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# Relationship of Neoadjuvant Chemotherapy Efficacy with Histopathologic Molecular Subtypes in Breast Cancer Patients

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## ABSTRACT

**Introduction:** Breast cancer is the most common malignancy in women, and it is the second leading cause of malignancy-related mortality in women after lung cancer. Locally advanced breast cancer is a clinically heterogeneous group with a broad spectrum. Neoadjuvant chemotherapy (NAC) is the standard treatment at this stage. The present study aimed to evaluate the efficacy of NAC in terms of histopathologic molecular subtypes.

**Methods:** The study included 183 patients receiving NAC. Patients were studied in three groups: Luminal tumors, human epidermal growth factor receptor-2 (HER-2)-positive tumors, and triple-negative tumors based on the expressed receptor status. In our retrospective review, we only examined pathological complete response (pCR) based on breast tumor shrinkage before and after chemotherapy. In this study, we evaluated factors affecting pathologic complete response in patients receiving NAC.

**Results:** According to breast cancer subtypes based on biopsy results, pCR developed in 8 of 20 patients with triple-negative tumors (40%), 24 of 61 patients with HER-2-positive tumors (39.3%), and 22 of 102 patients with luminal tumors (21.5%) (p=0.030). The pCR rate was available in 5 of 40 patients with lymphovascular invasion (LVI) (12.5%) and 49 of 143 patients without LVI (34.2%) (p=0.008). pCR was available in 1 of 16 patients with perineural invasion (PNI) (6.6%) and 53 of 168 patients without PNI (31.5%) (p=0.043). PCR was available in 2 of 25 patients with extracapsular lymph node invasion (8%) and in 52 of 158 patients without extracapsular lymph node invasion (32.9%) (p=0.011).

**Conclusion:** The NAC pCR rate of hormone-positive tumors was lower than that of hormone-negative tumors in breast cancer. This finding was related to the biological response of the tumor in heterogeneous breast cancer.

**Keywords:** Breast cancer, neoadjuvant chemotherapy, molecular subtype, pathological response

## Introduction

The main risk factor for breast cancer is female sex, as the lifetime risk of developing breast cancer is 1 in 8 for women (12%) compared with 1 in 833 for men (0.12%) (1). It is the most common malignancy and the second most common cause of malignancy-related mortality in women (2). Breast cancer is a multifactorial disease (3). The etiopathogenesis of the disease is influenced by demographic factors, such as sex, age, and race, and hereditary factors, such as family history and genetic mutations. Moreover, reproductive factors such as early menarche-late menopause, age at first pregnancy, breastfeeding, use of combined oral contraceptives, hormone replacement therapy, body mass index, physical activity, and medical risk factors such as smoking, alcohol, radiation, and benign diseases of the breast.

Neoadjuvant chemotherapy (NAC) is increasingly being used for locally advanced breast cancer. This is because NAC evaluates tumor response before surgery and provides information about tumor biology; furthermore, NAC reduces tumor size and allows for smaller-scale surgery in the breast and axilla. NAC provides a cosmetically better appearance and reduces post-operative complications, such as lymphedema (4-6). Therefore, NAC has become a standard treatment for locally advanced breast cancer. Pathological complete response (pCR) has been recognized as an important marker of NAC and a prognostic marker in many studies (7). In other studies, clinicopathological parameters such as hormone receptor status, human epidermal growth factor receptor-2 (HER-2) status, histological grade, proliferation index, tumor size, age, and laboratory values that may predict pCR have been studied. However,

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in various studies evaluating these factors that may predict pCR, it has been reported that a single factor is not sufficient to predict the efficacy of NAC because of the different pCR rates obtained (8).

Locally advanced breast cancer is a clinically heterogeneous group with a broad spectrum. The 8th edition of the American Joint Committee on Cancer staging system with prognostic data, such as tumor size, lymph node positivity, presence of distant metastasis, hormone receptor [estrogen receptor (ER), progesterone receptor (PR)] and HER-2 can be used by clinicians. Pre-operative treatment should be considered when planning the systemic treatment of stage 3A, 3B, 3C, and inoperable stage 2B T3N0 tumors, except for operable stage 2B tumors. This is because systemic treatments have many benefits for this group of patients. This group includes T3 tumors >5 cm in diameter, T4 tumors that are fixed to the chest wall, cause edema or ulceration of the breast skin, or have satellite skin nodules, and N2 and N3 tumors with ipsilateral supraclavicular, infraclavicular, internal mammary, or fissile axillary lymph node involvement (9). Inflammatory breast cancer is also classified as locally advanced.

