The Value of ^{18}F-FDG PET/CT Imaging in the Evaluation of İnterim Neoadjuvant Chemotherapy Response in Locally Advanced Breast Cancer

Lokal İleri Meme Kanserinde Neoadjuvan İnterim Kemoterapi Yanıtının Değerlendirilmesinde ^{18}F-FDG PET/BT Görüntülemenin Değeri

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Abstract

Objectives: Neoadjuvant chemotherapy (NAC) is the frequently used treatment option for locally advanced breast cancer (LABC). This study investigated the potential value of ^{18}fluorine-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) to estimate the pathological complete response (pCR) using maximum standardized uptake value (SUV$_{max}$) and change (ΔSUV$_{max}$) after 3-4 cycles of NAC. Additionally, it was established the relationship between PET/CT imaging findings and histopathological features in LABC patients whose treatment response was evaluated with interim PET/CT.

Methods: Patients were evaluated with pretreatment and interim PET/CT scans and operated after on NAC. Data on the age of patients, menopausal status, tumor placement, histopathological and molecular subgroups were noted. SUV$_{max}$ and ΔSUV$_{max}$ of the primary tumor and axillary lymph node (ALN) were calculated from PET/CT review.

Results: Pretherapy mean SUV$_{max}$ of the primary tumor and ALNs were 8.13±4.25 and 7.22±3.58, respectively. The highest mean primary tumor ΔSUV$_{max}$ and ALN ΔSUV$_{max}$ values were observed to be human epidermal growth factor receptor 2 positivity (p<0.001). SUV$_{max}$-T, SUV$_{max}$-N, ΔSUV$_{max}$-T, and ΔSUV$_{max}$-N values were significantly correlated with the ki-67 index (p<0.001). ΔSUV$_{max}$-T and ΔSUV$_{max}$-N values of pCR (+) patients were statistically higher than the ΔSUV$_{max}$-T and ΔSUV$_{max}$-N values of pCR (-) patients (p<0.001).

Conclusion: An earlier and more accurate response to NAC can be performed using interim ^{18}F-FDG PET/CT imaging. ΔSUV$_{max}$ levels of the breast tumor and ALNs may act as predictive for pCR in LABC patients receiving NAC.

Keywords: Neoadjuvant chemotherapy, ^{18}F-fluorodeoxyglucose, positron emission tomography, breast cancer

Öz

Amaç: Neoadjuvan kemoterapi (NAK) lokal ileri meme kanseri (LİMK) tedavisinde sıklıkla başvurulan tedavi seçeneğidir. Bu çalışmada, LİMK tanısı ile NAK alan hastalarda bazal ^{18}flor-florodeoksiglukoz (^{18}F-FDG) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT), maksimum

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standart alım değerinin (SUV$_{maks}$) ve 3-4 kür NAK sonrası SUV$_{maks}$ değişiminin (ΔSUV$_{maks}$) patolojik tam yanıtı (pTY) öngörmedeki potansiyel değerini belirlemek, ikincil olarak PET/BT ile ara tedavi yanıtı değerlendirilen LİMK hastalarında görüntüleme bulgularıyla histopatolojik özellikler arasındaki ilişkiyi değerlendirmek amaçlandı.

Yöntem: Hastalar tedavi öncesi ve interim tedavi sonrası ^{18}F-FDG PET/BT görüntüleme ile değerlendirildi ve NAK sonrası opere edildi. Hastaların yaşı, menopoz durumu, tümör lokalizasyonu, histopatolojik ve moleküler alt tipi ile ilgili veriler kaydedildi. PET/BT görüntülerinden primer tümör ve aksiller lenf nodları (ALN) için SUV$_{maks}$ ve ΔSUV$_{maks}$ hesaplandı.

