Correlation between breast and axillary pathologic complete response after neoadjuvant chemotherapy in breast cancer

Ann. Ital. Chir., 2023 94, 4: 336-345
pii: S0003469X23039325

Emine Yıldırım*, Sibel Bektas**, Fırat Yetıs*, Eren Ozan Yıldız*, Muhammed Ozdemir***, Neslihan Komut°, Mustafa Calik°°, Ahmet Muzaffer Er*

**Department of General Surgery, University of Health Sciences Turkey, Gaziosmanpasa Training and Research Hospital, Istanbul, Turkey*
**Department of Pathology, University of Health Sciences Turkey, Gaziosmanpasa Training and Research Hospital, Istanbul, Turkey.*
****Department of General Surgery, Siverek Government Hospital, Siverek, Sanliurfa, Turkey*
°Department of Pathology, Tekirdag City Hospital, University of Health Sciences, Turkey
°°Department of Emergency, University of Health Sciences Turkey, Gaziosmanpasa Training

Correlation between breast and axillary pathologic complete response after neoadjuvant chemotherapy in breast cancer

AIM: *The aim of this study was to evaluate the correlation of the pathological response in breast tissue and the axilla of patients with breast cancer who underwent surgery following neoadjuvant chemotherapy.*
Method: This retrospective cohort study included patients with T1-4, N1-3, M0 breast cancer who underwent surgery following neoadjuvant chemotherapy at Gaziosmanpasa Training and Research Hospital between 2013 and 2022. The response of the breast tissue to chemotherapy was evaluated with the Miller-Payne grading system, and the response of the axillary lymph nodes to chemotherapy was evaluated with the Pinder grading system. The patients were grouped histopathologically as luminal A, luminal B, Her-2 enriched, or triple negative breast cancer (TNBC).
RESULTS: *The study was completed with 140 patients. Pathological complete response (pCR) was seen in the breast in 40 patients and in the axilla in 34. Of the patients with pCR in the breast, pCR was also determined in the axilla in 45%. In the patients with pCR in both the breast and axilla, Her-2 enriched subtype, estrogen receptor negativity, progesterone receptor negativity, Her-2 neu positivity, and Ki-67 level >25% were determined to be effective ($p<0.05$). Her-2 neu positivity was evaluated as statistically significant in the development of pCR in both the breast and axilla (OR: 4.06, 95% CI:1.2-13.6, $p=0.023$).*
CONCLUSION: *The development of pCR in the breast, especially in the Her-2 enriched subgroup, can be accepted as a predictive factor for the evaluation of axillary response in patients with breast cancer. The least compatibility was seen in the luminal A subgroup.*

KEY WORDS: Breast cancer, Miller-Payne, Neoadjuvant chemotherapy Pathological complete response, Pinder

Introduction

Neoadjuvant chemotherapy (NAC) is the preferred initial treatment in locally advanced breast cancer (LABC). While NAC allows less extensive surgery by reducing the tumor, the early response to systemic treatment can also be evaluated [1,2]. Following NAC, pathological complete response (pCR) is seen at higher rates in Her-2 enriched and triple negative breast cancer (TNBC) than in patients with hormone receptor positivity.
This is an important marker of both disease-free survival (DFS) and mean overall survival (OS).
It has been reported that DFS and OS are significantly better in patients who develop pCR than in those who do not [3-5]. Taking all patients into consideration, the pCR rates after NAC have been reported as 25-30% in breast tissue and 40% in the axilla.
While pCR for the breast increases to 65% in TNBC, when Her-2 neu blockers are added to the treatment in

Pervenuto in Redazione Gennaio 2023. Accettato per la pubblicazione Aprile 2023
Correspondence Author: Emine Yildirim. Department of General Surgery, University of Health Sciences Turkey, Gaziosmanpasa Training and Research Hospital. Karayollari Mah., Osmanbey Cad., 621. Sokak, 34255 Gaziosmanpasa, Istanbul, Turkey (e-mail: opdreyildirim@gmail.com)

Her-2 enriched patients, pCR has been shown to increase to 69% in the breast and 74% in the axilla [6-8].

As for all other malignancies, studies of de-escalation in surgical treatment for breast cancer are ongoing. Increasing pCR rates have led to research of whether or not there is a group for which surgical treatment could be avoided. Therefore, studies have been conducted to attempt to predict the radiological response to NAC in the breast and to permit less intervention to the axilla [9]. There is also research about whether or not with radiological evaluation after NAC, the pathological response can be reliably identified by taking a biopsy from the tumor bed in the breast.

These studies have aimed to define pCR without surgery with sufficient biopsy in suitable patients. It has been reported that especially in breast cancer patients with clip placement first, not accompanied by ductal carcinoma in-situ, and not multicentric, the presence of residual cancer in the breast can be more accurately discounted with vacuum-assisted biopsy without the need for surgery [10]. It has also been shown that magnetic resonance imaging (MRI)-guided biopsy can predict pCR with 95% accuracy [11].

When the studies on this subject increase and adequate definitions are made, perhaps the watch and wait approach performed in rectal cancer can be defined in breast cancer after some time [12].

Following these studies, evaluation of the response in the axilla without surgical grading can be considered in patients developing pCR in the breast, and thus the morbidity of axillary surgery can be avoided. There are several studies in current literature which have compared the response in the breast and axilla after NAC, and have shown that there is a correlation. It has been demonstrated in those studies that the axillary residual burden decreased in patients with pCR in the breast, and increased rates of axillary pCR rates. When the increase in pCR rates in the axilla after NAC is considered in patients in different molecular subgroups who develop pCR in the breast, this suggests that there could be a de-escalation in the surgical approach to the axilla in the future [13-15].

The aim of this study was to investigate whether the correlation between treatment response in the breast and the axilla in patients with axillary involvement who received NAC, can be used as a guide for the axillary approach, and to determine whether or not axillary pCR can be predicted in a specific patient group who develop pCR in the breast.

Materials and Method

Study Design and Patient Population

Approval for this retrospective cohort study was granted by the Ethics Committee of Gaziosmanpasa Training and Research Hospital (decision no:368, dated: 24.11.2021). As the data were anonymous and used retrospectively, the requirement for patient informed consent was waived.

