# Relationship between 18-FDG-PET/CT and Clinicopathological Features and Pathological Responses in Patients with Locally Advanced Breast Cancers

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## ABSTRACT

**Objective:** We investigated the relationship between the maximum standardized uptake value (SUVmax) of whole-body positron emission tomography/computed tomography (PET/CT) performed before treatment and the demographical and histopathological features in locally advanced breast cancer (LABC), as well as the role of PET/CT in the evaluation of pathological complete response (pCR) after neoadjuvant chemotherapy (NAC).

**Materials and Methods:** Fifty-one LABC patients who received NAC in our center between 2011 and 2015 were retrospectively analyzed. Basal PET/CT was performed in all the patients before NAC. The $SUV_{max}$ levels and demographical and histopathological results were compared. The relationship between the $SUV_{max}$ values after NAC and pathological responses were evaluated.

**Results:** The mean age of the patients was 49 (32-69) years. PET/CT performed after NAC showed complete response in 20 patients (39.2%), partial response in 28 patients (54.9%), stable disease in 2 patients (3.9%), and progressive disease in 1 patient (2%). There was no significant difference between the mean $SUV_{max}$ values of the patients according to age (>50 and ≤50 years), menopausal status, tumor localization, clinical stage, and grade. The mean $SUV_{max}$ value was higher in the triple-negative group than those in the HER2 positive and luminal groups. There was a significant difference in the $SUV_{max}$ values between the group that achieved pCR after NAC and the group that could not achieve pCR ($SUV_{max}$ value for breast 2.92 vs. 0.30; p=0.01; $SUV_{max}$ value for axilla 1.5 vs. 0.0, p=0.02).

**Conclusion:** The $SUV_{max}$ values are independent of demographical features. There was a significant relationship between the pCR and $SUV_{max}$ values after NAC. PET/CT could be useful in the evaluation of patients to predict the biological characteristics of tumors.

**Keywords:** Breast cancer, 18F-FDG, neoadjuvant chemotherapy.

## Introduction

Locally advanced breast cancer (LABC) comprises a heterogeneous group of patients with slow-growing tumors in addition to those with a biologically aggressive disease. Because of high locoregional recurrence and metastasis risks in such patients, intensive treatment becomes imperative [1]. Neoadjuvant chemotherapy (NAC) is accepted as the standard treatment for LABC. NAC increases the effective resection rates and breast-preserving surgery rates [2, 3]. Furthermore, it aims toward achieving the in vivo evaluation of chemotherapy (CT) response [4, 5].

It has been shown that the pathological complete response (pCR) after NAC maintains the survival advantage in certain subtypes of breast cancers. Therefore, pCR may be used as a marker to evaluate treatment results [6, 7]. Nonetheless, breast cancers have different biological features. While recurrence occurs in some patients with pCR, certain patients without pCR have a good prognosis [8]. Therefore, new predictive and prognostic factors in addition to pCR after NAC need to be determined.

Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) is a valuable instrument in staging, restaging after recurrence, and evaluation of CT response for breast cancer patients [9]. The maximum standardized uptake value ($SUV_{max}$), expressed as the level of F18-FDG uptake, has been reported to be related with aggressive tumor biology in many studies. There are studies showing that histolopathological parameters such as tumor size, histo-

logical grade, or hormone receptor expression status are correlated with the FDG uptake level in breast cancers [10-12]. Further, studies have suggested that F18-FDG PET/CT is beneficial in the preoperative evaluation and prognosis of breast cancers and may be used in the decision toward CT [13, 14].

FDG PET/CT has advantages as compared to conventional imaging studies. There are studies showing that it is a sensitive method in the evaluation of an early response to NAC [15]. However, studies have also shown that its sensitivity is inadequate for the evaluation of pCR [16]. Therefore, the use of FDG PET/CT in NAC is controversial. In this study, we investigated the relationship between the demographical and histopathological features of LABC and $SUV_{max}$ values of PET/CT before treatment, as well as the role of PET/CT in the evaluation of pCR after NAC.