Bulgular: Primer tümör ve ALN'nin tedavi öncesi ortalama SUV$_{maks}$ değerleri sırasıyla; 8,13±4,25 ve 7,22±3,58 idi. En yüksek ortalama primer tümör ΔSUV$_{maks}$ ve ALN ΔSUV$_{maks}$ değerlerinin insan epidermal büyüme faktör reseptörü 2 pozitifliğinde olduğu gözlendi (p<0,001). Ki-67 ile SUV$_{maks}$-T, SUV$_{maks}$-N, ΔSUV$_{maks}$ -T ve ΔSUV$_{maks}$ -N değerleri arasında korelasyon görüldü (p<0,001). PCR (+) hastalarında ΔSUV$_{maks}$ -T ve ΔSUV$_{maks}$-N değerleri, pCR (-) hastalardan istatistiksel olarak daha yüksekti (p<0,001).

Sonuç: İnterim ^{18}F-FDG PET/BT görüntüleme ile daha erken ve daha doğru NAK yanıtı değerlendirilebilir. Primer tümör ve ALN ΔSUV$_{maks}$ değerleri, NAK uygulanan LİMK hastalarında pTY için prediktör görev üstlenebilir.

Anahtar kelimeler: Neoadjuvan kemoterapi, ^{18}F-florodeoksiglukoz, pozitron emisyon tomografisi, meme kanseri

Introduction

Breast cancer (BC) ranks first among women's cancers in the world (1). Locally advanced breast cancer (LABC) is found in approximately one-third of patients at the time of diagnosis (2). The accepted multidisciplinary treatment approach in LABC includes preoperative neoadjuvant chemotherapy (NAC), followed by surgery and adjuvant systemic and local treatment steps (3). NAC is currently the first-line therapy for LABC and is increasingly preferred in early-stage patients. The advantages of NAC include enabling breast-conserving surgery (BCS) by shrinking the breast lesion, eliminating micrometastasis, evaluating drug resistance, and estimating the prognosis.

Positron emission tomography (PET) integrated with computed tomography (CT), is a hybrid modality that provides the three-dimensional distribution and quantitative volume of positron-emitting radionuclides in the human body, which has been widely used in the field of oncology in recent years (4). ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) is the most preferred radiopharmaceutical in oncological PET studies to demonstrate its increased glycolytic activity in cancer cells (5). Evaluation of treatment response and determination of chemosensitivity in the NAC patient group in the early period is important in terms of changing the treatment regimen, discontinuing unnecessary treatments and preventing possible drug toxicity and side effects.

^{18}F-FDG PET/CT is a useful method for NAC response by evaluating decreased glucose metabolism in BC tissue. With the antitumor effect of chemotherapy, cellular glycolysis decreases before the appearance of shrinkage in the tumor (6). In this study, we aimed to evaluate the potential contribution of ^{18}F-FDG PET/CT in predicting the pathological complete response (pCR) using maximum standardized uptake value (SUV$_{max}$) and change (ΔSUV$_{max}$) after 3-4 cycles of NAC in patients with LABC. Second, it was determined the relationship between PET/CT imaging findings and histopathological features in LABC patients whose treatment response was evaluated with interim PET/CT.

Materials and Methods

Patients

A total of 48 female patients [aged 29-68 years; mean ± standard deviation (SD): 49.4±9.5] diagnosed with LABC were evaluated retrospectively between October 2020 and September 2021 with ^{18}F-FDG PET/CT imaging performed before and after interim NAC.

Each study participant signed the informed consent forms. The University of Health Sciences Turkey, Istanbul Training and Research Hospital, Clinical Research Ethics Committee approved (number: 2916, date: 10.09.2021) the study and Helsinki Declaration rules were followed to conduct this study.

^{18}F-FDG PET/CT Imaging Protocol

Since the serum glucose level was below 150 mg/dL, ^{18}F-FDG was injected intravenously at a dose of 3.7 MBq/kg. PET/CT imaging was obtained using a Discovery St PET/CT (General Electric, Milwaukee, WI, USA) scanner with routine imaging protocol. With the patient's arms up, firstly CT scan was acquired with 2 mm section thickness in the craniocaudal direction between the vertex-upper thighs, and then a PET scan was received in 7-9 bed positions at the same interval, in the caudocranial direction.