The data were retrospectively screened of 512 patients who underwent surgery in our hospital because of breast cancer. All the patients included were aged >18 years, classified as T_{1-4}, N_{1-3}, with axillary metastasis proven before NAC. The study exclusion criteria were defined as known distant metastasis at the time of diagnosis, receiving neoadjuvant endocrine treatment, receiving neoadjuvant radiotherapy, or having abandoned chemotherapy before completion.

The demographic, clinical, radiological, and pathological data of the patients, the NAC regime administered, and the surgical technique used were reviewed retrospectively from the medical records.

The clinical stage was determined from the physical examination and imaging at the time of diagnosis.

Tumor diameter before NAC was measured on ultrasonography, and in multicentric tumors, the measurement of the largest mass was used as the tumor diameter.

Histopathological Evaluation Before Nac

From patients diagnosed with breast cancer with a tru-cut biopsy taken from the mass in the breast, and thought to have metastasis in the axilla from physical examination and/or imaging, a fine-needle aspiration biopsy (FNAB) was taken under USG guidance.

The tru-cut biopsy material was evaluated in respect of histological-nuclear grade, Ki-67 level, estrogen receptor (ER), progesterone receptor (PR), and Her-2 neu status. In the evaluation of hormone receptors, positivity was accepted as nuclear reaction >1% for ER and PR. In the Her-2 neu evaluation, negativity was accepted as score 0 and score 1 (<10% incomplete reaction) and positivity was accepted as score 3 (>10% strong reaction). Materials with a score of 2 (>10% moderate reaction) were re-evaluated with fluorescent in-situ hybridisation (FISH).

Clinicopathological definitions of breast cancer subtypes were made as follows[16].

Luminal A: ER positive, PR positive (>20%), Ki-67 low, Her-2 neu negative.

Luminal B: ER positive, PR low (<20%), or ER positive, Her-2 neu positive, any PR. Ki-67 value or low PR may be used to distinguish between Luminal A and Luminal B.

Her-2 enriched: ER and PR negative, Her-2 neu positive

TNBC: ER, PR and Her-2 neu negative.

In the histological grading, the Bloom-Richardson grading system was used[17]. The presence of atypical cells in the axillary biopsy was accepted as malignancy.

Chemotherapy and surgery

All the patients included in the study received 4 cycles of AC+T (doxorubicin and cyclophosphamide followed by paclitaxel) as the NAC regimen, and for patients with Her-2 neu positivity, trastuzumab was added to the treatment. The surgical treatment was performed as segmental mastectomy or mastectomy with sentinel lymph node biopsy or axillary lymph node dissection.

Histopathological Evaluation of the Response To Chemotherapy

The response to NAC was evaluated using the Miller-Payne grading system in breast tissue, and the Pinder system in the axilla[18,19].
According to this Miller-Payne scoring system, evaluation has been defined as following:
– Grade 1, no reduction in overall cellularity (pathological no response, pNR);
– Grade 2, a minor loss of tumor cells (up to 30% loss);
– Grade 3, an estimated reduction between 30% and 90% in tumor cells;
– Grade 4, marked the disappearance of tumor cells (more than 90% loss);
– Grade 5 is defined as no identifiable malignant cells, although ductal carcinoma in situ may be present (pathological complete response, pCR)[18]. In the statistical evaluations of the breast tissue, comparisons were made by accepting Miller-Payne Grade 5 as pCR, Grades 2, 3, and 4 as pathological partial response (pPR), and Grade 1 as pathological no response (pNR).

According to Pinder pathological scoring system, evaluation has been defined as following
1. Pathological complete response: No evidence of metastatic disease and no evidence of changes in the lymph nodes.
2. Metastatic tumor not detected but evidence of response / down-staging, e.g., fibrosis.
3. Metastatic disease present but also evidence of response, such as nodal fibrosis.
4. Metastatic disease present with no evidence of response to therapy[19].
In the statistical evaluations of the axilla, comparisons were made by accepting Pinder Grade 1 as pCR, Grades 2 and 3 as pPR, and Grade 4 as pNR.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn. 21 and MedCalc software. Conformity of continuous variables to normal distribution was assessed with the Shapiro Wilk test.

Groups of variables with normal distribution were compared with One-Way ANOVA, those not showing normal distribution with the Mann Whitney U-test, and more than two groups with the Kruskal Wallis test. The Chi-square test was applied to categorical data. In the evaluation of pathological response and radiological response to predict each other, diagnostic coefficients were calculated. Receiver Operating Characteristic (ROC) curve analysis was used to determine the cutoff value of Ki-67 according to those with a complete response in both tests, and to determine the factors affecting complete response, a Multivariate Logistic Regression analysis model was formed. The level of statistical significance was accepted as 0.05. The predictive values of breast pCR as a diagnostic test for identifying concurrent axillary pCR were evaluated with diagnostic tests including sensitivity, specificity, positive predicted value (PPV), negative predicted value (NPV) and accuracy [20].

Results

Evaluation was made of a total of 140 patients with a mean age of 55.17±11.61 years (range, 29-87 years).
The mean tumor diameter was determined to be 36.11±18.41 mm (range, 10-90mm) before treatment and 19.68±21.72 mm (range, 0-105mm) after treatment. A diagnosis of invasive ductal cancer was made in 120 (85.7%) patients, of which 42 (30%) were grade 2A, 63 (45%) grade 2B, 26 (18.6%) grade 3A, 3 (2.1%) grade 3B, and 6 (4.3%) grade 3C. Multicentric tumor was observed in 21 (15%) patients.
The subtypes were determined as luminal A in 7%, luminal B in 30%, Her-2 enriched in 24.3%, and TNBC in 10% of the patient population. As the patients with no axillary metastasis in the TNBC and Her-2 enriched subgroups were excluded from the study, the number of patients in the luminal A and B subgroups was higher than expected.
Following treatment, pCR was determined in the breast in 40 (28.6%) patients and in the axilla in 34 (24.3%) patients. BCS was performed in 102 (73.4%) patients. ALND was performed in 126 (90%) patients, and axillary pCR was seen in 19 (15.8%) patients who underwent dissection. In the patient group with pCR, of those who underwent ALND, there was initially N_2 or perioperative sentinel lymph node could not be identified.