In this study, we aimed to investigate in patients with breast cancer treated with NAC the relationship between the efficacy of this treatment and histopathologic molecular subtypes, prognostic factors, and factors affecting pCR.

## Methods

### Patients

In our two-center study, 183 patients treated with NAC between February 2012 and July 2021 were retrospectively analyzed. Pre- and post-operative tumor diameters were evaluated using various methods, including ultrasound, mammography, and contrast-enhanced magnetic resonance imaging (MRI). Because the number of lymph nodes was not evaluated quantitatively before NAC, no post-operative comparison could be made. Patients underwent breast biopsy to determine histological subtype, hormone receptor, and HER-2 status before NAC.

### Ethics Committee Approval

The study was conducted in accordance with the Declaration of Helsinki and patient right regulations. The ethics committee approved the study by the Ethics Committee of the Gaziantep University Faculty of Medicine and the Gaziantep Provincial Directorate of Health (approval number: 2021/81, date: 01.09.2021).

### Chemotherapy Regimens

Various chemotherapy protocols were used when NAC regimes were reviewed. This may be due to the histologic subgroup effect, as well as the effect of the clinician's choice of treatment as it is a heterogeneous disease. One hundred and one patients (55.4%) received AC-T, i.e. 4 cycles of doxorubicin 60 mg/m$^2$ and cyclophosphamide 600 mg/m$^2$ every 3 weeks, followed by paclitaxel 80 mg/m$^2$ weekly for 12 weeks. Thirty-three patients (17.9%) received AC-taxane-trastuzumab, 14 patients (7.6%) received only AC, and 10 patients (5.4%) received AC-taxane-trastuzumab-pertuzumab (Table 1).

### Surgical Method

Surgical methods and axillary procedures performed in patients after NAC were analyzed. A total of 165 patients (90.16%) underwent modified radical mastectomy, 4 patients (2.18%) underwent mastectomy + sentinel lymph node dissection (SLND), 12 patients (6.55%) underwent breast-conserving surgery (BCS) + axillary lymph node dissection, and 2 patients (1.09%) underwent BCS + SLND (Table 2).

### Pathological Examination

Tumors were classified according to the standard criteria of the World Health Organization. ER and PR status was examined immunohistochemically and considered positive in cases of a positive value >10%. HER-2 status was assessed using immunohistochemistry and grading the intensity of membrane staining. Tumors graded as strong HER-2 homogeneous staining +3 were considered positive. Either fluorescence *in situ* hybridization or silver *in situ* hybridization was used to determine amplification in case of a moderately homogeneous staining +2. In microscopic examinations of the resection sample, regardless of carcinomas in situ, only the absence of invasive carcinoma

**Table 1. Types of neoadjuvant chemotherapy**

| Neoadjuvant chemotherapy regimens | n | % |
|---|---|---|
| AC→T | 101 | 55.4 |
| AC→T→trastuzumab | 33 | 17.9 |
| AC | 14 | 7.6 |
| AC→T→trastuzumab-pertuzumab | 10 | 5.4 |
| TCH | 10 | 5.4 |
| TAC | 7 | 3.8 |
| AC→T→carboplatin | 2 | 1.08 |
| TCH→AC | 2 | 1.08 |
| TC | 1 | 0.54 |
| EC | 1 | 0.54 |
| CMF | 1 | 0.54 |
| FEC→T | 1 | 0.54 |
| Total | 183 | 100 |

AC: Doxorubicin + cyclophosphamide, T: Taxane (paclitaxel or docetaxel), H: Trastuzumab, TAC: Dosexel + doxorubucin + cyclophosphamide, TC: Docetaxel + cyclophosphamide, EC: Epirubicin + cyclophosphamide, CMF: Cyclophosphamide + methotrexate + 5-FU, FEC: 5-FU + epirubicin + cyclophosphamide