Image Analysis

A semi-quantitative analysis method was used to evaluate PET/CT images by measuring the SUV$_{max}$ for the primary breast tumor and axillary lymph nodes (ALNs) with increased ^{18}F-FDG uptake on visual examination. Pre-treatment tumor SUV$_{max}$ (SUV$_{max}$-T) and ALN SUV$_{max}$ (SUV$_{max}$-N) values were calculated using the software with

"region of interest" drawn on the most metabolically active areas on attenuation-corrected PET/CT images. SUV_{max}-T and SUV_{max}-N values were measured from the region of the first lesions in the interim scan. Also, ΔSUV_{max} (%) was calculated using the baseline and interim SUV_{max} values according to the formula: (interim SUV_{max}-baseline SUV_{max}) / (baseline SUV_{max}) x100.

Pathological Evaluation and Treatment Protocol

Patients were graded according to the modified Scarff-Bloom-Richardson classification. In immunohistochemical analysis, estrogen receptor (ER) and progesterone receptor (PR) status were scored and accepted as positive if high (10%). Furthermore, human epidermal growth factor receptor type-2 (HER2) was classified with scores of 0, 1+, 2+ intense, and 3+ based on the maximum staining intensity and stain distribution. 3+ score is accepted as HER2 positive. When the score was 2+, gene amplification of the fluorescent *in situ* hybridization method was used to determine HER2 positivity. Patients were classified into luminal A, luminal B, triple-negative, and HER2-positive molecular subtypes. The high ki-67 index represents the ≥15 values.

All patients included in the study received adriamycin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 21 days for 3-4 cycles as a NAC protocol. After the interim evaluation PET/CT, NAC was continued with paclitaxel 80 mg/m^2 every 7 days for 12 weeks. In addition, trastuzumab (4 mg/kg as a loading dose, followed by 2 mg/kg) and pertuzumab (840 mg as a loading dose, followed by 420 mg) were given intravenously to HER2-positive patients. All patients underwent surgery after NAC.

The pCR was determined for the primary tumor and ALNs from surgical materials based on the Miller-Payne system (6). The Miller-Payne system has 5 grades and grade 5 indicates the pCR in the tumor means no invasive carcinoma but ductal carcinoma *in situ* may be present, and grades 1-4 define the pathological response rates relative to the tumor reduction ratio. We classified patients' pathological responses into two groups as pCR (+) vs pCR (-). For this study, Miller-Payne grade 5 responders were grouped as pCR (+), and partial responders or non-responders as pCR (-).

Statistical Analysis

Statistical analysis was performed by Macintosh Statistical Software (v27.0, IBM, Armonk, NY, USA) in this study. All descriptive data were expressed as mean, median, and SD. Mann-Whitney U and Kruskal-Wallis tests were used for variables with non-normal distribution. Comparison of numerical variables between groups was performed Student's t-test. The relationship between ki-67 and SUV

parameters was assessed by Pearson correlation analysis. p less than 0.05 was considered significant.

Results

Histopathology was invasive ductal carcinoma in 45 (93.75%) cases and invasive lobular carcinoma (ILC) in three (6.25%) cases. The tumor was in the right-sided breast in 26 (54.1%) patients and the left-sided breast in 22 (45.9%) patients. Of 48 patients, 14 (29.2%) were ER negative, 34 (70.8%) were ER positive, 17 (35.4%) were PR negative, 31 (64.6%) were PR positive. Nine (18.8%) of the patients were in luminal A, 25 (52%) were in luminal B, 8 (16.7%) were in the HER2 positive, and 6 (12.5%) were in the triple-negative molecular subgroup. ALN metastasis was negative in four (8.3%) patients at diagnosis. Sixteen patients (33.3%) were in clinical stage 2 and 33 (66.7%) were in stage 3 before treatment. The study patients and tumor characteristics are summarized in Table 1.