Breast and Axillary Pathological Response

In the evaluation made according to the pathological response in the breast and axilla, pre-treatment tumor diameter in the patient group with pCR in the breast was determined to be smaller than in the groups with pNR and pPR (27.95±11.16, 42.39±19.55, 38.72±19.82,

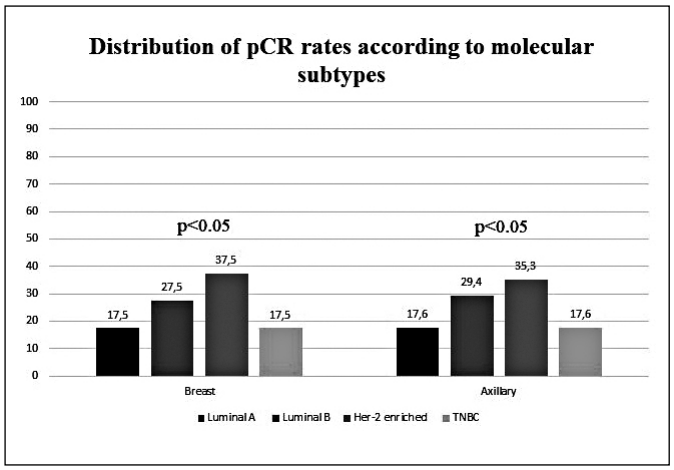

Fig. 1: Distribution of pCR rates according to molecular subtypes.

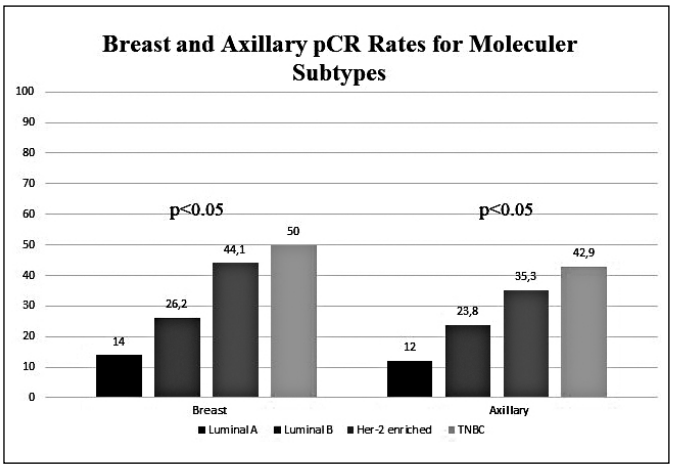

Fig. 2: Breast and Axilla pCR Rates for Moleculer Subtypes.

respectively, p=0.005). The response to treatment was evaluated as better in patients with a small tumor size. The postoperative tumor size was calculated as significantly smaller in the groups that developed pCR in the breast and in the axilla compared to the groups with pPR and pNR (p<0.001, p=0.006, respectively). No pCR was seen in the breast or axilla in any patient with multicentric tumor (p<0.05).

The mean age of patients was 55.32±11.01 years in those with pCR in breast tissue and 53.15±10.47 years in those with pCR in the axilla.

According to the Miller-Payne grading system, pCR was seen in the breast tissue of 40 (28.6%) patients, pPR in 82 (58.6%), and pNR in 18 (12.9%).

According to the Pinder grading system, pCR was seen in the axilla in 34 (24.3%) patients, pPR in 91 (65.0%), and pNR in 15 (10.7%).

When the evaluations of response to NAC were made according to tumor subtypes, pCR was determined at the rates of 50% in the breast and 42.85% in the axilla in TNBC. These pCR rates were 44.12% for the breast and 32.59% for the axilla in the Her-2 enriched group, 26.19% for the breast and 23.80% for the axilla in Luminal B, and 14% for the breast and 12% for the axilla in Luminal A. The distribution according to subtypes of the patients who developed pCR in the breast and axilla was determined as 17.5-17.6% Luminal A, 27.5-29.4% Luminal B, 37.5-35.3% Her-2 enriched, and 17.5-17.6% TNBC. The group with the highest pCR rate was TNBC, and when the distribution was examined of patients with pCR, the most patients with pCR in both the breast and axilla were seen to be in the Her-2 enriched subgroup, and the most patients with pNR were in the luminal B subgroup (p=0.025, p=0.003, respectively). The distribution of patients with pCR according to molecular subtypes is shown in Fig. 1. The rates of response of the subtypes are shown in Fig. 2.

ER positivity was determined in 114 (81.4%) patients. When the correlation was examined between pathological response and ER, there was seen to be ER positivity in 88.9% of the group with pNR in the breast and in 62.5% in the pCR group. ER positivity was determined in 93.3% of the group with pNR in the axilla and in 64.7% in the pCR group. In both groups, ER negativity was seen to increase the pCR rates (p=0.001, p=0.012, respectively).

Her-2 neu positivity was determined in 43 (30.7%) patients. Her-2 neu negativity was seen in 83% of the patients with pNR in the breast and in 93.3% of patients with pNR in the axilla. In the patients with Her-2 neu negativity, the rates of pPR and pNR were higher in both the breast and the axilla (p=0.019, p=0.014, respectively).

No correlation was observed between nuclear grade and stage and the pathological response in either the breast or axilla (p>0.05).

The clinicopathological data of the patients are shown in Table 1.

In the univariate analysis evaluation, Her-2 enriched subtype, ER negativity, PR negativity, Her-2 neu positivity, and Ki-67 level >25% were found to be effective in the development of pCR in both the breast and the axilla, and tumor diameter, age, nuclear grade and stage were determined not to have any effect.

In the multivariate analysis, Her-2 neu positivity was found to be 4-fold significant (OR: 4.06, 95%CI:1.2-13.6, p=0.023) in the determination of pCR in the breast and axilla together.

