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Original Article

Efficacy of Positron Emission Tomography in Evaluating Neoadjuvant Chemotherapy Response and Factors Affecting Pathological Response in Breast Cancer

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ABSTRACT

Objective: Pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) is associated with higher disease-free survival and overall survival (OS). Posttreatment clinical response (cR) should be evaluated, and the associated factors should be identified. Our aim was to define the efficacy of positron emission tomography (PET) in cR evaluation and possible factors affecting pCR.

Methods: The medical records of patients who were operated on for breast cancer between January 2015 and December 2020 were evaluated. Preoperative cRs were investigated with PET. College of American Pathologists (CAP) 2019 scoring system was used in the evaluation of pathological response. The factors affecting the clinical and pathological response were investigated by examining the menopausal status of the patients, the stage at the time of diagnosis, PET findings before and after NAC, histopathological type of the tumor, molecular subtype, and KI-67 level.

Results: The data of 234 female patients were examined. The mean age was 52.5±12.1 years. The pCR (CAP=0) was observed in 28% of the patients, while the pCR was observed in 40 (72.7%) of 55 (24%) patients with cCR. KI-67 increase and HER2 positivity were factors that positively affected the pathological response ($p<0.05$). The pCR rates in molecular subtypes were 0% in luminal A, 21% in luminal B, 52% in HER2-positive, and 44% in triple-negative groups, and the difference between the groups was statistically significant ($p<0.05$).

Conclusion: NAC reduces tumor size and avoids axillary dissection in patients with locally advanced breast cancer. The use of PET alone in evaluating cR after NAC is not sufficient to predict the pathological response. The pathological response is significantly higher in HER2-positive and triple-negative patients. The decision for NAC should be made considering the factors affecting the response to avoid unnecessary cost and time loss.

INTRODUCTION

Worldwide, breast cancer is the most common type of cancer in women and is the fourth main cause of cancer-related deaths.[1] The most important reason for the high mortality is the diagnosis of the disease in advanced stages. Locally advanced breast cancer (LABC) is defined according to the TNM staging system recommended by the American Joint Committee on Cancer, stages 2B, 3A, 3B, and 3C of the disease.

Neoadjuvant chemotherapy (NAC), also called primary systemic therapy or induction therapy, has become a crucial strategy for LABC worldwide. It aims to reduce the local–regional recurrence rates by reducing the size of the primary tumor and eliminating axillary lymph node metastasis, thus avoiding axillary lymph node dissection (ALND) by increasing the chance of breast-conserving surgery (BCS).[2] However, it is still observed that only 30% of the patients have a complete or almost complete response.

Higher disease-free survival (DFS) and overall survival (OS) rates have been reported in patients with a pathological complete response (pCR) after NAC.[3] Tumor size, hormone receptor (HR) status, human epidermal growth factor receptor 2 (HER2), molecular subtype, and histological type are the main factors associated with pCR. Tumor biology is the most critical factor related to pCR. Previous studies showed that estrogen receptor (ER) and progesterone receptor (PR) negativity, HER2 positivity,

high mitotic index, and KI-67 score were associated with pCR.[3–5] The pCR was highest in the triple-negative group and the lowest in the hormone-positive group.[6]

Clinical response (cR) is usually assessed by posttreatment imaging, as a response to treatment after NAC may differ between individuals. In this aspect, which patients will benefit from the treatment can be predicted, and the strategy can be changed accordingly. In previous studies, it was reported that magnetic resonance imaging (MRI) and ultrasonography (USG) could be used to evaluate cR after NAC.[7–9] However, we preferred to use positron emission tomography (PET) because it has the advantage of evaluating the lesion from both anatomical and metabolic aspects in our study.

This study aimed to investigate the effectiveness of PET alone in cR evaluation and identify possible factors affecting pCR.