The mean diameter of the primary tumor was 4.75±3.04 cm, the mean ALN size was 2.2±1.3 cm, and the ki-67 index was 42.77%±26.46%. Mean SUV_{max} levels of baseline breast tumor and ALN metastases were calculated as 8.13±4.25 and 7.22±3.58, respectively. Tumor and ALN SUV_{max} and ΔSUV_{max} levels of the three patients with

Table 1. Patients and characteristics of breast cancer		
Variables	**Number (n)**	**Percentage (%)**
Menopause status		
Premenopausal	31	64.6
Postmenopausal	17	35.4
Histopathology		
IDC	45	93.75
ILC	3	6.25
Axillary lymph node metastasis		
Positive	44	91.6
Negative	4	8.4
Histological grade		
Grade 1	2	4.2
Grade 2	25	52
Grade 3	21	43.8
Surgical treatment		
BCS + SLNB	10	20.8
BCS + axillary dissection	8	16.7
MRM + SLNB	6	12.5
MRM + axillary dissection	24	50
IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, BRC: Breast-conserving surgery, SLNB: Sentinel lymph node biopsy, MRM: Modified radical mastectomy		

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the initial diagnosis of ILC were 4.1±0.87 and 4.2±0.5, -42.40±21.27 and -41.51±18.05, respectively. The number of patients with pCR (+) for the primary tumor and ALN was 18 (37.5%) and 21 (47.7%), respectively. Total (breast & axilla) pCR (+) was obtained in 17 (35.4%) patients (Figure 1).
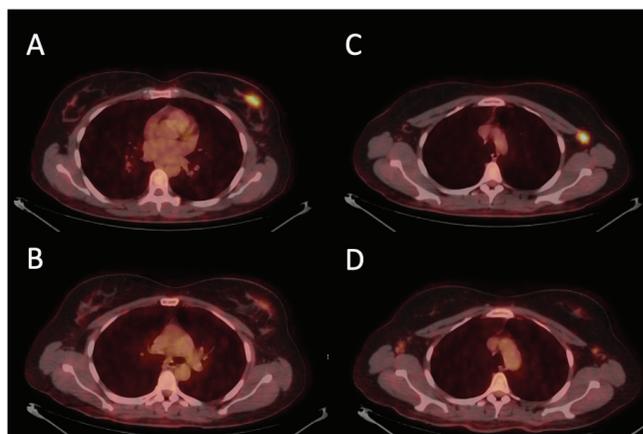

Figure 1. Thirty two-year-old woman with luminal B type invasive ductal left-sided breast cancer and axillary metastases achieved pCR at the end of NAC. Primary tumor SUV$_{max}$ was 5.4 in baseline ^{18}F-FDG PET/CT (A). SUV$_{max}$ was measured as 3.4 in interim evaluation PET/CT (B). Before and after interim treatment values of SUV$_{max}$-N were measured as 6.1 (C) and 2.9 (D), respectively

^{18}F-FDG: ^{18}Fluorine-fluorodeoxyglucose, NAC: Neoadjuvant chemotherapy, SUV$_{max}$: Maximum-standardized uptake value, PET/CT: Positron emission tomography/computed tomography, pCR: Pathological complete response

Relationship Between Histopathologicalc Features, pCR, and ^{18}F-FDG PET Analysis

The mean baseline SUV$_{max}$-T was statistically lower in the luminal A than in the triple-negative, HER2 positive, and luminal B groups (p=0.046, p<0.001, p=0.008), respectively. The mean baseline SUV$_{max}$-T was statistically higher in HER2 positives than in the luminal B group (p=0.017). The highest mean ΔSUV$_{max}$-T and ΔSUV$_{max}$-N were seen in HER2 positivity (p<0.01), but there was no significant difference in SUV$_{max}$-T levels of the positive and triple-negative groups (p=0.297). Additionally, SUV$_{max}$-T, SUV$_{max}$-N, ΔSUV$_{max}$-T, and ΔSUV$_{max}$-N levels had a highly significant correlation with the ki-67 index (Table 2).

