtyping post-NACT, with notable decreases in the PR and Ki67 percentages. Significant differences were found between the pCR and nonpCR patient groups in clinical N stage; ER, PR, and HER2 status; Ki-67 percentage; molecular subtyping; grade; axillary intervention; distant metastasis; overall survival (OS); and disease-free survival (DFS). Menopausal status, HER2 status, Ki-67 status, tumor grade, molecular subtyping, and the use of pertuzumab were identified as predictors of pCR.

NACT has been increasingly used in recent years. The primary reasons include shrinking the tumor to allow for additional breast-conserving surgeries (BCSs) and reducing axillary involvement to avoid axillary dissection. Another reason is to propose systemic treatment in patients at

Table 3. Comparison of pathologic features, treatments and clinical outcomes between patients who achieved a pCR and nonpCR patients via CNB before NACT

	pCR n=43 (24%)		Non-pCR n= 134 (76%)		p
	n	%	n	%	
Menopausal status					
Premenopausal	26	60	66	49	0.134
Postmenopausal	17	40	68	51	
Age, median (min-max)	47 (25-69)		50 (26-82)		0.045
Ki-67, median %	45 (5-90)		25 (1-98)		0.001
cT stage					
T0	-	-	4	3*	0.287
T1	5	12	14	10	
T2	27	63	74	55	
T3	7	16	14	10	
T4	4	9	28	21	
cN stage					
N0	6	14	11	8	0.038
N1	17	40	41	31	
N2	6	14	48	36	
N3	14	33	34	25	
Clinical stage					
II	23	54	53	40	0.077
III	20	46	81	60	
ER					
Negative	19	44	29	22	0.004
Positive	24	56	105	78	
PR					
Negative	21	49	40	30	0.019
Positive	22	51	94	70	
HER2					
Negative	13	30	97	72	<0.001
Positive	30	70	37	28	
Molecular subtype					
ER+ and/or PR+, HER2-negative	7	16	79	59	<0.001
HER2-positive	30	70	37	28	
Triple Negative	6	14	18	13	
Breast surgery					
Mastectomy	29	67	99	74	0.263
BCS	14	33	35	26	
Axillary intervention					
SBLN	24	56	30	22	<0.001
ALND	19	44	104	78	
Adjuvant RT					
No	1	2	-	-	0.243
Yes	42	98	134	100	
Adjuvant hormonotherapy					
No	19	44	26	19	0.002
Yes	24	56	108	81	
Grade					
1	10	23	15	11	0.044
2	16	37	76	57	
3	17	40	43	32	

Table 3. Cont.

	pCR n=43 (24%)		Non-pCR n= 134 (76%)		p
	n	%	n	%	
Recurrence					
Absent	42	98	131	98	0.675
Present	1	2	3	2	
Metastasis					
Absent	40	93	90	67	<0.001
Present	3	7	44	33	
Overall survival					
The 5-year (%)	96		60		0.005
The median (month)	NR		86		
Disease-free survival					
The 5-year (%)	91		57		0.003
The median (month)	NR		78		

*: Patients presenting with axillary involvement only. pCR: Pathologic complete response; non-pCR: Non-pathologic complete response; CNB: Core needle biopsy; NACT: Neoadjuvant chemotherapy; cT stage: Clinical T stage; cN stage: Clinical N stage; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; BCS: Breast conserving surgery; SLNB: Sentinel lymph node biopsy; ALND: Axillary lymph node dissection.