MATERIALS AND METHODS

The medical records of patients who were operated on with breast cancer diagnosis in general surgery clinic between January 2015 and December 2020 were retrospectively analyzed. A total of 234 patients who received at least four courses of NAC due to LABC were included in the study. According to TNM staging, 2B (T2-N1, T3-N0), 3A (T0-N2, T1/2-N2, T3-N1/2), 3B (T4, N0-2), and 3C (any T, N3) disease was evaluated as LABC.

The inclusion criteria were: diagnosis of invasive breast cancer, at least four cycles of standard NAC or trastuzumab, evaluation of cR with PET after NAC, and pathological evaluation after surgery. The exclusion criteria were: early-stage breast cancer (less than 2B), distant metastases, nonstandard NAC or hormone therapy only, patients receiving less than four cycles of NAC, and no imaging for cR assessment after NAC.

Most patients received a combination of AC-T (doxorubicin, cyclophosphamide, and taxane) for NAC. In addition to HER2-positive patients, trastuzumab was given, and HR-positive patients were given hormone therapy.

According to the College of American Pathologists, the age, menopausal status, clinical stage at diagnosis, PET findings before and after NAC, tumor type, molecular subtype, KI-67 index, surgical technique, pathology findings, and pathological response levels (CAP) 2019 scoring system were analyzed. Tumors were classified into four molecular subtypes: Luminal A (HR+ HER2– KI-67 <15%), Luminal B (HR+ KI-67 >15%), HER2-positive (HR– HER2+), and triple-negative breast cancer (ER– PR– HER2–).

PET findings before and after NAC were compared for evaluation of cR. cRs were evaluated in three groups: no response, partial response, and complete response. All patients included in the study underwent surgery for the breast and axilla. Sentinel lymph node biopsy negativity after NAC was accepted to remove at least three nonmetastatic lymph nodes after patent blue injection. Postsurgical pathological specimens were evaluated by pathologists specialized in the breast. According to the pathological response CAP of the tumor in the breast, 0 represents no residual tumor, 1 represents significant response, 2 represents moderate response, and 3 represents weak or no response. pCR was defined as the absence of invasive cancer and nodal involvement (ypT0/is ypN0) in the breast regardless of ductal carcinoma in situ.

Statistical analysis

Data were analyzed using SPSS version 22. Frequency, percentage, mean, standard deviation, median, and interquartile range were used as descriptive statistical methods. Continuous variables were evaluated with the Kolmogorov–Smirnov test and the Shapiro–Wilk test. One-way ANOVA test was used for normally distributed continuous variables, and the Mann–Whitney U and the Kruskal–Wallis tests were used for variables with skewed distributions. The Chi-squared test was used to evaluate the categorical data. $P<0.05$ was considered significant for all calculations.

RESULTS

The data of 234 female patients diagnosed with invasive breast cancer who met the inclusion criteria were evaluated. The mean age was 52.5±12.1 years, and most patients (62%) were in the postmenopausal period. According to the histopathological classification, 224 (96%) patients were diagnosed with ductal, 5 (2%) patients with lobular, and 5 (2%) patients with mixed pattern carcinoma. In the classification according to the molecular subtype of the tumor, there were 22 patients in luminal A, 139 patients in luminal B, 46 patients in the HER2-positive group, and 27 patients in the triple-negative group. A total of 55 (23.5%) patients had cCR, and 65 patients (27.8%) had pCR. The highest pCR was in the HER2-positive group (52%), and the lowest was in the luminal A (0%) group. In control imaging analysis, cR was not observed in 47 (20%) patients, and the pathological response was weak or absent in 101 (43%) patients. Detailed demographic and clinical information of the groups is presented in Table 1.

The clinical evaluation with PET-CT was significantly reliable in detecting the pathological response ($p<0.001$). Most of the patients (73.8%) without involvement in PET-CT were found to have pCR. Similarly, 93% of patients without cR also did not have pCR (Table 2).