Significant differences were seen between the SUV$_{max}$ levels of pCR (+) and pCR (-) patients. ΔSUV$_{max}$-T was significantly higher in the pCR (+) group for the primary tumor than in the pCR (-) group (p<0.001). For ALNs, interim SUV$_{max}$-N was lower in the pCR (+) group than in the pCR (-) group (p=0.016). In the evaluation of all groups, SUV$_{max}$-N levels of pCR (+) patients were statistically higher than the SUV$_{max}$-N values of pCR (-) patients (p<0.001).

The relationship between PET/CT parameters and pCR is shown in Table 3.

Discussion

PET/CT imaging in oncology practice, to clinical and pathological factors, has the importance of being a non-invasive method that provides timely determination of the response to therapy. PET/CT has an advantage over anatomical screening tools in demonstrating the metabolic nature of cancer by calculating the metabolic PET parameters before and in the interim period of NAC (7). Studies have documented that ^{18}F-FDG PET/CT images obtained interim, or at the end of NAC can estimate the response to therapy (8,9).

The value of radionuclide activity in breast lesions is related to tumor heterogeneity and molecular subgroups. Higher tracer accumulation has been found in negative ER status or triple-negative cases compared with positive ER status (10). In our study, it was shown that baseline SUV$_{max}$ was higher in HER2 positive and triple-negative cases compared to luminal groups, which supports the published research (Figure 2). Also, studies showing a significant relation between SUV$_{max}$ and the ki-67 levels or lymphatic and vascular invasion are available in the literature (11,12,13). Like studies on this subject, a statistically significant correlation was found between the ki-67 index and baseline SUV$_{max}$-T, SUV$_{max}$-N, ΔSUV$_{max}$-T, and ΔSUV$_{max}$-N.

Significant differences were observed in SUV$_{max}$ values of specific molecular subgroups. The highest ΔSUV$_{max}$-T was seen in the HER2 positive and luminal B groups, and the highest ΔSUV$_{max}$-N in the HER2-positive and triple-negative groups in the study (Figure 3). In research, the mean breast ΔSUV$_{max}$ level was found to be -73%±32% in HER2 positivity with more intense uptake values for the total breast & axilla, and -52%±33% in HER2 negativity (14). Similarly, the highest ΔSUV$_{max}$-T and ΔSUV$_{max}$-N levels were found in HER2-positive patients in our study.

The metabolic response of the primary malignancy to therapy is considered as a measure for assessing NAC response. Pathological CR is defined as the negativity of invasive cancer in the breast and axilla, which is seen in 10-40% of patients (15). In this study, pCR (+) was obtained in 35.4% of the patients and the most significant parameters for the pCR (+) were determined by ΔSUV$_{max}$-T and ΔSUV$_{max}$-N. Can et al. (16) investigated the prognostic role of PET/CT in the evaluation of newly diagnosed BC patients with ALN metastases, and reported pCR rates after neoadjuvant therapy as 37.2%, 42.2%, and 28.9% for breast, axilla, and breast & axilla, respectively. In a study evaluating the response to NAC with PET/CT in 32

Table 2. Histopathological analysis and ^{18}F-FDG PET/CT parameters

Molecular subgroup	n	%	SUV$_{max}$-T	ΔSUV$_{max}$-T	SUV$_{max}$-N	ΔSUV$_{max}$-N
Luminal A	9	18.7	3.5±0.7	-20.7±23.9	3.4±1.3	-21.7±8.0
Luminal B	25	52.0	7.8±3.3	-47.0±17.8	6.7±2.6	-44.6±18.6
HER2 positive	8	16.7	14.1±3.2	-59.7±6.5	11.0±3.5	-51.9±11.8
Triple-negative/BL*	6	12.5	8.3±2.6	-32.5±14.6	9.7±2.8	-45.3±10.3
p	**-**	**-**	**<0.001**	**<0.001**	**<0.001**	**0.003**
ER	-	-	-	-	-	-
Positive	34	70.8	7.3±4.3	-40.8±22.8	6.3±3.4	-38.0±19.2
Negative	14	29.2	9.9±3.4	-46.1±17.0	9.4±2.8	49.8±11.4
p	**-**	**-**	**0.052**	**0.008**	**0.005**	**0.013**
PR	-	-	-	-	-	-
Positive	31	64.6	7.6±4.2	-42.2±23.5	6.9±3.2	-42.6±19.0
Negative	17	35.4	8.9±4.2	-42.2±23.5	7.6±4.2	-39.3±16.5
p			0.339	**0.041**	0.547	0.549
Ki-67 index	-	-	-	-	-	-
High	9	18.8	3.5±0.7	-20.7±23.9	3.4±1.3	-21.7±8.0
Low	39	81.2	9.1±4.0	-47.3±17.4	8.1±3.3	-46.2±16.3
r	-	-	0.669	-0.509	0.602	-0.652
p	**-**		**<0.001**	**<0.001**	**<0.001**	**<0.001**