**Table 2. Surgical methods and axillary lymph node dissection procedures following neoadjuvant chemotherapy**

| | | n | % |
|---|---|---|---|
| The type of operation | MRM | 165 | 90.16 |
| | Mastectomy + SLND | 4 | 2.18 |
| | BCS + ALND | 12 | 6.55 |
| | BCS + SLND | 2 | 1.09 |
| | Total | 183 | 100 |
| Lymph node dissection | ALND | 177 | 96.72 |
| | SLND | 6 | 3.27 |
| | Total | 183 | 100 |

MRM: Modified radical mastectomy, ALND: Axillary lymph node dissection, BCS: Breast-conserving surgery, SLND: Sternal lymph node dissection

in the breast was considered as pCR because sufficient pre- and post-operative information on the axilla was not available.

### Statistical Analysis

The Shaphiro-Wilk test was used to analyze whether the numerical variables were normally distributed. To compare variables that were not normally distributed, the Mann-Whitney U test was used to compare variables in two groups, and the Kruskal-Wallis and Dunn's tests were used to compare variables in three groups. Relationships between categorical variables were tested using the chi-square and Bonferroni multiple comparison tests. A multinomial logistic regression analysis was used to estimate the variables that influenced the response outcome. The SPSS 22.0 Windows version package program was used in the analysis. $P<0.05$ is considered significant.

## Results

The characteristics according to breast cancer subtype are presented in Table 3. The median age of the patients was 48 years (29-78). Fifty-seven of 102 patients (55.8%) in the luminal group, 19 of 61 patients (31.15%) in the HER-2 group, and 11 of 20 patients (55%) in the triple negative group

**Table 3. Characteristics of breast cancer subtypes**

| Variables | | Subtypes of breast cancer | | | | | | | | p |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Luminal | | HER-2-positive | | Triple negative | | Total | | |
| | | n | % | n | % | n | % | n | | |
| Age (years) | ≤48 | 45 | 44.12 | 42 | 68.85 | 9 | 45.00 | 96 | 183 | **0.007** |
| | >48 | 57 | 55.88 | 19 | 31.15 | 11 | 55.00 | 87 | | |
| Pathological cancer | Invasive ductal | 97 | 95.10 | 61 | 100.00 | 18 | 90.00 | 176 | 183 | 0.090 |
| | Non-invasive ductal | 5 | 4.90 | 0 | 0.00 | 2 | 10.00 | 7 | | |