Relationships Between Breast and Axillary PCR

When the relationship between the pathological response in the breast and axilla was examined, pCR was seen in the axilla of 45% of the patients with pCR in the breast. Of the 34 patients with pCR in the axilla, pCR was

Table I - *Clinicopathologic characteristic of patients in two groups.*

Characteristic	Breast Pathological Response (Miller-Payne Staging System)							Axillary Pathological Response (Pinder Staging System)						
	pNR (n=18) mean±SD (min-max)		pPR (n=82) mean±SD (min-max)		pCR (n=40) mean±SD (min-max)		p1	pNR (n=15) mean±SD (min-max)		pPR (n=91) mean±SD (min-max)		pCR (n=34) mean±SD (min-max)		p1
Age (year)	54,72±10,20 (36-73)		55,20±12,30 (29-87)		55,32±11,01 (32-77)		0,983	51,67±12,02 (32-68)		49,93±11,64 (26-86)		53,15±10,47 (34-74)		0,654
Before treatment tumor diameter	42,39±19,55 (18-81)		38,72±19,82 (15-90)		27,95±11,16 (10-57)		0,005*	37,87±21,89 (17-90)		35,84±17,72 (10-90)		36,09±19,14 (14-84)		0,986*
Post surgery tumor diameter	46±29,35 (10-105)		23,27±16,34 (0-80)		0,75±4,74 (0-30)		<0,001*	28,93±32,66 (0-105)		21,28±20,35 (0-80)		11,44±16,87 (0-65)		0,006*
	n	%	n	%	n	%	p2	n	%	n	%			p2
Pathology														
Invazive ductal cancer	15	83,3	66	80,5	39	97,5		15	100,0	73	80,2	32	94,1	
Invazive lobular cancer	1	5,6	10	12,2	0	0	0,098	0	0,0	10	11	1	2,9	0,152
Other	2	11,1	6	7,3	1	2,5		0	0,0	8	8,8	1	2,9	
Multicentricity														
Absent	14	77,8	65	79,3	40	100ab	0,007	12	80,0	73	80,2	34	100ab	0,019
Present	4	22,2c	17	20,7c	0	0		3	20c	18	19,8c	0	0	
Subtype														
Luminal A	6	33,3	37	45,1c	7	17,5		4	26,7	40	44c	6	17,6	
Luminal B	8	44,4	23	28	11	27,5	0,025	10	66,7	22	24,2	10	29,4	0,003
Her-2 enriched	3	16,7	16	19,5	15	37,5b		1	6,7	21	23,1	12	35,3a	
TNBC	1	5,6	6	7,3	7	17,5		0	0,0	8	8,8	6	17,6	
Estrogen receptor														
Absent	2	11,1	9	11	15	37,5ab	0,001	1	6,7	13	14,3	12	35,3ab	0,012
Present	16	88,9c	73	89,0c	25	62,5		14	93,3c	78	85,7c	22	64,7	
Progesterone receptor														
Absent	6	33,3	24	29,3	20	50	0,079	1	6,7	13	14,3	12	35,3	0,133
Present	12	66,7	58	70,7	20	50		14	93,3	78	85,7	22	64,7	
Her-2 neu														
Absent	15	83,3c	61	74,4c	21	52,5	0,019	14	93,3c	65	71,4c	18	52,9	0,014
Present	3	16,7	21	25,6	19	47,5ab		1	6,7	26	28,6	16	47,1ab	
Nuclear Grade														
1	0	0	2	2,4	0	0		0	0,0	2	2,2	0	0	
2	11	61,1	54	65,9	18	45	0,130	8	53,3	59	64,8	16	47,1	0,263
3	7	38,9	26	31,7	22	55		7	46,7	30	33	18	52,9	
Stage														
2A	4	22,2	22	26,8	16	40		3	20,0	24	26,4	15	44,1	
2B	8	44,4	37	45,1	18	45	0,210	7	46,7	42	46,2	14	41,2	
3A	6	33,3	17	20,7	3	7,5		5	33,3	18	19,8	3	8,8	0,315
3B	0	0	3	3,7	0	0		0	0,0	3	3,3	0	0	
3C	0	0	3	3,7	3	7,5		0	0,0	4	4,4	2	5,9	

SD: Standard deviation, TNBC: Triple negative breast cancer, Her-2: Human epidermal growth factor receptor-2, pCR: Pathological complete response, pPR: Pathological parsiyel response, pNR: Pathological No Response,p1:One-Way ANOVA *Kruskal Wallis test, p2:Chi-Squared test, a:significantly high from pNR, b:significantly high from pPR, c:significantly high from pCR

determined in the breast in 52.9%. The relationships between breast and axillary pathological response are shown in Table II.

When evaluations were made in respect of the accuracy values of the breast and axilla to predict each other, they were determined to be significant for pCR, pPR, and pNR. When the sensitivity values were examined, there was no significance for the prediction of pCR in the axilla in the group with pCR in the breast. In the partial response group, sensitivity and PPV values were high for response in the breast to predict response in the axilla. The sensitivity, specificity, PPV, PNV, and accuracy values of the breast and axilla to predict response in each other are shown in Table III.

When evaluations were made according to molecular subtype, no significant differences were observed. The highest sensitivity of pCR in the breast as a diagnostic test in the prediction of axillary pCR was observed in TNBC (57.14%). PPV was high in the Her-2 enriched and TNBC groups (66.67%). The highest sensitivity of pCR in the axilla as a diagnostic test in the prediction of pCR in the breast was observed in the Her-2 enriched and TNBC groups (66.7%), and PPV was high in TNBC.

Although the findings seemed to have an effect on the diagnostic test results, there was no statistical significance. The results are shown in Tables IV(A)(B).

Discussion

The results of this study showed that the mean pCR rate in patients with T_{1-4}, N_{1-3}, M_0 breast cancer who underwent surgery after NAC was 28.6% in the breast and 24.3% in the axilla. There was seen to be pCR in the axilla of 45% of the patients with pCR in the breast and pCR in the breast of 52.9% of patients with pCR in the axilla. Unlike previous studies, the patients includ-

Table II - *The relationship between breast and axillary pathological response.*

	Breast pathological response category (Miller PayneStaging System)								
Axillary pathological response category	**pCR (n=40)**		**pPR (n=82)**		**pNR (n=17)**		**Total (n=140)**		**P value**
(Pinder Staging System)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
pCR (n=34)	18	45,0	12	14,6	4	22,2	34	24,3	
pPR (n=91)	20	50,0	60	73,2	11	61,1	91	65,0	0,006
pNR (n=15)	2	5,0	10	12,2	3	16,7	15	10,7	
	Axillary pathological response category (PinderStaging System)								
Breast pathological response category	**pCR (n=34)**		**pPR (n=91)**		**pNR (n=15)**		**Total (n=140)**		**P value**
(Miller Payne Staging System)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
pCR (n=40)	18	52,9	20	22,0	2	13,3	40	28,6	
pPR (n=82)	12	35,3	60	65,9	10	66,7	82	58,6	0,006
pNR (n=17)	4	11,8	11	12,1	3	0,2	17	12,2	

pCR= Pathological complete response; pPR= Pathological partial response; pNR= Pathological no response; p=Chi-Squared test