## Materials and Methods

### Patients

For the period between 2011 and 2015, a file search was performed involving 453 patients treated for breast cancer in our unit. Here 51 breast cancer patients with stage 2 to stage 3 diseases that received NAC were retrospectively evaluated. Basal PET/CT was applied to all the patients before NAC. Patients with distant metastasis and bilateral breast cancer were excluded. All the patients received 4–8 cycles of CT. All the patients underwent surgery after undergoing controlled PET/CT following NAC. Bone metastasis occurred in one patient, and this patient underwent a mastectomy operation. The study was approved by the local ethics committee. Written informed consent was obtained from patients who participated in this study.

### Clinicopathological Evaluations

Clinical data and pathological findings for all the patients were recorded by the investigation of polyclinic follow-up files and hospital archives. Age, menopausal status, clinical stage, and tumor localization of the patients were recorded. All the patients were diagnosed by a Tru-cut biopsy. Tumors were graded according to the modified Scarff–Bloom–Richardson grading system. Estrogen (ER), progesterone (PR), HER2, and Ki67 expression statuses were analyzed from the routine pathological evaluation results conducted in our center. Here, 1% or more positively stained nuclei in 10 high-power fields was considered to be positive for ER and PR [17]. HER2 was analyzed by immunohistochemistry, and the staining intensity was reported as 0, 1+, 2+, or 3+. A score of 3+ was denoted as HER2 positive, and a score of 0 or 1+ was denoted as HER2 negative. If the score was 2+, then gene amplification using fluorescence in situ hybridization was used. When the ratio of HER2 gene copies to chromosome 17 signals was found to be greater than 2.2, HER2 was considered to be positive [18]. After NAC, modified radical mastectomy (MRM) along with axillary dissection (AD) or breast-conserving surgery (BCS) was performed in all the patients. Tumor size; histological grade; presence of vascular, lymphatic, or perineural invasion; and lymph nodal involvement were assessed by means of surgical materials. The precise definition of pCR in breast carcinoma is uncertain. We adopted a pCR of ypT0/is ypN0, which means there is no residual invasive cancer in the breast and axillary lymph nodes, but noninvasive breast residuals are permitted.

### NAC

A large majority of patients received four cycles of anthracycline-based regimens and four cycles of taxane regimens. Only one patient was evaluated after receiving three cycles of dose-dense anthracycline-based treatment. There was CR in PET/CT imaging; after surgery, three more cycles were administered. The operation was performed in one patient after six cycles of docetaxel/doxorubicin/cyclophosphamide (TAC) regimen. BCS or MRM with AD was performed in all the patients after the completion of NAC. All the patients received anti-HER2 treatment, radiotherapy, and endocrine therapy, if necessary, according to standard guidelines.

### 18F-FDG PET/CT Imaging

Patients were fasted overnight at least 12 h before whole-body PET/CT imaging was performed. Patients with a fasting blood sugar level above 120 mg/dl were excluded. After an intravenous injection of approximately 12 mCi (444 MBq) of 18F-FDG, the patient waited in a silent room for about 1 h; thereafter, the patient was imaged using an integrated PET/CT camera, which comprised a 16-slice CT gantry, integrated with an LSO-based full-ring PET scanner (Siemens Biograph 16; Siemens, Knoxville, TN, USA). CT was applied with 120-200 mAs at 120 kV adjusted to the body weight of the patient. Scanning was performed proximal to the thigh from the base of the skull. The PET images were reconstructed by a repetitive method (ordered-subset expectation maximization: two iterations, eight subsets) to achieve attenuation correction and image fusion. After reconstruction, the PET, CT, and fused images were visualized by using commercially available software (e-soft/VSIM, Siemens Medical Solutions) along the axial, coronal, and sagittal planes. The maximum intensity projection for the PET images and co-recorded PET/CT images were obtained and analyzed by a nuclear medicine practitioner. This was calculated by using the following formula: measured activity concentration [Bq/mL] × body weight [kg]/injected activity [Bq]. The $SUV_{max}$ value was determined by drawing the region of interest around the primary tumor on the transaxial slices.

### Statistical Analysis

The data were presented as mean, standard deviation, median, minimum, maximum, percentage, and number. The normal distribution of the constant variables was analyzed with the Shapiro–Wilk test. While comparing two groups, independent samples t test was used if the normal distribution condition was achieved; otherwise, the Mann–Whitney U test was used. While comparing more than two groups, the ANOVA test was used if the normal distribution condition was achieved; otherwise, the Kruskal–Wallis test was used. Pearson correlation was used for numerical data. Spearman's correlation was used for nominal data. To assess diagnostic accuracy, we performed the receiver operating characteristic (ROC) curve analysis. Subsequently, the area under the ROC curve (AUC) was estimated. Here, $p<0.05$ was considered to be statistically significant. The Statistical Package for the Social Sciences (SPSS) software version 20 (IBM Corp.; Armonk, NY, USA) was used for all the performed statistical analyses.