In multivariate analysis, adequate cR, high KI-67, and HER2 positivity were determined as independent factors that positively affected pCR ($p<0.005$). It was determined that menopausal status and tumor size did not affect the pathological response ($p>0.005$). According to tumor grade, complete and partial response was better in high grade (2 and 3) tumors than in low grade (1) tumors, but this difference was not statistically significant ($p=0.082$). It was observed that there was a significant difference in pathological responses between molecular subtypes after

Table 1. Detailed demographic and clinical data considering molecular subtypes

	All patients (n=234)	Luminal A (n=22)	Luminal B (n=139)	HER2+ (n=46)	Triple– (n=27)	p
Age (years)	52.51±12.10	56.72±13.45	52.63±12.14	52.37±11.55	48.70±11.03	0.147*
Menopausal status, n (%)						
Premenopause	61 (21.6)	5 (22.7)	37 (26.6)	12 (26.1)	7 (25.9)	0.934†
Perimenopause	27 (11.5)	3 (13.6)	14 (10.1)	5 (10.9)	5 (18.5)	
Postmenopause	146 (62.4)	14 (63.6)	88 (63.3)	29 (63.0)	15 (55.6)	
Histological type, n (%)						
Ductal	224 (95.7)	21 (95.5)	132 (95.0)	46 (100.0)	25 (92.6)	0.176†
Lobular	5 (2.1)	–	5 (3.6)	–	–	
Other	5 (2.1)	1 (4.5)	2 (1.4)	–	2 (7.4)	
Histopathological grade, n (%)						
1	17 (7.3)	8 (36.4)	9 (6.5)	–	–	<0.001†
2	156 (66.7)	14 (63.6)	104 (74.8)	27 (58.7)	11 (40.7)	
3	61 (26.1)	–	26 (18.7)	19 (41.3)	16 (59.3)	
KI-67 level	35.00 [25.00]	10.00 [5.00]	30.00 [15.00]	40.00 [26.25]	60.00 [30.00]	<0.001‡
cT, n (%)						
1	47 (20.1)	7 (31.8)	26 (18.7)	11 (23.9)	3 (11.1)	0.129†
2	132 (56.4)	11 (50.0)	84 (60.4)	26 (56.5)	11 (40.7)	
3	31 (13.2)	3 (13.6)	15 (10.8)	6 (13.0)	7 (25.9)	
4	24 (10.3)	1 (4.5)	14 (10.1)	3 (6.5)	6 (22.3)	
PET-CT findings, n (%)						
Involvement (–)	80 (34.2)	4 (18.2)	40 (28.8)	24 (52.2)	12 (44.4)	0.007†
Involvement (+)	154 (65.8)	18 (81.8)	99 (71.2)	22 (47.8)	15 (55.6)	
Clinical response, n (%)						
No response	47 (20.3)	6 (27.3)	31 (22.6)	3 (6.5)	7 (25.9)	0.033†
Partial response	130 (56.0)	13 (59.1)	78 (56.9)	24 (52.2)	15 (55.6)	
Complete response	55 (23.7)	3 (13.6)	28 (20.4)	19 (41.3)	5 (18.5)	
Surgery type, n (%)						
BCS + SLNB	38 (16.2)	3 (13.6)	18 (12.9)	12 (26.1)	5 (18.5)	0.010†
BCS + ALND	25 (10.7)	2 (9.1)	20 (14.4)	2 (4.3)	1 (3.7)	
Mastectomy + SLNB	44 (18.8)	1 (4.5)	23 (16.5)	16 (34.8)	4 (14.8)	
Mastectomy + ALND	53 (22.6)	9 (40.9)	33 (23.7)	6 (13.0)	5 (18.5)	
MRM	74 (31.6)	7 (31.8)	45 (32.4)	10 (21.7)	12 (44.4)	
Pathological response, n (%)						
No residual tumor	65 (27.8)	0 (0.0)	29 (20.9)	24 (52.2)	12 (44.4)	<0.001†
Obvious response	29 (12.4)	2 (9.1)	16 (11.5)	9 (19.6)	2 (7.4)	
Moderate response	39 (16.7)	3 (13.6)	26 (18.7)	4 (8.7)	6 (22.2)	
Weak/no response	101 (43.2)	17 (77.3)	68 (48.9)	9 (19.6)	7 (25.9)	