Table II - *The relationship between breast and axillary pathological response.*

	Breast pathological response category (Miller PayneStaging System)								
Axillary pathological response category	**pCR (n=40)**		**pPR (n=82)**		**pNR (n=17)**		**Total (n=140)**		**P value**
(Pinder Staging System)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
pCR (n=34)	18	45,0	12	14,6	4	22,2	34	24,3	
pPR (n=91)	20	50,0	60	73,2	11	61,1	91	65,0	0,006
pNR (n=15)	2	5,0	10	12,2	3	16,7	15	10,7	
	Axillary pathological response category (PinderStaging System)								
Breast pathological response category	**pCR (n=34)**		**pPR (n=91)**		**pNR (n=15)**		**Total (n=140)**		**P value**
(Miller Payne Staging System)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
pCR (n=40)	18	52,9	20	22,0	2	13,3	40	28,6	
pPR (n=82)	12	35,3	60	65,9	10	66,7	82	58,6	0,006
pNR (n=17)	4	11,8	11	12,1	3	0,2	17	12,2	

pCR= Pathological complete response; pPR= Pathological partial response; pNR= Pathological no response; p=Chi-Squared test

Table III - *Sensitivity, specificity, PPV, NPV and accuracy in predicting each other for breast and axilla*

Breast pathological response category (Miller-Payne Staging System)	Axillary pathological response category (Pinder Staging System) Pathological Complete Response				
	Breast Sensitivity (%) Axillary PPV (%)	**Breast Specificity (%) Axillary NPV (%)**	**Breast PPV (%) Axillary Sensitivity (%)**	**Breast NPV (%) Axillary Specificity (%)**	**Accuracy (%)**
Pathological Complete Response	52,94 (35,13-70,22)	79,25 (70,28-86,51)	45,00 (33,42-57,15)	84,00 (78,39-88,37)	72,86 (64,69-80,02)
	Pathological Parsiyel Response				
	Breast Sensitivity (%) Axillary PPV (%)	**Breast Specificity (%) Axillary NPV (%)**	**Breast PPV (%) Axillary Sensitivity (%)**	**Breast NPV (%) Axillary Specificity (%)**	**Accuracy (%)**
Pathological Parsiyel Response	65,93 (55,25-75,55)	55,10 (40,23-69,34)	73,14 (65,92-79,36)	46,55 (37,23-56,06)	62,14 (53,56-70,20)
	Pathological No Response				
	Breast Sensitivity (%) Axillary PPV (%)	**Breast Specificity (%) Axillary NPV (%)**	**Breast PPV (%) Axillary Sensitivity (%)**	**Breast NPV (%) Axillary Specificity (%)**	**Accuracy (%)**
Pathological No Response	20,00 (4,33-48,09)	88,00 (80,98-93,13)	16,67 (6,14-37,95)	90,16 (87,59-92,25)	80,71 (73,20-86,89)

PPV: Positive predictive value, NPV: Negative predictive value.

ed at the beginning of this study were those with cN_{1-3} and axillary involvement proven with biopsy, and the comparisons between breast and axillary pCR were conducted on this cohort.

The first study in literature on this subject was probably the study by Kuerer et al. in 1998. In that study, pCR was determined in the axilla in 60.3% of the patients with complete response in the breast after NAC, and it was reported that pCR in the breast following NAC in LABC predicted axillary pCR with a high probability [21].

There are few studies in current literature that have researched the breast and axillary response after NAC in breast cancer patients and that have reported that pCR in the breast strongly predicts the response in the axilla [13,14,22-24].

In a study by Tadros et al. of N_{0-1} patients before NAC, it was reported that of the patients who developed pCR in the breast, pCR was seen in the axilla in 89.6% of the group with initial axillary lymph node involvement[22]. Lim et al. reported pCR at 29.1% in the breast and 41.2% in the axilla. The highest pCR rates in that study were calculated as 66.7% in the breast and 84.2% in the axilla in the Her-2 enriched subgroup. A strong correlation was shown between node positivity and breast and axillary pCR in the Her-2 enriched and TNBC subtypes, and pCR in the breast was reported to have 90% PPV in identifying axillary pCR[14].

In a study that evaluated the long-term results of ACOSOG Z1071, the pCR rates were found to be 33.5% for the breast and 40.9% for the axilla. Complete response was obtained in 27.8% of the patients in both the breast and the axilla. In the TNBC subgroup, the pCR rate in the breast was 51.2% and axillary pCR was seen in 82% of these patients. In the Her-2 enriched subtype, the pCR rate in the breast was 50.5% and axillary pCR was determined in 89.3% of these patients. In the hormone receptor positive Her-2 neu negative subgroup, although pCR in the breast was only seen in 15.5%, pCR in the axilla was seen in 74.2% of these patients[23].

In a study by Vugts et al., of the patients with initial axillary involvement, pCR was determined in the breast in 31.4%, in the axilla in 40.9% and in both the breast and axilla in 24.5%. The development of pCR in the breast was reported to be a strong predictor of pCR in the axilla (OR: 10.89, 95% CI: 4.20-28.22). In the same study, Her-2 enriched and TNBC subtypes were seen to be predictors for pCR in the breast, and Her-2 neu positivity was seen to be a predictor for axillary pCR[13]. Similarly, in a study by Barron et al., pCR for the breast was found to be at the rate of 43.3% in the Her-2 enriched subgroup, and the rate of residual axillary disease was seen to be 12.4% in these patients with pCR in the breast. In other words, axillary pCR was found at the rate of 87.6% in patients with breast pCR.

In hormone receptor positive, Her-2 neu negative patients, pCR in the breast was found to be 12.7% and pCR in the axilla was determined in 69.5% of these patients[24].