## Results

### Patient Characteristics

The clinicopathological features of the patients are summarized in Table 1. A total of 51 patients were analyzed. Only one patient was male. The mean age of the patients was 49 (32–69) years. Out of these patients, 52.9% (n=27) were premenopausal. Further, 92.2% (n=47) had stage 3 disease and the tumor was localized in the right breast in 54.9% (n=28). Out of these patients, 90.2% (n=46) had IDC, 5.9% had ILC, 2% (n=1) had mucinous carcinoma, and 2% (n=1) had phyllodes tumor as the histological subtype. The following histologic grades were used: grade 1 for 1 patient (2%), grade 2 for 22 patients (43%), and grade 3 for 8 patients (15.6%). ER was positive in 43 patients (84.3%), and PR was positive in 39 patients (76.4%). When the ER and/or PR receptors were simultaneously analyzed, the hormone receptors in 45 patients (88.2%) were found to be positive. HER2 positivity was observed in 60.8%, and 9.8% had the triple-negative molecular subtype. Out of these patients, 39.2% (n=20) achieved a complete response, 54.9% (n=28) achieved a partial response, 2.9%

**Table 1.** Clinical and pathologic characteristics of the patients

| | Number | % |
|---|---|---|
| Age | | |
| Median | 49 | |
| Range | 32-69 | |
| Tumor localisation | | |
| Right | 28 | 54.9 |
| Left | 23 | 45.1 |
| Menapousal status | | |
| Premenapous | 27 | 52.9 |
| Postmenapous | 23 | 47.1 |
| Histological Type | | |
| IDC | 46 | 90.1 |
| ILC | 3 | 5.9 |
| Musinous carcinoma | 1 | 2 |
| Phyloides tumor | 1 | 2 |
| Stage before NAC | | |
| Stage II | 4 | 7.8 |
| Stage III | 47 | 92.2 |
| Type of surgery | | |
| Breast-conserving surgery | 1 | 2 |
| Mastectomy | 50 | 98 |
| Type of axial surgery | | |
| Sentinel lymph node biopsy | 1 | 2 |
| Axial dissection after sentinel lymph node biopsy | 0 | |
| Axial dissection | 49 | 96 |
| Subtype | | |
| Luminal A and luminal B | 15 | 29.4 |
| Luminal HER2 | 30 | 58.8 |
| HER2 positive | 1 | 2 |
| Triple negative | 5 | 9.8 |
| Nuclear grade | | |
| I | 1 | 2 |
| II | 22 | 43.1 |
| III | 8 | 15.6 |
| Unknown | 20 | 39.2 |
| Ki67 | | |
| High (>20) | 35 | 68.6 |
| Low (≤20) | 5 | 9.8 |
| Pathologic complete response,positive | 15 | 29.4 |

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, NAC: Neoadjuvant chemotherapy

(n=2) exhibited a stable disease, and progressive disease was observed in 2% (n=1) in PET/CT that was performed after NAC.

**Table 2.** Metabolic characteristics of the primary tumor according to the clinical and histopathological status

| Feature | | N | Mean | SD | Min | Max | p |
|---|---|---|---|---|---|---|---|
| Age (years) | <50 | 30 | 8.42 | 6.40 | 1.61 | 27.07 | 0.882 |
| | ≥50 | 20 | 7.61 | 5.23 | 1.13 | 19.85 | |
| Menopausal status | premenopausal | 26 | 8.52 | 6.78 | 1.61 | 27.07 | 0.802 |
| | postmenopausal | 23 | 7.85 | 4.90 | 1.13 | 19.85 | |
| Localisation | right | 27 | 7.04 | 4.43 | 1.13 | 19.20 | 0.436 |
| | left | 23 | 9.33 | 7.19 | 1.61 | 27.07 | |
| Grade | grade 2 | 22 | 7.81 | 5.09 | 2.13 | 17.22 | 0.639 |
| | grade 3 | 8 | 9.25 | 6.04 | 1.80 | 19.20 | |
| Ki67 | High (>20) | 34 | 7.18 | 4.36 | 1.13 | 17.10 | 0.943 |
| | Low (≤20) | 5 | 7.03 | 6.16 | 2.63 | 17.22 | |
| Subtypes (breast) | Luminal A, B | 14 | 5.78 | 4.97 | 1.13 | 19.20 | 0.134 |
| | Luminal HER2 | 31 | 8.41 | 6.30 | 1.61 | 27.07 | |
| | Triple Negative | 5 | 11.43 | 4.09 | 6.05 | 17.10 | |
| Subtypes (axiller) | Luminal A, B | 10 | 3.82 | 1.60 | 2.22 | 7.32 | 0.02 |
| | Luminal HER2 | 25 | 6.95 | 4.37 | 1.93 | 14.87 | |
| | Triple Negative | 5 | 9.08 | 4.27 | 4.30 | 17.50 | |