The data were presented as mean±standard deviation, median [IQR], and n (%). *One-way ANOVA test. †Chi-squared test. ‡Kruskal–Wallis test. BCS: Breast-conserving surgery; SLNB: Sentinel lymph node biopsy; ALND: Axillary lymph node dissection; PET: PET: Positron emission tomography; CT: Computed tomography.

NAC (p<0.001). Both clinical and pathological responses were observed at higher rates in HER2-positive and triple-negative groups (Table 3).

Although breast-preserving surgery is usually performed in patients with cR after NAC, modified radical mastectomy was preferred in cases unresponsive to treatment.

DISCUSSION

NAC is a commonly used treatment to increase the minimally invasive surgery chance in LABC patients.[10] Early cR assessment after NAC is crucial in predicting pCR. Response to NAC is challenging to monitor, and there is no consensus on the best modality. Although palpation and USG are the most frequently used methods in clinical practice, breast MRI is increasing gradually.[8–11] In our clinical practice, PET is used because of its superiority in diagnosing possible metastases in the whole body and preventing loss of time that may occur due to unnecessary examinations.

In our study, overall cR rate was 79% (complete + partial), and the total pathological response rate was 57% (CAP

Table 2. Comparison of clinical and pathological responses according to findings in PET-CT

PET-CT	Pathological response				p
	No residual tumor (n=65)	Obvious response (n=29)	Moderate response (n=39)	Weak/no response (n=101)	
	n (%)	n (%)	n (%)	n (%)	
Involvement (–)	48 (73.8)	14 (48.3)	11 (28.2)	7 (6.9)	<0.001
Involvement (+)	17 (26.2)	15 (51.7)	28 (71.8)	94 (93.1)	

		Clinical response			p
		No (n=47)	Partial (n=130)	Complete (n=55)	
		n (%)	n (%)	n (%)	
Pathological response	No residual tumor (n=65)	2 (4.3)	23 (17.7)	40 (72.7)	<0.001
	Obvious response (n=29)	0 (0.0)	19 (14.6)	9 (16.4)	
	Moderate response (n=39)	4 (8.5)	31 (23.8)	4 (7.3)	
	Weak/no response (n=101)	41 (87.2)	57 (43.8)	2 (3.6)	

PET: Positron emission tomography; CT: Computed tomography.

Table 3. Factors affecting pathological response in multivariate analysis

	Pathological response				p
	No residual tumor (n=65)	Obvious response (n=29)	Moderate response (n=39)	Weak/no response (n=101)	
	n (%)	n (%)	n (%)	n (%)	
Menopausal status					
Premenopause	21 (32.3)	7 (24.1)	8 (20.5)	25 (24.8)	0.338*
Perimenopause	7 (10.8)	1 (3.4)	3 (7.7)	16 (15.8)	
Postmenopause	37 (56.9)	21 (72.4)	28 (71.8)	28 (59.4)	
Tumor size					
cT1	14 (21.5)	5 (17.2)	5 (12.8)	23 (22.8)	0.198*
cT2	38 (58.5)	19 (65.5)	20 (51.3)	55 (54.5)	
cT3	6 (9.2)	4 (13.8)	5 (12.8)	16 (15.8)	
cT4	7 (10.8)	1 (3.4)	9 (23.1)	7 (6.9)	
Histopathological grade					
Grade 1	0 (0.0)	1 (3.4)	5 (12.8)	11 (10.9)	0.082*
Grade 2	45 (69.2)	19 (65.5)	23 (59.0)	69 (68.3)	
Grade 3	20 (30.8)	9 (31.0)	11 (28.2)	21 (20.8)	
KI-67	40.0 [30.0]	40.0 [37.5]	40.0 [40.0]	25.0 [18.5]	<0.001†
HER2					
Negative	21 (32.3)	9 (31.0)	24 (61.5)	77 (76.2)	<0.001*
Positive	44 (67.7)	20 (69.0)	15 (38.5)	24 (23.8)	
Clinical response					
Complete	48 (73.8)	14 (48.3)	11 (28.2)	7 (6.9)	<0.001*
Partial or none	17 (26.2)	15 (51.7)	28 (71.8)	94 (93.1)	
Molecular subtype					
Luminal A	0 (0.0)	2 (9.1)	3 (13.6)	17 (77.3)	<0.001*
Luminal B	29 (20.9)	16 (11.5)	26 (18.7)	68 (48.9)	
HER2+	24 (52.1)	9 (19.6)	4 (8.7)	9 (19.6)	
Triple–	12 (44.4)	2 (7.4)	6 (22.2)	7 (26)	