| Pre-operative tumor diameter | T1-T2 | 83 | 81.37 | 47 | 77.05 | 14 | 70.00 | 144 | 183 | 0.488 |
| | T3-T4 | 19 | 18.63 | 14 | 22.95 | 6 | 30.00 | 39 | | |
| Grade | 1-2 | 35 | 74.47 | 10 | 37.04 | 0 | 0.00 | 45 | 183 | **0.001** |
| | 3 | 12 | 25.53 | 17 | 62.96 | 3 | 100.00 | 31 | | |
| | Unknown | 55 | | 34 | | 17 | | 107 | | |
| Ki-67 status (%) | ≤20 | 45 | 52.94 | 22 | 46.81 | 2 | 11.76 | 69 | 183 | **0.008** |
| | >20 | 40 | 47.06 | 25 | 53.19 | 15 | 88.24 | 80 | | |
| | Unknown | 17 | | 14 | | 3 | | 34 | | |
| Pre-operative lymph node metastasis | Present | 75 | 73.53 | 52 | 85.25 | 16 | 80.00 | 143 | 183 | 0.211 |
| | Absent | 27 | 26.47 | 9 | 14.75 | 4 | 20.00 | 40 | | |
| The type of surgery | MRM | 91 | 89.22 | 56 | 91.80 | 18 | 90.00 | 165 | 183 | 0.686 |
| | Mastectomy + SLND | 1 | 0.98 | 2 | 3.28 | 1 | 5.00 | 4 | | |
| | BCS + ALDN | 8 | 7.84 | 3 | 4.92 | 1 | 5.00 | 12 | | |
| | BCS + SLND | 2 | 1.96 | 0 | 0.00 | 0 | 0.00 | 2 | | |
| Lymph node dissection | Axillary dissection | 99 | 97.06 | 59 | 96.72 | 19 | 95.00 | 177 | 183 | 0.894 |
| | Sentinel dissection | 3 | 2.94 | 2 | 3.28 | 1 | 5.00 | 6 | | |
| Laterality | Right | 49 | 48.04 | 33 | 54.10 | 13 | 65.00 | 95 | 183 | 0.350 |
| | Left | 53 | 51.96 | 28 | 45.90 | 7 | 35.00 | 88 | | |
| Localization | Top-exterior | 58 | 56.86 | 33 | 54.10 | 12 | 60.00 | 103 | 183 | 0.710 |
| | Top-interior | 7 | 6.86 | 7 | 11.48 | 2 | 10.00 | 16 | | |
| | Bottom-exterior | 25 | 24.51 | 10 | 16.39 | 3 | 15.00 | 38 | | |
| | Bottom-interior | 8 | 7.84 | 9 | 14.75 | 3 | 15.00 | 20 | | |
| | All | 4 | 3.92 | 2 | 3.28 | 0 | 0.00 | 6 | | |
| Multifocality | Present | 26 | 25.49 | 14 | 22.95 | 5 | 25.00 | 45 | 183 | 0.935 |
| | Absent | 76 | 74.51 | 47 | 77.05 | 15 | 75.00 | 138 | | |
| LVI | Present | 27 | 26.47 | 12 | 19.67 | 1 | 5.00 | 40 | 183 | 0.092 |
| | Absent | 75 | 73.53 | 49 | 80.33 | 19 | 95.00 | 143 | | |
| PNI | Present | 12 | 11.76 | 3 | 4.92 | 0 | 0.00 | 15 | 183 | 0.112 |
| | Absent | 90 | 88.24 | 58 | 95.08 | 20 | 100.00 | 168 | | |
| Lymph node extracapsular invasion | Present | 20 | 19.61 | 3 | 4.92 | 2 | 10.00 | 25 | 183 | **0.027** |
| | Absent | 82 | 80.39 | 58 | 95.08 | 18 | 90.00 | 158 | | |

