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

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 ($\Delta$SUV$_{max}$) 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 $\Delta$SUV$_{max}$ 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 $\Delta$SUV$_{max}$ and ALN $\Delta$SUV$_{max}$ values were observed to be human epidermal growth factor 2 positivity (p<0.001). SUV$_{max}$-T, SUV$_{max}$-N, $\Delta$SUV$_{max}$-T, and $\Delta$SUV$_{max}$-N values were significantly correlated with the ki-67 index (p<0.001). $\Delta$SUV$_{max}$-T and $\Delta$SUV$_{max}$-N values of pCR (+) patients were statistically higher than the $\Delta$SUV$_{max}$-T and $\Delta$SUV$_{max}$-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. SUV$_{max}$ 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 sıkıla başyurulan tedavi seçeneğidir. Bu çalışmada, LİMK tanısi ile NAK alan hastalarda bazal $^{18}$fluor-florodeoksiglukoz ($^{18}$F-FDG) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/CT), maksimum
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). \(^{18}\)F-fluorodeoxyglucose \((^{18}\text{F-FDG})\) 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.

\(^{18}\text{F-FDG} \) 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 \(^{18}\text{F-FDG} \) PET/CT in predicting the pathological complete response \((\text{pCR})\) using maximum standardized uptake value \((\text{SUV}_{\text{max}})\) and change \((\Delta \text{SUV}_{\text{max}})\) 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 \([\text{aged 29-68 years; mean } \pm \text{ standard deviation (SD): 49.4} \pm 9.5]\) diagnosed with LABC were evaluated retrospectively between October 2020 and September 2021 with \(^{18}\text{F-FDG} \) 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 \((\text{number: 2916, date: 10.09.2021})\) the study and Helsinki Declaration rules were followed to conduct this study.

\(^{18}\text{F-FDG} \) PET/CT Imaging Protocol
Since the serum glucose level was below 150 mg/dL, \(^{18}\text{F-FDG} \) was injected intravenously at a dose of 3.7 MBq/kg. PET/CT imaging was obtained using a Discovery St PET/CT \((\text{General Electric, Milwaukee, WI, USA})\) 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 \(\text{SUV}_{\text{max}} \) for the primary breast tumor and axillary lymph nodes \((\text{ALNs})\) with increased \(^{18}\text{F-FDG} \) uptake on visual examination. Pre-treatment tumor \(\text{SUV}_{\text{max}} \) \((\text{SUV}_{\text{max}}-\text{T})\) and ALN \(\text{SUV}_{\text{max}} \) \((\text{SUV}_{\text{max}}-\text{N})\) values were calculated using the software with
“region of interest” drawn on the most metabolically active areas on attenuation-corrected PET/CT images. $SUV_{\text{max}}^\text{T}$ and $SUV_{\text{max}}^\text{N}$ values were measured from the region of the first lesions in the interim scan. Also, $\Delta SUV_{\text{max}}$ (%) was calculated using the baseline and interim $SUV_{\text{max}}$ values according to the formula: $(\text{interim } SUV_{\text{max}} - \text{baseline } SUV_{\text{max}}) / (\text{baseline } SUV_{\text{max}}) \times 100$.

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 $\geq 15$ 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$_{\text{max}}$ 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$_{\text{max}}$ and $\Delta SUV_{\text{max}}$ 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
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).

**Relationship Between Histopathological Features, pCR, and \(^{18}\)F-FDG PET Analysis**

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

Significant differences were observed between the \(SUV_{\text{max}}\) levels of pCR (+) and pCR (-) patients. \(\Delta SUV_{\text{max}}-T\) was significantly higher in the pCR (+) group for the primary tumor than in the pCR (-) group (p=0.001). For ALNs, interim \(SUV_{\text{max}}-N\) was lower in the pCR (+) group than in the pCR (-) group (p=0.016). In the evaluation of all groups, \(SUV_{\text{max}}-N\) levels of pCR (+) patients were statistically higher than the \(SUV_{\text{max}}-N\) 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 \(SUV_{\text{max}}\) 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 \(SUV_{\text{max}}\) 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 \(SUV_{\text{max}}-T\), \(SUV_{\text{max}}-N\), \(\Delta SUV_{\text{max}}-T\), and \(\Delta SUV_{\text{max}}-N\). Significant differences were observed in \(SUV_{\text{max}}\) values of specific molecular subgroups. The highest \(\Delta SUV_{\text{max}}-T\) was seen in the HER2 positive and luminal B groups, and the highest \(\Delta SUV_{\text{max}}-N\) in the HER2-positive and triple-negative groups in the study (Figure 3). In research, the mean breast \(\Delta SUV_{\text{max}}\) 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 \(\Delta SUV_{\text{max}}-T\) and \(\Delta SUV_{\text{max}}-N\) 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 \(\Delta SUV_{\text{max}}-T\) and \(\Delta SUV_{\text{max}}-N\). 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...
Additional, mean ΔSUVmax measured on PET/CT imaging after NAC was shown to be more prognostic in patients

