

Research Article

Factors Influencing Complete Pathological Response Following Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer

 **Muhammet Cengiz**,  **Ayşe Nuransoy Cengiz**,  **Oktay Bozkurt**,  **Mevlûde İnanç**,  **Metin Özkan**

Department of Medical Oncology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

Abstract

Objectives: Triple-negative breast cancer (TNBC) is an aggressive subtype with a high risk of recurrence. Consequently, neoadjuvant chemotherapy (NAC) and subsequent responses may influence the course of the disease. Therefore, we investigated the efficacy of pathological complete response (pCR) and the factors that influence it.

Methods: A total of 97 patients were included in this single-center study. All patients were diagnosed with TNBC and had received NAC. We conducted a retrospective analysis of chemotherapy subtypes, their efficacy, pCR rates, weak positivity for hormone receptors and HER2 receptors, Ki-67 index levels, baseline biochemical markers, and factors influencing this response.

Results: Event-free survival (EFS) was 94.5 months in those with a pCR, compared with 64 months in the non-pCR group. Furthermore, the EFS was 39 months in patients with lymph node stage 2–3, whereas those with N0–1 reached 88.7 months. Additionally, elevated baseline CRP levels may be an independent prognostic indicator.

Conclusion: Post-NAC lymph node stage, elevated CRP levels, and pCR progression may be independent prognostic factors in patients with TNBC. HR and HER2 receptor statuses did not influence pCR. However, adding chemotherapy to the pCR regimen may not be a sound strategy. At this stage, further studies on immunotherapy and other alternative treatments are needed.

Keywords: C-reactive protein, lymph node stage, neoadjuvant chemotherapy, pathological complete response, triple negative breast cancer

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Triple-negative breast cancer (TNBC), accounting for approximately 15–20% of all breast cancer cases, is the only subtype of breast cancer for which no targeted treatment options are available.^[1] Clinical evaluations have shown that this type of cancer is negative for human epidermal growth factor receptor 2 (HER2) and, based on immunohistochemical staining, exhibits estrogen receptor

(ER) and progesterone receptor (PR) expression at levels below 1%. Characterized by rapidly proliferating cancer cells with moderate or high differentiation, TNBC is biologically highly aggressive and has the most unfavorable prognosis among breast cancer subtypes.^[2] Anthracyclines, cyclophosphamides, and taxanes are the most commonly used agents in neoadjuvant chemotherapy (NAC) for tri-

Address for correspondence: Muhammet Cengiz, MD. Department of Medical Oncology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

Phone: +90 534 610 00 64 **E-mail:** mhmmtcengiz@hotmail.com

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ple-negative breast cancer (TNBC).^[3] The use of NAC can help eliminate micrometastases while reducing tumor size, lowering the disease stage, and increasing the likelihood of breast-conserving treatment; thus, both curative treatment success and breast conservation rates improve, while also providing important information regarding the tumor's response to drugs.^[4] However, the risk of recurrence peaks in the third year following surgery and declines rapidly thereafter. When metastatic recurrence occurs, survival is shorter than that of other subtypes of breast cancer, treatment options are limited, response rates are low, and the responses achieved are generally not durable.^[5] Response to neoadjuvant therapy is typically determined in breast cancer clinical trials by assessing the rates of pathological complete response (pCR), which is based on microscopic examination of surgically removed specimens.^[6] Previous studies have demonstrated associations between pCR and event-free survival (EFS) and overall survival (OS) in the general population of patients with breast cancer and across different subtypes.^[7] A pooled analysis of 12 FDA-supported neoadjuvant chemotherapy clinical trials for breast cancer found that patients with breast cancer who achieved pCR had significantly improved survival outcomes. The magnitude of this association varied by breast cancer subtype and was strongest in patients with aggressive subtypes, such as TNBC.^[8] Nevertheless, a pCR can only be achieved in 30–50% of patients with TNBC, NAC, highlighting that a large proportion of patients fail to achieve the expected treatment success despite being exposed to the toxic effects of standard chemotherapy.^[9] Therefore, predicting NAC effectiveness based on clinical findings and preoperative pathological data is crucial for guiding initial treatment in stage II–III TNBC patients^[10]; however, real-world data in this area are limited. In this study, the clinical and pathological characteristics, treatment protocols, and other relevant data of patients with TNBC who underwent NAC and surgical treatment were retrospectively examined to identify factors affecting pCR and to develop a study that provides insights for the selection of initial treatment strategies in TNBC.