All the patients underwent surgery. One patient had BCS, and one patient who underwent negative sentinel lymph node sampling underwent a simple mastectomy operation. All the other patients (96%) had MRM with AD. The patient exhibiting bone metastasis was defined and this patient also underwent surgery after NAC, but did not receive radiotherapy to the breast: this patient died during the second year of treatment. In the follow-up period, recurrence was determined in 15.7% (n=8) patients with bone metastasis as the most common site (50%, n=4). The second-most-common site of recurrence was the brain. Out of the three patients with brain metastasis, two died related to the disease. Acute leucosis occurred in one patient who was receiving adjuvant endocrine therapy, because of which the patient died. In the follow-up period, 7.8% (n=4) patients died. The treatments of other patients with recurrence are continuing.

## Relationship between Demographical and Histopathological features and PET/CT Pretreatment

The mean $SUV_{max}$ value of 51 patients was 8.53. There was no statistically significant difference between the mean $SUV_{max}$ value and age (> 50 and ≤ 50 years), menopausal status (premenopausal or postmenopausal), tumor localization, clinical stage, tumor Ki67 index, and tumor grade of the patients. The mean $SUV_{max}$ value is higher in the triple-negative group than those in the HER2 positive and luminal groups. The lowest $SUV_{max}$ value was observed in the luminal group. Although there was a relationship between the mean $SUV_{max}$ value and the molecular subtypes, the axillary $SUV_{max}$ values were statistically significant (Table 2).

A correlation analysis was formulated between the age, stage, menopausal status, localization, grade, Ki67, subtypes breast/axillary with after/before CT primary tumor, and axillary $SUV_{max}$ values among all the patients, but no statistically significant relationship was revealed.

## Role of PET/CT in pCR Evaluation

PET/CT FDG uptake after NAC was observed in 3 out of the 15 patients in which pCR was achieved. Furthermore, pCR could not be achieved in 8 out of 20 patients that did not show any abnormal FDG uptake in PET/CT. There was no significant difference between the pretreatment mean $SUV_{max}$ value of the patients with or without pCR. However, there was a significant difference between the $SUV_{max}$ values of these groups after NAC ($SUV_{max}$ breast 2.92 vs. 0.30, p=0.01; $SUV_{max}$ axillary 1.5 vs. 0.0, p=0.02) (Table 3).

ROC analysis was performed between the post-CT primary tumor and axillary $SUV_{max}$ with/without pCR. The sensitivity was 75% and specificity was 75% for the primary tumor, and the sensitivity was 55% and specificity was 100% for the axillary lymph nodes (Table 4) (Figure 1).

While none of the patients with a complete response in PET/CT exhibited recurrence, an abnormal FDG uptake in control PET/CT after NAC continued in all the patients in which metas-

**Table 3.** Tumor metabolic characteristics according to achievement of pCR

| | | N | Mean | St.Dev | Min | Max | p |
|---|---|---|---|---|---|---|---|
| Before CT primary tumor $SUV_{max}$ | No-pCR | 35 | 7.82 | 5.12 | 1.80 | 19.20 | 0.751 |
| pCR | 15 | 8.73 | 7.62 | 1.13 | 27.07 | | |
| Before CT axillar $SUV_{max}$ | No-pCR | 30 | 6.16 | 4.20 | 1.93 | 17.50 | 0.316 |
| pCR | 12 | 7.57 | 4.11 | 2.94 | 14.74 | | |
| After CT primary tumor $SUV_{max}$ | No-pCR | 36 | 2.92 | 4.10 | 0.00 | 20.95 | 0.001 |
| pCR | 15 | 0.30 | 0.72 | 0.00 | 2.60 | | |
| After CT axillar $SUV_{max}$ | No-pCR | 36 | 1.5 | 2.4 | 0.00 | 12.6 | 0.002 |
| pCR | 15 | 0.00 | 0.00 | 0.00 | 0.00 | | |