**Table 3. Continued**

| Variables | | Subtypes of breast cancer | | | | | | | | p |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Luminal | | HER-2-positive | | Triple negative | | Total | | |
| | | n | % | n | % | n | % | n | | |
| Surgical margin | Negative | 97 | 95.10 | 58 | 95.08 | 20 | 100.00 | 175 | 183 | 0.599 |
| | Positive | 5 | 4.90 | 3 | 4.92 | 0 | 0.00 | 8 | | |
| Skin invasion | Present | 12 | 11.76 | 9 | 14.75 | 1 | 5.00 | 22 | 183 | 0.504 |
| | Absent | 90 | 88.24 | 52 | 85.25 | 19 | 95.00 | 161 | | |
| *In situ* carcinoma | Present | 14 | 13.73 | 5 | 8.20 | 1 | 5.00 | 20 | 183 | 0.366 |
| | Absent | 88 | 86.27 | 56 | 91.80 | 19 | 95.00 | 163 | | |

P<0.05. HER-2: Human epidermal growth factor receptor-2, MRM: Modified radical mastectomy, SLND: Sternal lymph node dissection, BCS: Breast-conserving surgery, ALND: Axillary lymph node dissection, LVI: Lymphovascular invasion, PNI: Perineural invasion

were >48 years of age, which was statistically significant (p=0.007). One hundred and seventy-six patients (96.17%) had a pathological type, the majority of which was invasive ductal carcinoma. Pre-operative tumor diameters calculated according to the TNM staging system were analyzed in two subgroups as T1-T2 and T3-T4. The grade was not specified in 107 patients (58.46%), and the remaining patients were analyzed in two subgroups as grade 1-2 and grade 3 patients. The grade was unknown in 55 patients and 12 of the remaining 47 patients (25.53%) had grade 3 tumors in the luminal group; the grade was unknown in 34 patients and 17 of the remaining 27 patients (63.96%) had grade 3 tumors in the HER-2-positive group, and the grade was unknown in 17 patients and available only for 3 patients and 3 patients had grade 3 tumors (100%) in the triple negative group, and grades according to subgroups were statistically significant (p=0.001). The percentage of patients with Ki-67 was not recorded in the pathology reports of 34 of 183 patients (18.57%). The percentage of Ki-67 was unknown in 17 patients and 40 of 85 patients (47.06%) had Ki-67 >20 in the luminal group; the percentage of Ki-67 was unknown in 14 patients and 25 of 47 patients (53.19%) had Ki-67 >20 in the HER-2-positive group, and the percentage of Ki-67 was unknown in 3 patients and 15 of 17 patients (88.24%) had Ki-67 >20 in the triple negative group. Therefore, the high percentage of Ki-67 was higher and statistically significant in the HER-2-positive and triple-negative groups (p=0.008). The lymph node extracapsular invasion was significantly negative in all subtypes, and percentages were negative in 82 of 112 patients (80.39%) in the luminal group, 58 of 61 patients (95.08%) in the HER-2-positive group, and 18 of 20 patients (90%) in the triple negative group, respectively (p=0.027).

### Pathological Complete Response Rate

The factors influencing the response to NAC are presented in Table 4. Patients who did not have invasive carcinoma in the breast tumor size on pathological examination after neoadjuvant therapy were evaluated as having pCR, and the others were considered non-responders. The axillary pCR rate was not analyzed because it was not available in the pathological reports. Fifty four of 183 patients (29.5%) had pCR. According to subtypes, 22 of 102 patients (21.6%) in the luminal group, 24 of 61 patients (39.3%) in the HER-2-positive group, and 8 of 20 patients (40%) in the triple negative group had a pCR (p=0.030). Lymphovascular invasion (LVI) was absent in 49 of 54 patients with pCR (90.74%) and in 94 of 129 patients without pCR (72.87%) (p=0.008). Perineural invasion was absent in 53 of 54 patients with pCR (98.15%) and in 115 of 129 patients without pCR (89.15%) (p=0.043). Lymph node extracapsular invasion was absent in 52 of 54 patients with pCR (96.3%) and in 106 of 129 patients without pCR (82.17%) (p=0.011).

For the significant variables (p<0.05) influencing the response to NAC, a univariate regression analysis was first performed (Table 5). In the univariate analysis of the factors influencing the response to NAC, the luminal group was taken as a reference among breast cancer subtypes, and the HER-2-positive group and the triple negative group were found to have more responses (p-values were p=0.033 for luminal group, p=0.016 for HER-2-positive group and p=0.086 for triple negative group). Patients without LVI and those with lymph node extracapsular invasion had a better response (p-values of 0.011 and 0.022, respectively). Multivariate regression analysis was performed for the variables that were significant (p<0.05) in the univariate regression analysis, and it was found that only LVI tumors had an independent effect on pCR (p=0.048).

## Discussion

Neoadjuvant therapies have been used more frequently in recent years for large tumors that are not suitable for surgery and in cases requiring extensive axillary resection. The routine use of chemotherapy in luminal group breast cancers is controversial because of its lower efficacy. Neoadjuvant therapy is used more frequently in HER-2-positive and triple-negative patients. In this study, we investigated the relationship between neoadjuvant therapy efficacy and molecular subtypes and other factors that contribute to pCR. For this purpose, we categorized the patients as luminal, HER-2-positive, and triple-negative. Rouzier et al. (10) also categorized patients in a similar way. In a study conducted by Galvez et al. (11) that included 435 patients who received NAC and evaluated the clinicopathological characteristics of patients according to molecular subtypes, it was found that the majority of luminal A cases (97%) were low grade, whereas luminal B, HER-2-positive, and triple negative type tumors were mostly high grade (61%, 69%, 72%, respectively). In our study, the majority of patients in the luminal group were grade 1-2 and the majority of patients in the HER-2 group were grade 3, which was consistent with the literature (p=0.001) (11,12). When the pCR was analyzed according to the breast cancer subtypes, it was observed in our study that the response rates were higher in HER-2-positive and triple-negative tumors compared with luminal type