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

| Molecular subgroup | n  | %   | SUV<sub>max</sub>-T | ΔSUV<sub>max</sub>-T | SUV<sub>max</sub>-N | ΔSUV<sub>max</sub>-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                 | -  | -   | -                    | -                    | -                   | -                   |
| tive-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<sub>max</sub>: Maximum standardized uptake value, mean ± standard deviation values are given, ΔSUV<sub>max</sub>: Change maximum standardized uptake value, 18F-FDG: 18Fluorine-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<sub>max</sub> 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<sub>max</sub>-N value was 8.4 (C). The complete metabolic response was observed after NAC (D)

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<sub>max</sub> value of 13.2 in the baseline PET/CT scan (A). SUV<sub>max</sub> was measured as 11.8 in the interim evaluation (B). Under the partial metabolic response, the pre-treatment (C) and interim treatment (D) SUV<sub>max</sub>-N were 12.3 and 8.5, respectively

ALN: Axillary lymph node, pCR: Pathological complete response, NAC: Neoadjuvant chemotherapy, SUV<sub>max</sub>: 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<sub>max</sub> measured on PET/CT imaging after NAC was shown to be more prognostic in patients
In our study, the mean was found to be more significant in the patients with pCR (+). Breast and axilla with triple-negative and HER2 group response evaluation was performed separately for the patients with pCR (+) groups than in patients with non-pCR. In another study, in which the metabolic and pathological evaluation with F-FDG uptake was observed, higher ΔSUVmax-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 SUVmax-T did not differ significantly among the patients with and without pCR, while ΔSUVmax-T was found to be more significant in the patients with pCR (+) (20). In our study, the mean ΔSUVmax-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, ΔSUVmax-T was determined as the strongest estimator of pCR in LABC patients receiving NAC. ΔSUVmax levels of primary tumor and ALN can be used to predict pCR in LABC patients receiving NAC.

**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 18F-FDG PET/CT imaging. PET/CT may also detect unresponsive patients in the early period and allow changes in treatment plans. Additionally, ΔSUVmax levels of primary tumor and ALN can be used to predict pCR in LABC patients receiving NAC.

**Ethics**

**Ethics Committee Approval:** 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.

**Informed Consent:** Each study participant signed the informed consent forms.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: G.T., Ö.Ö., G.A., Concept: G.T., Ö.Ö., G.A., Design: G.T., Ö.Ö., G.A., Data Collection or Processing: G.T., Ö.Ö., G.A., Analysis or Interpretation: G.T., Ö.Ö., G.A., Literature Search: G.T., Ö.Ö., G.A., Writing: G.T., Ö.Ö., G.A.

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| Table 3. PET/CT parameters and pCR analysis |
|--------------------------------------------|
|                                          |
| pCR (+) | pCR (-) | p  |
|----------------------------------------|
| pCR (+) | pCR (-) | p  |
| Baseline SUVmax-T | 9.8±3.9 | 7.1±4.1 | 0.034 |
| Interim SUVmax-T | 4.1±1.2 | 4.0±2.0 | 0.773 |
| ΔSUVmax-T | -55.1±9.2 | -34.7±22.8 | <0.001 |
| Baseline SUVmax-N | 8.5±3.0 | 6.9±3.4 | 0.119 |
| Interim SUVmax-N | 3.3±0.7 | 4.5±1.9 | 0.016 |
| ΔSUVmax-N | -57.4±7.3 | -31.8±12.5 | <0.001 |

ΔSUVmax: Maximum-standardized uptake value (mean values ± standard deviation), pCR: Pathological complete response, T: Tumor, N: Axillary lymph node metastasis, SUVmax: Maximum-standardized uptake value, PET/CT: Positron emission tomography/computed tomography.
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