CT: Chemotherapy, PCR: Pathologic complete response

**Table 4.** Sensitivity, specificity, AUC, cut-off and asymptotic significance of ROC analysis of parameters

| | Sensitivity (%) | Specificity (%) | AUC | Cut-off | p |
|---|---|---|---|---|---|
| SUV2T | 75.9 | 75 | 0.815 | 0.185 | 0.002 |
| SUV2N | 55.2 | 100 | 0.776 | 0.525 | 0.006 |

To assess the diagnostic accuracy, we performed receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) was then estimated.

AUC: area under curve; SUV2T: $SUV_{max}$ in the primary tumor after chemotherapy; SUV2N: $SUV_{max}$ in the lymph nodes after chemotherapy.

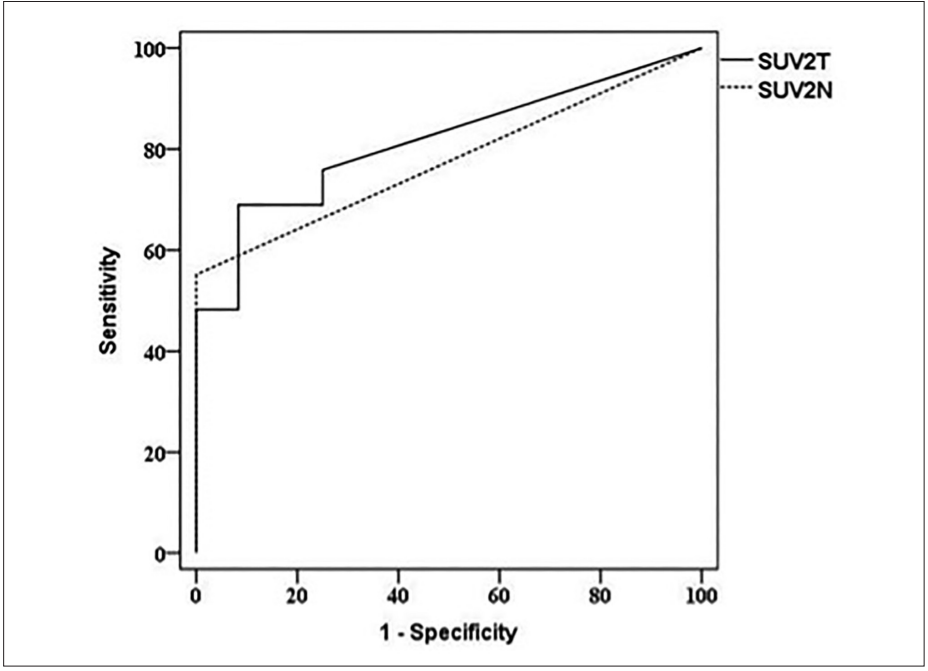


**Figure 1.** ROC curve analysis of PET2 $SUV_{max}$ for prediction of pCR. SUV2T: $SUV_{max}$ in the primary tumor after chemotherapy; SUV2N: $SUV_{max}$ in the lymph nodes after chemotherapy.

tasis occurred during the follow-up period. DFS and OS analyses were not performed because of the short follow-up period of the patients.

## Discussion

18F-FDG PET/CT-a noninvasive imaging modality-reveals both tumor metabolism and anatomical details. Higher 18F-FDG uptake in malignant cells makes the tumor visible. $SUV_{max}$ is a semi-quantitative value, and it indicates the 18F-FDG uptake. The increased proliferation activity in tumor cells is related to the density of 18F-FDG uptake of the tumor [19]. A large space exists between the 18F-FDG uptake values in our study ($SUV_{max}$: 1.13-27.07), and this situation reflects the heterogeneity of the glucose metabolism of breast carcinomas.