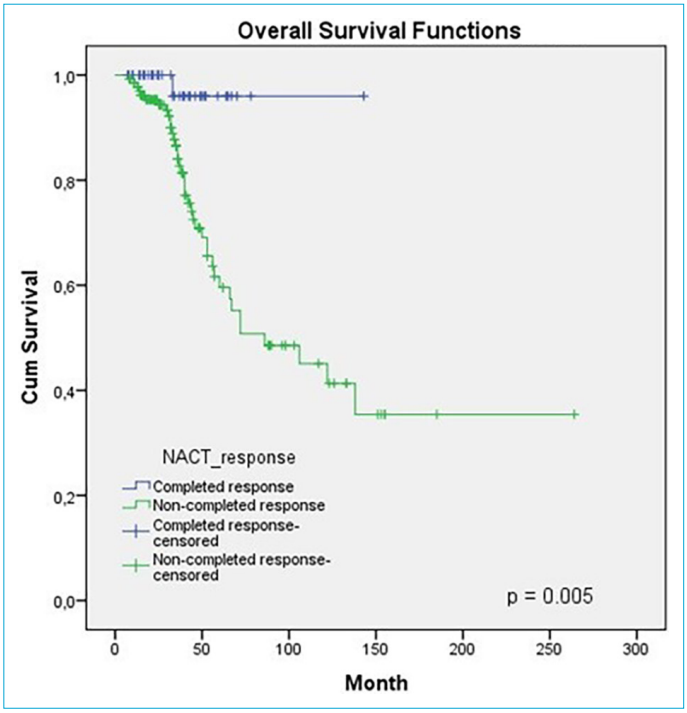

Figure 1. Overall survival curves of patients who achieved a pCR and nonpCR after NACT.

NACT: Neoadjuvant chemotherapy; pCR: Pathologic complete response; non-pCR: Non-pathologic complete response.

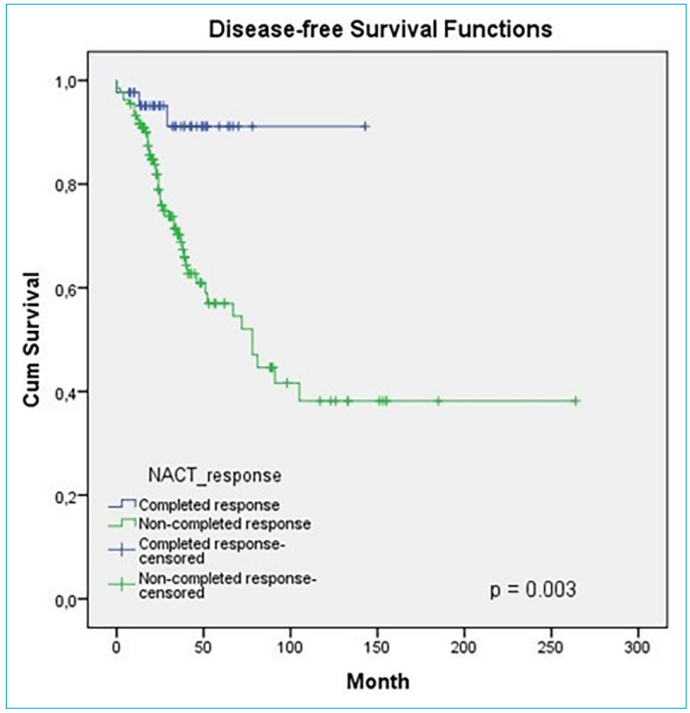

Figure 2. Disease-free survival curves of patients who achieved a pCR or nonpCR after NACT.

NACT: Neoadjuvant chemotherapy; pCR: Pathologic complete response; non-pCR: Non-pathologic complete response.

high risk of systemic spread to prevent early microscopic dissemination. In a retrospective analysis of 646 patients receiving NACT, Chen et al.[10] observed that 118 (18.2%) achieved pCR, while 528 (81.7%) did not achieve pCR. In a retrospective study involving 365 breast cancer patients, Krishnan et al.[12] reported that the overall pCR rate post-NACT was 13.7%. Zaher et al.[3] performed a retrospective study to estimate the proportion of 147 breast cancer pa-

Table 4. Multivariate logistic regression model for predicting pCR

	OR	95% CI	p
Menopause			
Pre-menopause	Reference		
Post-menopause	0.32	0.10-0.96	0.044
cT stage			
I-II	Reference		
III-IV	1.46	0.49-4.35	0.995
cN stage			
Negative	Reference		
Positive	0.84	0.23-3.49	0.818
ER			
Negative	Reference		
Positive	0.58	0.97-3.50	0.554
PR			
Negative	Reference		
Positive	0.93	0.16-5.23	0.942
HER2			
Negative	Reference		
Positive	9.97	3.49-28.42	<0.001
Molecular subtype			
ER+ and/or PR+, HER2-negative	Reference		
HER2-positive	9.91	3.56-27.39	<0.001
Triple Negative	2.70	0.75-9.68	0.126
Pertuzumab			
Absent	Reference		
Present	5.59	1.04-29.85	0.044

pCR: Pathologic complete response; OR: Odds ratio; CI: Confidential interval; cT stage: Clinical T stage; cN stage: Clinical N stage; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2.