Methods

Patients and Study Design

Clinical and pathological data and treatment information for patients with TNBC who underwent NAC and surgical treatment at Erciyes University Faculty of Medicine between January 2018 and September 2023 were collected retrospectively. This study received ethical approval, including a waiver of informed consent owing to its retrospective nature, from the Erciyes Health Sciences Research Ethics Committee (no: 2026/68; date: 18.02.2026). All procedures

were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Declaration of Helsinki, as revised in 2024.

Inclusion criteria:

- (1) Age ≥ 18 years;
- (2) Histopathological confirmation of Stage II–III TNBC diagnosis
- (3) Immunohistochemical (IHC) examination showing negative ER, PR, and HER-2 expression
- (4) Diagnosis of invasive breast carcinoma by methods such as fine-needle aspiration biopsy or Tru-cut biopsy
- (5) Patients who received all courses of NAC
- (6) Standard surgical treatment after NAC
- (7) Availability of pre-treatment imaging data (MRI, USG, etc.);
- (8) Recording of pathological evaluation data and pCR status after NAC
- (9) Complete availability of clinical and pathological data;

Exclusion criteria

- (1) Patients with breast cancer types other than triple-negative breast cancer or with a diagnosis of metastatic breast cancer
- (2) Patients who received NAC for a shorter period than planned.
- (3) Patients with incomplete clinical or pathological information.
- (4) Patients who have previously undergone surgery, chemotherapy, or radiotherapy for breast cancer.

Clinical TNM stage was evaluated before NAC (cTNM) and in the post-surgical period (ypTNM). Tumor size and lymph node status were evaluated using magnetic resonance imaging (MRI), ultrasonography (USG), and positron emission tomography/computed tomography (PET-CT). Distant metastases were detected by computed tomography (CT) and PET-CT.

ER and PR negativity were defined as nuclear staining below 1% on immunohistochemical examination. HER-2 negativity was defined as IHC0, IHC1+, or IHC2+ with a negative in situ hybridization analysis result. Tumor grade was determined using the Nottingham grading system. The Ki-67 proliferation index was calculated as the percentage of tumor cells showing positive nuclear staining in immunohistochemical evaluation and was classified as low (<30%) and high ($\geq 30\%$) proliferation using a 30% cutoff. The response to NAC was determined by the pathological evaluation of specimens obtained after surgery. The patho-

logical response to NAC was graded from I (no response) to V (complete pathological response) using the Miller–Payne grading system.^[11] In this study, pCR was defined as the absence of residual invasive tumor cells (ypT0N0M0).

A total of 97 patients with triple-negative breast cancer were included in the study according to the inclusion and exclusion criteria.

Treatment

In patients suspected of having breast cancer based on imaging methods and physical examination, fine-needle aspiration biopsy or core needle biopsy was performed on both the primary tumor focus in the breast and the axillary lymph nodes suspected of being positive.

Immunohistochemical staining was performed on patients whose breast cancer diagnosis was pathologically confirmed. For labeling purposes, metallic markers were placed in the breast tumor focus and metastatic axillary lymph nodes. After TNBC diagnosis was confirmed, systemic metastasis screening was performed to assess for distant organ metastasis. Patients with tumors larger than 20 mm in diameter, axillary lymph node metastasis, and those scheduled for breast-conserving surgery were given NAC treatment.

According to treatment guidelines, the chemotherapy regimen used was TAC (taxane + anthracycline + cyclophosphamide) or TAC + platinum. Regimens were selected considering the patient's suitability for treatment, access to medication, and individual clinical characteristics. The response to NAC was assessed after each course of treatment by physical examination and every four courses, by imaging methods according to the RECIST radiological evaluation criteria.^[12] If the response to treatment was insufficient after four courses, patients were evaluated by a breast tumor multidisciplinary council, and surgical treatment was considered.

In patients with a significantly good chemotherapy response, surgery was performed after the completion of all chemotherapy courses. Immunohistochemical (IHC) examination and tumor size measurement were performed again on pathological specimens obtained after breast surgery. Data from the study were recorded.

Parameters Examined

1. General clinical parameters: Patient age, comorbidities, menstrual status, chemotherapy regimen, number of chemotherapy cycles, tumor size, and axillary lymph node status at initial diagnosis were evaluated.
2. Pathological parameters: Tumor subtype, histological grade, HER-2, Ki-67, ER, PR receptor status, and whether

er pCR was obtained were examined.

3. The pCR rates were examined.

Statistical Analysis

Statistical analyses were performed using "IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as counts and percentages (n, %) for categorical variables and as mean $\pm$ SD and median (min-max) for continuous variables. Receiver operating characteristic (ROC) curve analysis was performed for exploratory purposes to assess cohort-specific discrimination and consistency with previously published threshold values.