Table IV (A) - *Diagnostic parameters of breast pCR as a diagnostic test for identifying concurrent axillary pCR.*

Breast pCR (n=40)	Prevalence of axillary pCR	Sensitivity	Specificity	PPV	NPV	Accuracy
Luminal A (n=7)	0 (0,0%)	0 (0-40,96)	86,05 (72,07-94,70)	0	84,09 (82,41-85,64)	74,00 (59,65-85,37)
Luminal B (n=11)	6 (54,5%)	54,55 (23,38-83,25)	87,10 (70,17-96,37	60,00 (34,16-81,27)	84,38 (73,60-91,27)	78,57 (63,18-89,70)
Her-2 enriched (n=15)	8 (53,3%)	53,33 (26,59-78,73)	78,95 (54,44-93,95)	66,67 (42,61-84,35)	68,18 (54,32-79,43)	67,65 (49,47-82,61)
TNBC (n=7)	4 (57,1%)	57,14 (18,41-90,10)	71,43 (29,04-96,33)	66,67 (38,47-88,38)	62,50 (38,59-81,55)	64,29 (35,14-87,24)

Table IV (B) - *Diagnostic parameters of axillary pCR as a diagnostic test for identifying concurrent breast pCR.*

Axillary pCR (n=34)	Prevalence of breast pCR	Sensitivity	Specificity	PPV	NPV	Accuracy
Luminal A (n=6)	0 (0,0%)	0 (0-45,93)	84,09 (69,94-93,36)	0	86,05 (84,43-87,52)	74,00 (59,65-85,37)
Luminal B (n=10)	6 (60,0%)	60 (26,24-87,85)	84,38 (67,21-94,73)	54,55 (31,67-75,65)	87,10 (75,69-93,60)	78,57 (63,18-89,70)
Her-2 enriched (n=12)	8 (66,7%)	66,67 (34,88-90,08)	68,18 (45,13-86,14)	53,33 (35,49-70,36)	78,95 (61,59-89,76)	67,65 (49,47-82,61)
TNBC (n=6)	4 (66,7%)	66,67 (22,28-95,67)	62,5 (24,9-91,48)	57,14 (31,63-79,35)	71,43 (41,67-89,74)	64,29 (35,14-87,24)

TNBC: Triple negative breast cancer, Her-2: Human epidermal growth factor receptor-2, pCR: Pathological complete response, PPV: Positive predictive value, NPV: Negative predictive value.

Samiei et al. evaluated T_{1-3} N_{0-1} patients and reported low rates of both breast and axillary pCR in T_3 and ER positive Her-2 negative groups. Of the patients with initial axillary involvement, pCR in the axilla was seen in 45% of the patients with pCR in the breast after NAC, and this rate was lower than those reported in other studies [15].

In a recently published study, the 10-year records of the Korean Breast Cancer Society were examined, and it was reported that pCR developed in the breast of 21.6% and in the axilla of 59.7% of patients who received NAC. Of the patients with initial node positivity, pCR in the axilla was determined in 86.6% of the patients with pCR in the breast. In TNBC and Her-2 neu positive breast cancer patients with initial clinical N_0 or N_1 who developed pCR in the breast there was reported to be a low risk of nodal metastasis after treatment [25].

In a study by Choi et al, pCR in the breast was found to be at the rate of 28.2% and axillary pCR at 51.9% after NAC, and pCR in the axilla was determined in 87.1% of those with pCR in the breast. This study emphasized the strong correlation between breast and axillary pCR and biological tumor subtype, clinical grade and initial node involvement [26].

Wang et al. reported that in patients with initial node positivity whose treatment was started with NAC, clinical T stage, primary tumor response, and ER and PR status were effective in predicting axillary response, and a nomogram was developed for this [27].

Also, Qiu et al. found pCR in the breast as 6.6% and in the axilla as 18.9% in hormone receptor-positive patients receiving NAC. They developed a prediction model to predict axillary pCR in hormone receptor positive patients [28].

In a study that was conducted using the Shanghai Jiao Tong University Breast Cancer Database, breast pCR was found to be 24.2% in N_1 disease, and 19.3% in LABC, and the axillary pCR rates for these were 39.7% and 33.6%, respectively. In those with breast pCR, axillary pCR was 74.3% in the patient group with initial clinical N_1 and 66.1% in LABC. The development of axillary pCR in patients with breast pCR was determined most in the Her-2 neu positive subtype. According to the multivariate analysis, the initial clinical grade, PR status, Her-2 neu status, and molecular subtype were determined to be factors affecting axillary response in the group that developed pCR in the breast. Advanced stage and PR positivity had a positive effect on residual nodal disease, and Her-2 neu positivity had a negative effect [29].

In the current study, pCR was observed in the breast at the rate of 44.12%, and axilla at 35.3% in Her-2 enriched subtype, and in the breast at 50% and in the axilla at 42.85% in TNBC. Her-2 enriched subtype, ER negativity, PR negativity, Her-2 neu positivity and Ki-67 level >25% were found to have an impact on the development of pCR in the breast and axilla. In patients with pCR in the breast, the rate of pCR in the axilla was 45%, and this compatibility was seen most in the Her-2 enriched subgroup. When pCR was seen in both the breast and axilla, Her-2 neu positivity was determined to be 4.062-fold significant (OR:4.062, 95%CI:1.2-13.6, p=0.023). Unlike previous studies, evaluation was made of the accuracy values of the breast and axilla in the prediction of each other, and they were found to be significant both for pCR and pPR and pNR. However, when the sensitivity, specificity, PPV and NPV values were examined in the group that developed pCR

in the breast, they were not significant for the prediction of pCR in the axilla.
LIMITATIONS: The primary limitations of this study can be considered to be the retrospective design and the relatively low number of patients as it was a single-center study. However, being conducted in a single center allowed full and detailed access to the patient data. The most important factor that reduced the number of patients was that patients with axillary involvement only were excluded from the study, and therefore the research question of to what extent the development of pCR in the breast can predict axillary response could be examined in detail, which was the aim of the study. Despite the determination of clinical differences in the multivariate analysis, as this was conducted with a low number of patients who developed pCR in both the breast and axilla at the same time, the sample was not sufficient for statistical significance to be determined.
CONCLUSION: The results of this study demonstrated compatibility between the pathological responses in the breast and axilla following NAC in patients with initial clinical node positivity. The pathological response in the breast was significant in respect of the accuracy values in predicting the axillary response. This accordance was higher in patients in the Her-2 enriched subtype in particular. These results suggest that there could be de-escalation in axillary surgery in the future in the patient group where there is a high probability of pCR in the axilla, with complete response considered radiologically and pCR in the breast determined with image-guided biopsy.