tients who became eligible for BCS after NACT. It has been shown that pCR occurs in 58.5% of patients after NACT, and more patients are eligible for BCS. In another retrospective study that excluded locally advanced patients and included only early-stage (cT2N0/N1) patients, 28% achieved pCR post-NACT.[19] This study reported that 38% of pre-NACT N1 patients were downstaged to N0 post-NACT, and most patients avoided mastectomy and ALND.[19] In our study, 24% of patients achieved pCR, and 76% did not achieve pCR (20% of all patients had no response to NACT). Despite an 80% response rate post-NACT, most patients underwent mastectomy (72%) or ALND (70%). These outcomes may be explained by factors such as advanced initial tumor stage, low tumor response, and surgical preference for mastectomy or ALND. Even in patients who achieved a complete response, mastectomy was performed in 67% of patients, and ALND was performed in 44%. The type of breast surgery was similarly applied in both pCR and nonpCR patients, but ALND was performed less frequently in pCR patients. Our study revealed significant reductions in clinical T and N stages in postoperative specimens compared to pre-NACT data. These results are provided in Table 1.

Discordance in IHC characteristics between CNB and SS post-NACT is common. In particular, studies have shown negative results for hormone receptor (HR) expression and decreased Ki-67 expression (4,5). Gupta et al.[4] investigated the HR after NACT and reported an increase of approximately 8% (p=0.76) in the ER and 17% (p=0.54) in the PR. PR mismatch was found to be more common than ER mismatch. Anand et al.[5] retrospectively evaluated 78 patients who received NACT. Total HR discordance rate was 21.7%, the ER was 8.7%, and the PR was 13%. It has been reported that the change from PR-positive to PR-negative is more frequent in these patients. In our study, discordance was observed at 4% for ER, 10% for PR, 7% for HER2, and 12% for histopathological subtyping. According to other studies, changes such as PR negativity, a reduction in the percentage of PRs, a decrease in the percentage of Ki-67 percentage, and changes in histopathological subtyping were found to be statistically sig-

nificant. Although there was a decrease in HER2 positivity, no significant difference was observed.

The question of which patients should receive NACT can potentially be answered by examining the characteristics of patients who achieved a pCR versus those who did not. Chen et al.,[10] in their retrospective study, reported that the majority of pCR patients were predominantly HER2-positive (41.5%) and had Ki-67 >25% (50.8%). In nonpCR patients, tumors were generally HR-positive, HER2-negative (49.6%), and Ki-67 <25% (58.1%). It has been confirmed in other studies that HR positivity is not responsive to NACT and is resistant to chemotherapy, with more pCRs observed in the HER2-positive and TNBC subtypes, and that pCRs are closely related to molecular subtypes.[3,12,19] Krishnan et al.[12] investigated the association of pCR with HR status, HER2 status, and histopathological subtype post-NACT. One study revealed that pCR rates were greater in HR-negative tumors than in HR-positive tumors, with the highest pCR rates observed in the HR-positive/HER2-positive and HR-negative/HER2-positive patient groups. Kim et al.,[19] in their study that included 257 breast cancer patients, investigated pCR rates according to molecular subtypes defined by IHC staining and reported the highest rates in the HER2-positive and TNBC subgroups. In our study, similar to the above studies, compared with nonpCR patients, pCR patients were younger, had higher Ki-67 percentages, lower ER and PR positivity, and greater HER2 positivity. However, unlike in other studies, a higher rate of pCR was not observed in TNBC patients. This result can be explained by the relatively lower number of TNBC patients in our series.