Although our analyses were not intended as the primary basis, they were conducted to assess the discriminatory ability of individual parameters. Independent risk factors were evaluated using Cox regression analysis. In the Cox regression analysis, a stepwise backward selection method was used at the $p < 0.10$ significance level.

The proportional hazards assumption was evaluated using log-minus-log plots and time-dependent covariate analysis. Missing data were assessed for randomness and handled using complete-case analysis, given the low missingness rate. Given the exploratory nature of secondary analyses, multiple testing correction was not applied; therefore, p -values should be interpreted cautiously.

The Kaplan-Meier method was used to compare overall survival (OS) and EFS times between clinical groups. EFS was calculated as the time from TNBC diagnosis with biopsy to the date of progression in months. OS was calculated by recording the time from TNBC diagnosis with biopsy to the date of death or the last follow-up, in months. Patients who were still alive at the time of the analysis were censored at their last follow-up.

Results

Our study included 97 patients with TNBC. In our study, 54.6% of patients achieved pCR, while 45.4% did not. No difference in distribution was observed between the two groups (Table 1). In our study, 88.7% of the patients had intraductal and lobular carcinomas. Of these, 76% had a Ki67 index $>30\%$, and 42% had grade 3 disease. Only 11% of patients had T2 tumors on radiological staging before NAC. All remaining patients had T3 or more advanced disease. Adriamycin + cyclophosphamide + taxan (AC + taxan) therapy was administered to 69.1% of the patients, while 30.9% also received platinum therapy (Table 1).

Univariate analyses of EFS retained significant associations with C-reactive protein (CRP), lymph node stage, and pathological complete response. The statistical signif-

Table 1. Characteristics of participants according to pCR

Variables	pCR Group		Total (n=97)	p
	Non-pCR n=53(%)	pCR n=44 (%)		
Age (years)				
<45	22 (41.5)	18 (40.9)	40 (41.2)	0.95
≥45	31 (58.5)	26 (59.1)	57 (58.8)	
Smoke				
No	42 (79.2)	40 (90.9)	82 (84.5)	0.11
Yes	11 (20.8)	4 (9.1)	15 (15.5)	
Menopausal status				
Premenopausal	42 (79.2)	31 (70.5)	73 (75.3)	0.31
Postmenopausal	11 (20.8)	13 (29.5)	21 (24.3)	
Histology				
Invasive ductal and lobular carcinoma	48 (90.6)	38 (86.4)	86 (88.7)	0.51
Others	5 (9.4)	6 (13.6)	11 (11.3)	
Ki 67 status				
≤30	14 (26.6)	9 (20.5)	23 (23.7)	0.49
>30	39 (73.6)	35 (79.5)	74 (76.3)	
Grade				
1	0 (0)	1 (1)	1 (1)	0.54
2	30 (56.6)	24 (54.5)	54 (55.7)	
3	23 (43.4)	19 (43.2)	42 (43.3)	
Tumor				
T2	4 (7.5)	7 (15.9)	11 (11.3)	0.33
T3	29 (54.7)	24 (54.5)	53 (54.6)	
T4	13 (24.5)	11 (25.1)	24 (24.7)	
Inflammatory breast	7 (13.3)	2 (4.5)	9 (9.4)	
Neoadjuvant chemotherapy				
AC+Taxane	37 (69.8)	30 (68.2)	67 (69.1)	0.86
AC+Taxane+Platinum	16 (30.2)	14 (31.8)	30 (30.9)	

Values are expressed as n(%). pCR: Pathological complete response; AC: Anthracyclines+cyclophosphamides. Statistically significant *p* values are shown in bold.

icances are as follows: CRP levels ($p=0.009$), lymph node stage ($p<0.001$), pathological complete response ($p=0.002$) (Table 2). Multivariate analysis retained the prognostic significance of lymph node stage and pathological complete response. The statistical significances are as follows: pathological complete response (HR 0.1, $p = 0.04$), and lymph node stage (HR 0.4, $p=0.002$) for EFS (Table 2).

The median EFS was 88.7 months (95% CI:82.1–95.3) in the group with lymph node stage 0-1 and 39 months (95% CI: 23.3–54.7) in the group with lymph node stage 2-3 ($p<0.001$) (Fig. 1). The median EFS was 94.5 months (95% CI:88–101) in the group with pCR and 64 months (95% CI: 54.8–73.2) in the group with non-pCR ($p=0.002$) (Fig. 2). The median EFS was 85.9 months (95% CI: 78–93.7) in the group with TAC and 46 months (95% CI: 40–53.3) in the TAC+platinum ($p=0.6$) (Fig. 3).