*Basal-like, ER: Estrogen receptor, PR: Progesterone receptor, T: Tumor, N: Axillary nodal metastasis, SUV$_{max}$: Maximum standardized uptake value; mean ± standard deviation values are given, ΔSUV$_{max}$: Change maximum standardized uptake value, ^{18}F-FDG: ^{18}Fluorine-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, HER2: Human epidermal growth factor receptor type-2
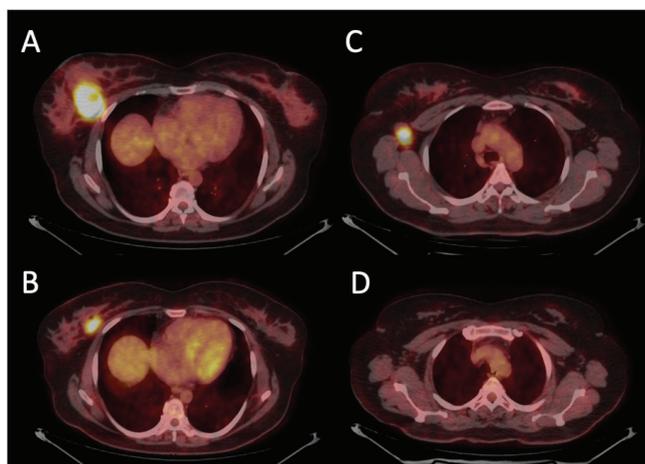

Figure 2. Fifty four-year-old patient with HER2 positive right-sided breast tumor and axillary metastases showed pCR in the axilla after NAC. Primary tumor SUV$_{max}$ values were 11.0 and 4.9 in the fusion PET/CT images performed at baseline (A) and interim NAC (B). The partial metabolic response was detected in the primary tumor on interim treatment evaluation PET/CT. The baseline SUV$_{max}$-N value was 8.4 (C). The complete metabolic response was observed after NAC (D)

HER2: Human epidermal growth factor receptor type-2, pCR: Pathological complete response, NAC: Neoadjuvant chemotherapy, SUV$_{max}$: Maximum-standardized uptake value, PET/CT: Positron emission tomography/computed tomography
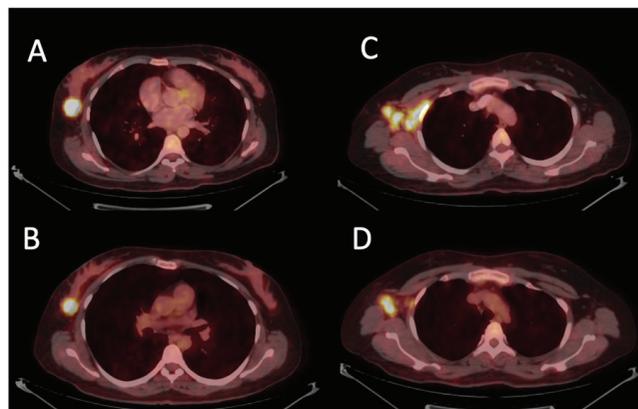

Figure 3. Forty one-year-old woman with triple-negative right-sided breast tumor and ALN metastases, whose pCR could not be obtained after NAC, had a primary tumor SUV$_{max}$ value of 13.2 in the baseline PET/CT scan (A). SUV$_{max}$ was measured as 11.8 in the interim evaluation (B). Under the partial metabolic response, the pre-treatment (C) and interim treatment (D) SUV$_{max}$-N were 12.3 and 8.5, respectively