The data were presented as median [IQR] and n (%). *Chi-squared test. †Mann–Whitney U test. HER2: Human epidermal growth factor receptor 2.

0.1, 2). We observed that cases with a clinically adequate response to NAC, especially in HER2-positive tumors, were associated with a high pCR rate in PET evaluation. In the same line with the literature, tumor remnants can be observed in patients who have a complete cR.[12–14] In our study, pCR was observed in 40 of 55 patients (72.7%) with cCR, while residual tumor cells were histologically confirmed in the remaining 15 patients (27.3%).

Although it is stated in some studies that PET has similar accuracy to MRI in evaluating the cR after NAC, it can never replace USG and MRI in clinical use.[15–17] In fact, the evaluation of the metabolic activity of the tumor is the most prominent advantage of PET. However, it is challenging to perform volumetric analysis from the standardized uptake value parameter, representing the total metabolically active tumor cells. In studies conducted for other malignancies, it has been reported that volume measurement with PET helps evaluate the response to treatment.[18,19] In a prospective study including results of 142 breast cancer cases, the positive predictive value (PPV), sensitivity, and specificity of PET in evaluating NAC response were significantly higher than MRI.[20] We did not have the chance to compare PET with another imaging method, but we observed that pCR prediction rate and early detection of patients with no cR were relatively high in our study. Although PET is insufficient to show the residual tumor after chemotherapy, it is reliable in detecting unresponsive cases to treatment and has a complete response.

A variety of recent studies show that the response to NAC is essential in predicting the prognosis of the disease. The reaction to NAC varies according to the subtypes of breast cancer. Many prospective randomized studies are showing that pCR is higher in HER2-positive and triple-negative tumors. Our study showed that NAC response was higher in these subgroups, which was consistent with the literature. Although it is known that the response to neoadjuvant therapy is better in HER2-positive breast cancer, there is a lack of data in the literature about clinical or tumor-specific factors that predict treatment response.

Previous studies stated that tumors with more proliferative activity would benefit more from chemotherapy, and KI-67 could be a predictor in predicting the response.[21] HR-positive breast cancer subtypes generally have low KI-67 expression and a lower response to chemotherapy. Similar to previous studies, our study showed that tumor-specific factors such as high KI-67 index and histological grade could be used as predictors of response to NAC. Although some studies define cutoff values of 12%–25% without a valid explanation, the median value is generally used.[22,23] In our study, pCR increased significantly at KI-67 values above 30%. On the other hand, obtaining pCR is not the only target of NAC. Some evidence showed that pCR was ineffective in prolonging DFS and OS.[24] Therefore, other possible benefits, such as increasing BCS and reducing ALND, should be targeted through NAC. In the current study, 27% of patients were treated with BCS, but we do not know how many patients chose a mastectomy without considering the doctor's recommendation. In 35% of the patients, there was no need for ALND after NAC.