Discussion

As TNBC remains one of the most aggressive types of breast cancer, research has focused on this area.^[13] Because achieving pCR significantly improves survival, studies have

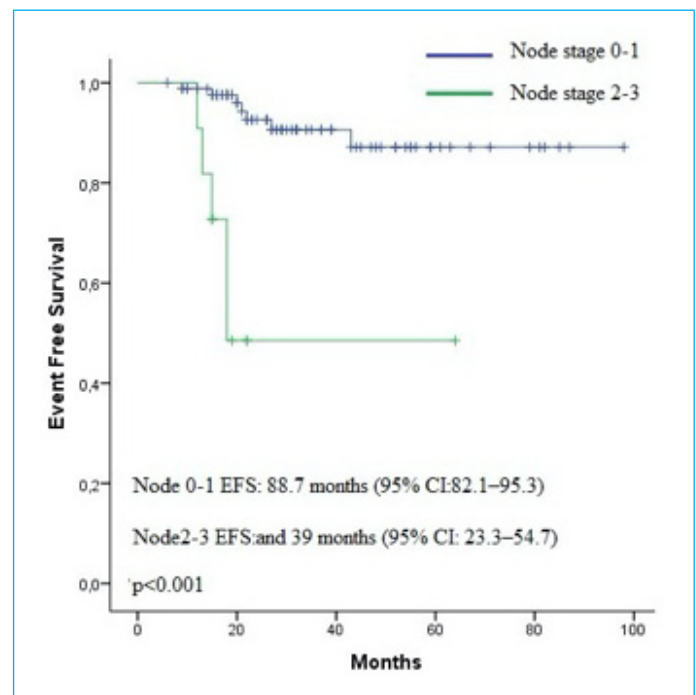
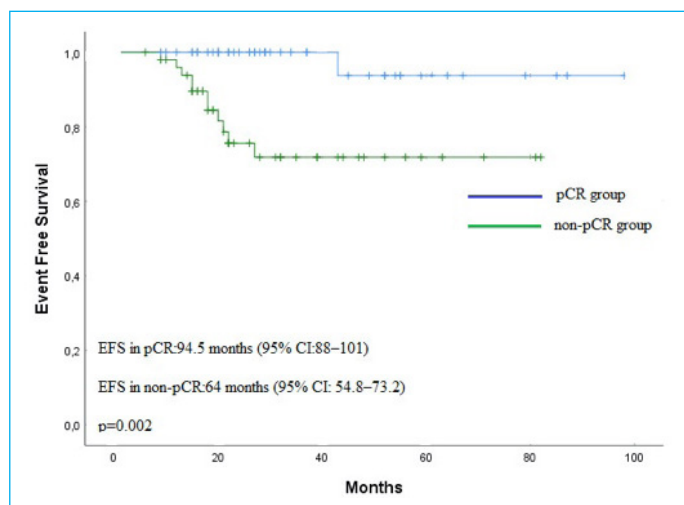
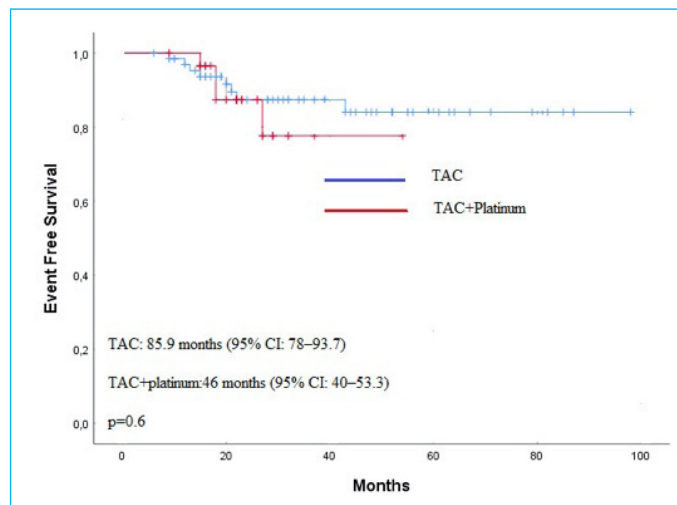


Figure 1. Kaplan-Meier curves for EFS by lymph node group.