**Table 4. Factors influencing pathologic complete response**

| Variables | | Pathological complete response | | | | | p |
|---|---|---|---|---|---|---|---|
| | | Pathological complete response | | Pathological complete response | | Total | |
| | | n | % | n | % | n | |
| Age (years) | ≤48 | 31 | 57.41 | 65 | 50.39 | 96 | 183 | 0.386 |
| | >48 | 23 | 42.59 | 64 | 49.61 | 87 | | |
| Histopathologic subtype | Invasive ductal | 53 | 98.15 | 123 | 95.35 | 176 | 183 | 0.368 |
| | Non-invasive ductal | 1 | 1.85 | 6 | 4.65 | 7 | | |
| Pre-operative tumor diameter | T1-T2 | 42 | 77.78 | 102 | 79.07 | 144 | 183 | 0.846 |
| | T3-T4 | 12 | 22.22 | 27 | 20.93 | 39 | | |
| Grade | 1-2 | 13 | 72.22 | 32 | 54.24 | 45 | 183 | 0.175 |
| | 3 | 5 | 27.78 | 27 | 45.76 | 32 | | |
| | Unknown | 36 | | 70 | | 106 | | |
| Ki-67 status (%) | ≤20 | 21 | 47.73 | 48 | 45.71 | 69 | 183 | 0.822 |
| | >20 | 23 | 52.27 | 57 | 54.29 | 80 | | |
| | Unknown | 10 | | 24 | | 34 | | |
| Pre-operative lymph node metastasis | Present | 43 | 79.63 | 100 | 77.52 | 143 | 183 | 0.753 |
| | Absent | 11 | 20.37 | 29 | 22.48 | 40 | | |
| Breast cancer subtype | Luminal | 22 | 40.7 | 80 | 62 | 102 | 183 | **0.030** |
| | HER-2-positive | 24 | 44.4 | 37 | 28.7 | 61 | | |
| | Triple negative | 8 | 14.8 | 12 | 9.3 | 20 | | |
| Laterality | Right | 30 | 55.56 | 65 | 50.39 | 95 | 183 | 0.523 |
| | Left | 24 | 44.44 | 64 | 49.61 | 88 | | |
| Localization | Top-exterior | 25 | 46.30 | 78 | 60.47 | 103 | 183 | 0.067 |
| | Top-interior | 7 | 12.96 | 9 | 6.98 | 16 | | |
| | Bottom-exterior | 9 | 16.67 | 29 | 22.48 | 38 | | |
| | Bottom-interior | 10 | 18.52 | 10 | 7.75 | 20 | | |
| | All | 3 | 5.56 | 3 | 2.33 | 6 | | |
| Multifocality | Present | 11 | 20.37 | 34 | 26.36 | 45 | 183 | 0.391 |
| | Absent | 43 | 79.63 | 95 | 73.64 | 138 | | |
| LVI | Present | 5 | 9.26 | 35 | 27.13 | 40 | 183 | **0.008** |
| | Absent | 49 | 90.74 | 94 | 72.87 | 143 | | |
| PNI | Present | 1 | 1.85 | 14 | 10.85 | 15 | 183 | **0.043** |
| | Absent | 53 | 98.15 | 115 | 89.15 | 168 | | |
| Lymph node extracapsular invasion | Present | 2 | 3.70 | 23 | 17.83 | 25 | 183 | **0.011** |
| | Absent | 52 | 96.30 | 106 | 82.17 | 158 | | |
| Presence of *in situ* carcinoma | Present | 4 | 7.41 | 16 | 12.40 | 20 | 183 | 0.323 |
| | Absent | 50 | 92.59 | 113 | 87.60 | 163 | | |

P<0.05. HER-2: Human epidermal growth factor receptor-2, LVI: Lymphovascular invasion, PNI: Perineural invasion

**Table 5. Univariate and multivariate analyses of pathological complete response**

| Variables | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | OR | CI | p | OR | CI | p |
| Breast cancer subtype | Luminal (reference) | | | **0.033** | | | 0.135 |
| | HER-2-positive | **2,359** | **1,174-4,738** | **0.016** | 2,103 | 0.979-4,140 | 0.057 |
| | Triple negative | 2,424 | 0.882-6,665 | 0.086 | 1,887 | 0.666-5,345 | 0.232 |
| LVI | | **3,649** | **1,344-9,906** | **0.011** | 2,837 | 1,007-7,992 | **0.048** |
| PNI | | 6,452 | 0.827-50,355 | 0.075 | | | |
| Lymph node extracapsular invasion | | **5,642** | **1,281-24,845** | **0.022** | 3,634 | 0.792-16,672 | 0.097 |