One of the primary objectives across all treatment modalities is to achieve improvements in survival. After neoadjuvant chemotherapy (NACT), pathological complete response (pCR) appears to be the most critical prognostic factor for survival.[10,12,19] Especially when the pCR rate is greater in HR-negative, HER2-positive, high-grade patients post-NACT, this treatment can provide a survival advantage for those with aggressive tumors. In a study by Chen et al.,[10] overall survival (OS) and relapse-free survival (RFS) were better in patients who achieved a pCR. According to their findings, the 5-year OS was approximately 95% for pCR patients compared to 78% for nonpCR patients ($p<0.001$), and the 5-year RFS was 95% for pCR patients versus 73% for nonpCR patients ($p<0.001$). Additionally, the 5-year RFS was found to be similar across molecular subtypes in patients who achieved pCR. In a study by Krishnan et al.,[12] OS and DFS were shown to be better in pCR patients after a 10-year follow-up. In a study by Kim et al.,[19] the 5-year DFS for the pCR group (88.4%) was higher than that for the nonpCR group (65.6%), although it did not reach statistical significance ($p=0.228$). In our study, OS and DFS were better in patients who achieved pCR. These findings support the finding that the pCR rate is the most important factor for predicting survival in patients receiving NACT. Additionally, distant metastasis was observed less frequently in pCR patients than in nonpCR patients, indicating better systemic control in pCR patients.

There is a strong correlation between the absence of an invasive tumor focus post-NACT and patient prognosis. Determining which patients should receive NACT and which patients should receive adjuvant treatment remains a pivotal question. Therefore, identifying factors that predict pCR is crucial. In a study by Chen et al.,[10] a multivariate logistic regression model used to predict the pCR rate post-NACT identified clinical stage III disease as the HER2-positive and TNBC subtypes, the presence of lymphovascular invasion (LVI), and histology as significant factors. In a multicentric, retrospective study by Qian et al.,[20] age, T stage, pre-NACT Ki-67 index, HER2 status, and HR status were confirmed as criteria in a multivariate logistic regression model to predict the likelihood of pCR. Additionally, another study showed that adding pertuzumab to NACT in patients with HER2-positive disease increased the rate of pCR.[21] In our study, being premenopausal, being HER2-positive, having a Ki-67 of over 25%, being in the HER2-positive subgroup according to molecular subtyping, and receiving pertuzumab were found to be factors that increase the likelihood of achieving pCR. These data support the notion that patient clinical characteristics, tumor biology, and administered treatment are decisive in the response to NACT.

Limitations

The retrospective nature of this analysis is a significant limitation of this study. Another limitation is that post-NACT surgery was performed by different surgeons, which could have affected the desired outcomes for targeted breast-conserving surgery (BCS) and sentinel lymph node biopsy (SLNB). Pathological assessments were conducted at Cumhuriyet University's Department of Pathology, yet evaluations by different doctors could lead to variability in the results for parameters that might be subjective.

Conclusion

A pathological complete response (pCR) of 24% was achieved post-NACT. A statistically significant discordance was observed in the PR status and molecular subtyping post-NACT, while notable reductions in the PR and Ki-67 percentages were observed. Patients who achieved pCR were observed to be younger, to have higher Ki-67 percentages, to have lower ER and PR positivity, to have higher HER2 positivity, and to have higher grade 3 disease than nonpCR patients were. No differences were found in the type of breast surgery between the groups, although SLNB was performed

at a higher rate in patients who achieved a pCR. Additionally, patients who achieved pCR had fewer distant metastases and longer OS and DFS than did those without pCR. Being premenopausal, being HER2-positive, having a Ki-67 percentage >25%, being in the HER2-positive subgroup according to molecular subtyping, and receiving pertuzumab were identified as positive predictive factors for pCR.

Post-NACT pCR significantly influences survival. Even if pCR is not achieved, the reduction in mastectomy rates leading to cosmetic improvement and the development of new treatment plans based on changing IHC characteristics are among the factors driving the increasing application of NACT.

Disclosures

Ethics Committee Approval: The study was approved by the Cumhuriyet University Faculty of Medicine Ethics Committee (date: 18.04.2024, no: 2024/04-38).

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