Learning Points
– pCR in the breast and axilla is most common in TNBC and Her2 enriched subtypes.
– pCR was seen in the axilla of 45% of the patients with pCR in the breast.
– Her-2 neu positivity is significant in the detection of
– pCR in breast and axilla together.

Riassunto

Lo scopo di questo studio era di valutare la correlazione della risposta patologica nel tessuto mammario e nell'ascella di pazienti con carcinoma mammario sottoposti a intervento chirurgico dopo chemioterapia neoadiuvante. Nello studio, di tipo retrospettivo, sono state incluse pazienti con carcinoma mammario T1-4, N1-3, M0 che sono state sottoposte a intervento chirurgico dopo chemioterapia neoadiuvante presso l'Ospedale XXX tra il 2013 e il 2022.
La risposta del tessuto mammario alla chemioterapia è stata valutata con la classificazione Miller-Payne, e la risposta dei linfonodi ascellari alla chemioterapia è stata valutata con il sistema di classificazione Pinder. I pazienti sono stati raggruppati istopatologicamente come carcinoma mammario luminale A, luminale B, Her-2 arricchito o triplo negativo (TNBC).
RISULTATI: Lo studio è stato completato con 140 pazienti. La risposta patologica completa (pCR) è stata osservata nella mammella in 40 pazienti e nell'ascella in 34. Delle pazienti con pCR nella mammella, la pCR è stata determinata anche nell'ascella nel 45%. Nelle pazienti con pCR sia nella mammella che nell'ascella, il sottotipo arricchito di Her-2, la negatività del recettore degli estrogeni, la negatività del recettore del progesterone, la positività di Her-2 neu e il livello di Ki-67 >25% sono risultati efficaci (p<0,05) . La positività di Her-2 neu è stata valutata come statisticamente significativa nello sviluppo di pCR sia nel seno che nell'ascella (OR: 4,06, IC 95%: 1,2-13,6, p=0,023).
CONCLUSIONE: Lo sviluppo di pCR nel seno, specialmente nel sottogruppo arricchito di Her-2, può essere accettato come fattore predittivo per la valutazione della risposta ascellare in pazienti con carcinoma mammario. La minore compatibilità è stata osservata nel sottogruppo luminale A.

References

1. Korde LA, Somerfield MR, Carey LA, Crews JR, Denduluri N, Hwang ES, et al.: Ne*oadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline*. J Clin Oncol. 2021 May 1;39(13):1485-1505. doi: 10.1200/JCO.20.03399.

2. Franceschini G, Di Leone A, Natale M, Sanchez MA, Masett R: *Conservative surgery after neoadjuvant chemotherapy in patients with operable breast cancer*. Ann Ital Chir. 2018;89:290. PMID: 30352955.

3. Krystel-Whittemore M, Xu J, Brogi E, Ventura K, Patil S, Ross DS, et al.: *Pathologic complete response rate according to HER2 detection methods in HER2-positive breast cancer treated with neoadjuvant systemic therapy.* Breast Cancer Res Treat. 2019; 177(1):61-66. doi: 10.1007/s10549-019-05295-9.

4. Huang M, O'Shaughnessy J, Zhao J, Haiderali A, Cortés J, Ramsey SD, Briggs A, et al.: *Association of Pathologic Complete Response with Long-Term Survival Outcomes in Triple-Negative Breast Cancer: A Meta-Analysis*. Cancer Research. 2020 Dec 15;80(24):5427-34. doi: 10.1158/0008-5472.CAN-20-1792.

5. Spring LM, Fell G, Arfe A, Sharma C, Greenup R, Reynolds KL, et al.: *Pathologic Complete Response after Neoadjuvant Chemotherapy and Impact on Breast Cancer Recurrence and Survival: A Comprehensive Meta-analysis.* Clin Cancer Res. 2020 Jun 15;26(12):2838-2848. doi: 10.1158/1078-0432.CCR-19-3492.

6. Dominici LS, Negron Gonzalez VM, Buzdar AU, Lucci A, Mittendorf EA, Le-Petross HT, et al.: C*ytologically proven axillary lymph node metastases are eradicated in patients receiving preoperative chemotherapy with concurrent trastuzumab for HER2-positive breast cancer.* Cancer. 2010 Jun 15;116(12):2884-9. doi: 10.1002/cncr.25152

7. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al.: *KEYNOTE-522 Investigators. Pembrolizumab for Early*

Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549

8. Yu KD, Liu GY, Chen CM, Li JW, Wu J, Lu JS, et al.: Weekly *paclitaxel/carboplatin/trastuzumab therapy improves pathologic complete remission in aggressive HER2-positive breast cancers, especially in luminal-B subtype, compared with a once-every-3*-weeks schedule. Oncologist. 2013;18(5):511-7. doi: 10.1634/theoncologist.2012-0057

9. Yıldırım E , Uçar N, Yetiş F , Kayadibi Y, Bektaş S: *Diagnostic performance of breast imaging with ultrasonography, magnetic resonance and mammography in the assessment of residual tumor after neoadjuvant chemotherapy in breast cancer patients.* J Surg Med. 2022; 6(1): 43-48. DOI: 10.28982/josam.1034379.

10. Koelbel V, Pfob A, Schaefgen B, Sinn P, Feisst M, Golatta M, et al.: *Vacuum-Assisted Breast Biopsy After Neoadjuvant Systemic Treatment for Reliable Exclusion of Residual Cancer in Breast Cancer Patients.* Ann Surg Oncol. 2022 Feb;29(2):1076-1084. doi: 10.1245/s10434-021-10847-9.