Our study had some limitations. First and foremost, incomplete data and variables can lead to erroneous results, as the data of the study were extracted from the retrospective medical records. The second limitation was due to incomplete data on the NAC regime. Therefore, it was not possible to evaluate the effects of different regimens on the pathological response. A third limitation is that our study was retrospective, so we do not know the rate of cases with a chance of BCS after NAC and how many patients voluntarily chose mastectomy.

In conclusion, the use of PET is helpful in the evaluation of cR after NAC, but it is not sufficient alone to predict the pathological response. The NAC decision should be made considering the factors affecting the response (molecular subtype, KI-67 level, HER2 status) to avoid unnecessary cost and time loss.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (Date: 30.12.2020, Decision No: 514/192/1).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: E.M.; Design: R.S.; Supervision: E.M.; Fundings: E.M.; Materials: R.S.; Data: E.M.; Analysis: R.S.; Literature search: E.M.; Writing: R.S.; Critical revision: E.M.

Conflict of Interest

None declared.

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Meme Kanserinde Neoadjuvan Kemoterapi Yanıtını Değerlendirmede PET'nin Etkinliği ve Patolojik Yanıtı Etkileyen Faktörler

Amaç: Neoadjuvan kemoterapi (NAK) sonrası patolojik tam yanıt (pCR) daha yüksek hastalıksız sağ kalım (DFS) ve genel sağ kalım (OS) ile ilişkilidir. Tedavi sonrası klinik yanıt (cR) değerlendirilmeli ve ilişkili faktörler belirlenmelidir. Çalışmamızdaki amacımız cR değerlendirmede PET'nin etkinliğini ve pCR'ye etkili olası faktörleri tanımlamaktır.

Gereç ve Yöntem: Ocak 2015–Aralık 2020 tarihleri arasında meme kanseri tanısıyla opere edilen hastaların dosyaları incelendi. Operasyon öncesi klinik yanıtlar PET ile değerlendirildi. Patolojik yanıt değerlendirilmesinde College of American Pathologists (CAP) 2019 skorlama sistemi kullanıldı. Hastaların menapozal durumu, tanı anındaki evresi, NAK öncesi ve sonrası PET bulguları, tümörün histopatolojik tipi, moleküler alt tipi ve Kİ-67 düzeyi incelenerek klinik ve patolojik yanıtı etkileyen faktörler araştırıldı.

Bulgular: Toplam 234 kadın hasta incelendi ve yaş ortalaması 52.5±12.1 yıl idi. Hastaların %28'inde patolojik tam yanıt (CAP=0) görülürken, klinik tam yanıt gözlenen 55 (%24) hastanın 40'ında (%72.7) patolojik olarak da tam yanıt izlendi. Kİ-67 yüksekliği ve HER-2 pozitifliği patolojik yanıtı olumlu etkileyen faktörlerdi ($p<0.05$). Moleküler alt tiplerdeki patolojik tam yanıt oranları; lüminal A'da %0, lüminal B'de %21, HER-2 pozitifte %52, üçlü negatif grupta ise %44 olarak bulundu ve gruplar arasındaki fark istatistiksel olarak da anlamlıydı ($p<0.05$).

Sonuç: NAK, lokal ileri meme kanserli hastalarda tümör boyutunu küçültmek ve aksiller diseksiyondan kaçınmak için kullanılır. NAK sonrası klinik yanıt değerlendirmesinde PET kullanımı patolojik yanıtı öngörmede tek başına yeterli değildir. Patolojik yanıt HER-2 pozitif ve triple negatif hastalarda belirgin derecede yüksektir. NAK kararı yanıtı etkileyen faktörler göz önünde bulundurularak verilmeli, gereksiz maliyet ve zaman kaybı önlenmelidir.

Anahtar Sözcükler: Klinik yanıt; neoadjuvan tedavi; patolojik yanıt; PET.