ALN: Axillary lymph node, pCR: Pathological complete response, NAC: Neoadjuvant chemotherapy, SUV$_{max}$: Maximum-standardized uptake value, PET/CT: Positron emission tomography/computed tomography

BC patients, pCR was seen in 17 patients (43.8%) (17). Additionally, mean ΔSUV$_{max}$ measured on PET/CT imaging after NAC was shown to be more prognostic in patients

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Table 3. PET/CT parameters and pCR analysis			
	pCR (+)	pCR (-)	p
Baseline SUV_{max}-T	9.8±3.9	7.1±4.1	0.034
Interim SUV_{max}-T	4.1±1.2	4.0±2.0	0.773
ΔSUV_{max}-T	-55.1±9.2	-34.75±22.8	<0.001
Baseline SUV_{max}-N	8.5±3.0	6.9±3.4	0.119
Interim SUV_{max}-N	3.3±0.7	4.5±1.9	0.016
ΔSUV_{max}-N	-57.4±7.3	-31.8±12.5	<0.001
pCR: Pathological complete response, T: Tumor, N: Axillary lymph node metastasis, SUV_{max}: Maximum-standardized uptake value (mean values ± standard deviation), ΔSUV_{max}: Change maximum standardized uptake value, PET/CT: Positron emission tomography/computed tomography			

with pCR (+) (18). In another study of luminal group B cancers, the authors showed no difference between patients' pathological responses for baseline SUV_{max}, but a higher ΔSUV_{max}-T was reported for pCR (+) (19).

BC comprises various subtypes in terms of tumor nature, therapy options, and clinical outcomes. The heterogeneous feature is also seen in the metabolic behavior of the tumor. In a prospective study evaluating triple-negative patients, the median baseline SUV_{max}-T did not differ significantly among the patients with and without pCR, while ΔSUV_{max}-T was found to be more significant in the patients with pCR (+) (20). In our study, the mean ΔSUV_{max}-T was higher in patients with pCR (+) groups than in patients with non-pCR. In another study, in which the metabolic and pathological response evaluation was performed separately for the breast and axilla with triple-negative and HER2 group patients, ΔSUV_{max}-T was determined as the strongest estimator of pCR in the primary tumor and ΔSUV_{max}-N was the most predictive of the total pCR (21).

Accurately revealing the response to NAC also affects surgical planning. The evaluation of response with anatomical imaging, which traditionally uses size-based criteria, has limitations. Anatomical and metabolic evaluation with PET/CT overcomes many of these limitations and plays an indispensable place in the assessment of NAC response in BC. Additionally, response to NAC in ALNs may affect the decision for axillary dissection. Colfry et al. (22) emphasized that axillary dissection may be unnecessary in LABC with complete response after NAC in their study, and they recommended its application, especially in unresponsive patients. In our study, pCR (+) was not established in 62.5% (30/48) of breast tumors and 52.2% (23/44) of axillary metastases after the NAC strategy. Only 17 cases (35.4%) achieved pCR (+) in both primary breast tumors and ALN metastases. Low ^{18}F-FDG uptake was observed in primary breast tumor ± ALN metastases of patients who did not respond to treatment, and this situation was

primarily evaluated about the histopathological type (ILC) of the tumor. Similarly, Schwarz-Dose et al. (23) found high response rates in HER2 positive patients at post-treatment examination and low pCR rates after NAC in tumors with low glucose metabolism.

Study Limitations

The heterogeneity and the limited number of the patient population, with its retrospective design, can be considered the limitations of our study, and this may have weakened some of the statistical analysis.

Conclusion

An earlier and more accurate response to NAC could be performed with interim ^{18}F-FDG PET/CT imaging. PET/CT may also detect unresponsive patients in the early period and allow changes in treatment plans. Additionally, ΔSUV_{max} levels of primary tumor and ALN can be used to predict pCR in LABC patients receiving NAC.

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