11. Sutton EJ, Braunstein LZ, El-Tamer MB, Brogi E, Hughes M, Bryce Y, et al.: *Accuracy of Magnetic Resonance Imaging-Guided Biopsy to Verify Breast Cancer Pathologic Complete Response After Neoadjuvant Chemotherapy: A Nonrandomized Controlled* Trial. JAMA Netw Open. 2021 Jan 4;4(1):e2034045. doi: 10.1001/jamanetworkopen.2020.34045.

12. López-Campos F, Martín-Martín M, Fornell-Pérez R, García-Pérez JC, Die-Trill J, Fuentes-Mateos R, et al.: *Watch and wait approach in rectal cancer: Current controversies and future directions.* World J Gastroenterol, 2020; 26(29):4218-4239. doi: 10.3748/wjg.v26.i29.4218.

13. Vugts G, Van den Heuvel F, Maaskant-Braat AJG, Voogd AC, Van Warmerdam LJC, Nieuwenhuijzen GAP, et al.: *Predicting breast and axillary response after neoadjuvant treatment for breast cancer: The role of histology vs receptor status*. Breast J, 2018; 24(6):894-901. doi: 10.1111/tbj.13085.

14. Lim DW, Greene BD, Look Hong NJ: *Relationship Between Breast and Axillary Pathologic Complete Response in Women Receiving Neoadjuvant Chemotherapy for Breast Cancer.* Ann Surg Oncol, 2021; 28(10):5495-5506. doi: 10.1245/s10434-021-10519-8.

15. Samiei S, van Nijnatten TJA, de Munck L, Keymeulen KBMI, Simons JM, Kooreman LFS, et al.: *Correlation Between Pathologic Complete Response* in the Breast and *Absence of Axillary Lymph Node Metastases After Neoadjuvant Systemic Therapy*. Ann Surg, 2020; 271(3):574-580. doi: 10.1097/SLA.0000000000003126.

16. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, et al.: *Personalizing the treatment of women with early breast cancer: Highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013.* Ann Oncol 24(9): 2206-2223, 2013. doi: 10.1093/annonc/mdt303

17. Fitzgibbons P, Connolly J, Bose S, Chen Y, Baca M, Ergerton M: *CAP protocol for the examination of specimens from patients with ınvasive carcinoma of the breast. Available at: https://documents.cap.org/*protocols/cp-breast-invasive-18protocol-4100.pdf [Last accessed on Jan 30, 2022].

18. Ogston KN, Miller ID, Payne S, Hutcheon AW, Sarkar TK, Smith I, et al.: *A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival.* Breast. 2003; 12:320–327. doi: 10.1016/s0960-9776(03)00106-1

19. Pinder SE, Provenzano E, Earl H, Ellis IO: *Laboratory handing and histology reporting of breast specimens from patients who have received neoadjuvant chemotherapy.* Histopathology, 2007; 50: 409-17. doi: 10.1111/j.1365-2559.2006.02419.x.

20. MedCalc: *Software Ltd. Diagnostic test evaluation calculator.* https://www.medcalc.org/calc/diagnostic_test.php (Version 20.011; accessed Jun 28, 2021

21. Kuerer HM, Newman LA, Buzdar AU, Dhingra K, Hunt KK, Buchholz TA, et al.: *Pathologic tumor response in the breast following neoadjuvant chemotherapy predicts axillary lymph node status.* Cancer J Sci Am, 1998; 4(4):230-36.

22. Tadros AB, Yang WT, Krishnamurthy S, Rauch GM, Smith BD, Valero V, et al.: *Identification of Patients With Documented Pathologic Complete Response in the Breast After Neoadjuvant Chemotherapy for Omission of Axillary Surgery.* JAMA Surg, 2017; 152(7):665-670. doi: 10.1001/jamasurg.2017.0562.

23. Boughey JC, Ballman KV, McCall LM, Mittendorf EA, Symmans WF, Julian TB, et al.: *Tumor Biology and Response to Chemotherapy Impact Breast Cancer-specific Survival in Node-positive Breast Cancer Patients Treated With Neoadjuvant Chemotherapy: Long-term Follow-up From ACOSOG Z1071 (Alliance).* Ann Surg, 2017; 266(4):667-676. doi: 10.1097/SLA.0000000000002373.

24. Barron AU, Hoskin TL, Day CN, Hwang ES, Kuerer HM, Boughey JC: *Association of Low Nodal Positivity Rate Among Patients With ERBB2-Positive or Triple-Negative Breast Cancer and Breast Pathologic Complete Response to Neoadjuvant Chemotherapy.* JAMA Surg, 2018; 153(12):1120-1126. doi: 10.1001/jamasurg.2018.2696.

25. Ryu JM, Choi HJ, Park EH, Kim JY, Lee YJ, Park S, et al.: *Korean Breast Cancer Society. Relationship Between Breast and Axillary Pathologic Complete Response According to Clinical Nodal Stage: A Nationwide Study From Korean Breast Cancer Society.* J Breast Cancer, 2022; 25(2):94-105. doi: 10.4048/jbc.2022.25.e17.

26. Choi HJ, Ryu JM, Kim I, Nam SJ, Kim SW, Yu J, et al.: *Prediction of axillary pathologic response with breast pathologic complete response after neoadjuvant chemotherapy.* Breast Cancer Res Treat, 2019; 176(3):591-596. doi: 10.1007/s10549-019-05214-y.

27. Wang W, Wang X, Liu J, Zhu Q, Wang X, Wang P*: Nomogram for predicting axillary lymph node pathological response in node-positive breast cancer patients after neoadjuvant chemotherapy*. Chin Med J (Engl), 2021; 135(3):333-340. doi: 10.1097/CM9.0000000000001876.

28. Qiu J, Zheng Y, Qian D, Guan D, Zheng Q, Xu Y, Ju S, Meng X, Tang H: *Predicting Axillary Response in Hormone Receptor-Positive Breast Cancer after Neoadjuvant Chemotherapy Using Real-World Data.* J Oncol, 2022; 2022:6972703. doi: 10.1155/2022/6972703.

29. Hong J, Tong Y, He J, Chen X, Shen K: *Association between tumor molecular subtype, clinical stage and axillary pathological response in breast cancer patients undergoing complete pathological remission after neoadjuvant chemotherapy: potential implications for de-escalation of axillary surgery*. Ther Adv Med Oncol, 2021; 13:1758835921996673. doi: 10.1177/1758835921996673.