P<0.05, LVI: Lymphovascular invasion, PNI: Perineural invasion, OR: Odds ratio, CI: Confidence interval

tumors. These results are in line with the literature (11-14). The Ki-67 cut-off value was set at 20 in accordance with the ESMO 2021 Guideline, and luminal groups were classified as luminal B in cases where Ki-67 was ≥20 and luminal A in cases where Ki-67 was <20. In both our study and the study by Rouzier et al. (10), patients with HER-2-positive and triple-negative tumors had a higher response to NAC than patients with luminal tumors. In a study by Kaufmann et al. (15), the pCR was higher in patients with a negative hormone profile than in those with a positive hormone profile. Osako et al. (14) designed a study in which the response status was evaluated based on the percentage of hormone receptor positivities. In their study, patients with ER positivity >30% and PR positivity >1% (p=0.0001) had a lower pCR rate. On the other hand, a pCR was 18.6 times more common in patients with a negative ER than in patients with a positive ER of ≥30% (14). In our study, similar to the findings of Kaufmann et al. (15), pCR was observed more frequently in patients with a negative hormone profile and in HER-2-positive patients, which was in line with the literature. Nishimura et al. (16) demonstrated a significant relationship between the Ki-67 percentage and pCR in a multivariate analysis. In our study, we investigated whether there was a relationship between the Ki-67 percentage and pCR. However, no statistically significant relationship was found. A study by Spring et al. (17) showed that the tumor grade was an independent predictive factor for pathological response. They reported that the neoadjuvant therapy response was higher, and a greater pathologic response was obtained in high-grade tumors (17). In our study, no relationship was found between tumor grade and pCR. This may be due to the fact that pathology reports did not specify grade information for all patients. A study by Uematsu et al. (18) showed that the absence of LVI in surgical specimens after NAC was associated with a pathological response. Another study showed that the degree of LVI was associated with tumor recurrence and tumor-related deaths (19). Therefore, it is important to evaluate LVI to predict the pathological response after NAC. In our study, LVI was an independent factor influencing pathological response (p=0.048).

### Study Limitations

Our study is a retrospective study. The pathological data of some patients were obtained from other centers, and these could not be obtained. Finally, the follow-up time was short.

## Conclusion

In the present study, although the complete response rate following neoadjuvant therapy was approximately 30%, it was noteworthy that the rate of BCS was approximately 10%. Mastectomy after neoadjuvant therapy is usually performed for inflammatory breast cancer and multicentric focal tumors, and this approach constituted the majority of our study cohort. High mastectomy rates may be due to patient insistence and clinician preference. Tumor marking before neoadjuvant therapy and similar imaging methods of pre-operative restaging (with breast MRI, if possible) will increase the rates of BCS, thereby providing better cosmetic results with less breast tissue loss.

In conclusion, both the treatment response and pCR rates of patients who received NAC for breast cancer were higher in patients with HER-2-positive and triple-negative breast cancers. Similar to other studies in the literature, we found that luminal tumors had a lower sensitivity to NAC.

**Ethics Committee Approval:** The ethics committee approved the study by the Ethics Committee of the Gaziantep University Faculty of Medicine and the Gaziantep Provincial Directorate of Health (approval number: 2021/81, date: 01.09.2021).

**Informed Consent:** Retrospective study.

**Authorship Contributions:** Surgical and Medical Practices - F.T., Ay.A., Al.A., L.Y.; Concept - Ç.Y., F.T., İ.G., Ay.A., Al.A., L.Y., Ç.U.A.; Design - Ç.Y., F.T., İ.N.Ö., İ.G., Ay.A., Al.A., L.Y., Ç.U.A.; Data Collection or Processing - Ç.Y., İ.N.Ö.; Analysis or Interpretation - Ç.Y., F.T., İ.N.Ö., İ.G., Ç.U.A.; Literature Search - Ç.Y., F.T., Ay.A.; Writing - Ç.Y., F.T.

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