Table 2. Univariate and multiple Cox regression analysis of variables for EFS

Variables	Univariate		Multiple	
	HR (95%CI)	p	HR (95%CI)	p
Age (years)				
≥45	1.00	-		
<45	0.7 (0.6-0.8)	0.9		
Smoke				
Yes	1.00	-		
No	0.8 (0.7-0.9)	0.1		
C-reactive protein				
≥ 5	1.00	-	1.00	-
< 5	0.6 (0.5-0.7)	0.009	0.3 (0.09-1.1)	0.08
Ki 67 status				
≥ %30	1.00	-		
< %30	0.6 (0.5-0.8)	0.4		
Grade Status				
Grade 3	1.00	-		
Grade1-2	0.7 (0.6-0.8)	0.6		
Pathology				
Others	1.00	-		
Ductal+Lobuler Carcinoma	0.8 (0.7-0.9)	0.1		
Tumor				
≥ 2 cm	1.00	-		
< 2 cm	0.7 (0.5-1.0)	0.5		
Lymph node				
N 2-3	1.00	-	1.00	-
N 0-1	0.8 (0.7-0.9)	<0.001	0.4 (0.3-0.5)	0.002
Lactate dehydrogenase (LDH) ^a				
≥ULN	1.00	-		
<ULN	0.5 (0.4-0.6)	0.2		
Pathological complete response				
No	1.00	-	1.00	-
Yes	0.9 (0.8-1.0)	0.002	0.1 (0.01-0.9)	0.04

CI: Confidence interval; HR: Hazard ratio; EFS: Event Free Survival, a: Upper limit of reference range: 250 U/L; ULN: Upper limit of normal; Statistically significant p values are shown in bold.

**Figure 2.** Kaplan-Meier curves for EFS by pCR group.**Figure 3.** Kaplan-Meier curves for EFS by NAC group.

focused on the factors that influence pCR. Real-world outcomes are crucial for progress in this field.^[8,14] In our study, patients with a statistically significant pCR had a longer EFS. The EFS in the pCR group was 94.5 months, whereas it decreased to 64 months in the non-pCR group. Therefore, factors influencing pCR are of utmost importance.

A study by Perry et al.^[15] demonstrated that chemotherapy plus immunotherapy increases pCR when a single tumor focus is present. However, they argued that lymph node status does not significantly contribute to this. Conversely, our data show that lymph node stage does influence pCR. In patients with stage N2–3 disease following neoadjuvant chemotherapy (NAC), disease-free survival was shorter. Consequently, the lymph node stage may be an independent prognostic indicator. The use of chemoimmunotherapy as the NAC regimen in Perry et al.'s study^[15] may have influenced the results.

Research continues to investigate the critical role of the immune system in cancer elimination. Certain immune markers may predict disease progression.^[16] Chen et al.^[17] reported that a high baseline lymphocyte count may be associated with a higher pCR rate. However, as the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio increased, the pCR response decreased. In our study, however, elevated CRP levels prior to NAC may serve as an independent prognostic marker for pCR. In other words, patients with high baseline CRP levels may have a more aggressive disease course. This finding is one of the most notable outcomes of our study.

When we assessed the subfactors influencing pCR, the choice of TAC or TAC plus platinum as the neoadjuvant chemotherapy regimen did not affect pCR. The EFS was 85.9 months in the TAC group and 46 months in the platinum-based therapy group. Although not statistically significant, this finding was numerically considerable. Consequently, the addition of platinum reduced the EFS. This may be due to increased toxicity as more drugs are administered. However, the number of patients in our study was limited. Patients were enrolled from a single center. There is a need for results from multi-center studies involving a larger number of patients, particularly regarding NAC treatment with the addition of immunotherapy. Nevertheless, our study may help guide NAC selection. Therefore, adding more chemotherapeutic agents may not always be beneficial.

When examining the other results of our study, HER2 receptor status (0, +1, +2, or negative by FISH), HR positivity at any level up to 10%, or a Ki-67 index of >30% were not found to be factors influencing pCR. In other words, low HR and HER2 receptor positivity in patients with TNBC may not affect pCR following NAC. Therefore, NAC strategies may

play a significant role in achieving pCR. Further studies are required to address this issue.

Conclusion

In conclusion, post-NAC lymph node stage, elevated CRP levels, and pCR progression may be independent prognostic factors in patients with TNBC. HR and HER2 receptor statuses did not influence pCR. However, adding chemotherapy to the pCR regimen may not be a sound strategy. At this stage, further studies on immunotherapy and other alternative treatments are needed.

Disclosures

Ethics Committee Approval: The study was approved by the Erciyes Health Sciences Research Ethics Committee (no: 2026/68; date: 18.02.2026).

Informed Consent: Informed consent was waived due to the retrospective nature of the study.

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