The 18F-FDG uptake value has been found to be related to tumor biology in various malignities in several studies [20]. There are studies comparing the histopathological parameters in breast cancer with 18F-FDG uptake. Several studies that have supported this relationship have shown that the 18F-FDG uptake values are lower in invasive lobular carcinomas than that in invasive ductal carcinomas [11]. The authors defined that the lower intensity of tumor cells in lobular carcinomas, lower expression of GLUT1, lower proliferation rates, and diffuse infiltrative tumor growth patterns of the surrounding tissue could be defined by this relationship [21]. A comparison could not be made in this study owing to the lower number of patients with invasive lobular carcinoma (three patients).

No relationship was determined between the demographical features of the patient and $SUV_{max}$. No relationship was observed between patient age and $SUV_{max}$ in several studies in the literature [8, 12], similar to our study. Further, no significant relationship was observed between the menopausal status of the patient and $SUV_{max}$. Although the study revealed that the 18F-FDG uptake value was 1.3 times higher in premenopausal patients [11], another study revealed that menopausal status and tumor $SUV_{max}$ were independent [22].

The tumor grade is a significant predictive factor in breast carcinomas. Pathologists classify breast carcinomas according to the modified Bloom–Richardson grading system. In this system, parameters such as nuclear grade, tubule formation, and mitotic rate are scored from one to three. The calculation of the final score yields the histological grade. A strong positive correlation has been revealed between the histological grade and 18F-FDG uptake levels in certain studies [10, 14]. Further, a relationship between 18F-FDG uptake and nuclear pleomorphisms and mitotic activity has been reported by Berriolo-Riedinger et al. [23], but they found no relationship with tubular formation. This may be because of the fact that the role of mitotic count and nuclear pleomorphism is much more in the glycolytic pathway and glucose consumption. Although the mean $SUV_{max}$ values of patients with a grade 3 disease was higher in our study, no relationship between the grade and $SUV_{max}$ value was observed, possibly because of the limited number of patients.

Ki67 is a marker that indicates proliferation activity and is used in various cancers. High Ki67 value was found to be related with poor prognosis in patients [24]. The major disadvantage of Ki67 value is the high variability between the observers evaluating this value [25]. There are articles that have revealed a positive correlation

between the $SUV_{max}$ values and Ki67 proliferation index and lymphovascular invasion [10, 12]. However, no correlation has been shown between Ki67 and $SUV_{max}$ in our study. Because lymphovascular invasion was not defined in the pathological reports of certain patients, it was not evaluated in this study.

Prognosis is better in ER (+) patients than ER (-) ones [26]. Data regarding the relationship between 18F-FDG uptake and hormone receptor status is unclear. While no relationship was reported between the receptor positivity and FDG uptake in certain studies [21], higher $SUV_{max}$ values were determined in ER (-) patients in many studies [11]. Further, higher $SUV_{max}$ values were established in receptor-negative patients than receptor-positive patients in our study.

Furthermore, cerbB2 overexpression is associated with the aggressiveness of tumor and poor prognosis. Although Ueda et al. [14] reported a correlation between cerbB2 oncogene overexpression and $SUV_{max}$, this was not shown in many other studies [23]. Further, a significant relationship with the primary tumor could not be shown in our study. Groheux et al. [11] suggested that there may be a minor role of the HER2 gene in the glycolytic pathway.

Triple-negative breast cancer (TNBC) comprises approximately 15% of all the invasive breast cancers. It has a high recurrence rate and poor OS time [27]. This poor prognosis is a result of the aggressive characteristic of the disease and lack of effective targeted therapy options [28]. Because of the high $SUV_{max}$ uptake, PET-CT is found to be more useful in TNBC [29]. The 18F-FDG uptake of TNBC patients was found to be high in our study, supporting many other studies [10-12].

PET-CT FDG uptake can facilitate the identification of metabolic changes earlier than conventional imaging methods during or at the end of treatment. It is found to be more sensitive (87%) in the evaluation of a treatment response than clinical examination (39%) and CT imaging (56%) [1]. Therefore, it becomes a guideline for the effectiveness of CT and treatment processes. Wahl et al. [30] showed that PET-CT facilitated the determination of a decrease in glucose metabolism in the tumor and pathological tumor response after the effective treatment of primary breast cancers. Tateishi et al. [16] showed that the sensitivity of PET-CT in the evaluation of pCR was not acceptable, but its specificity was high. There is a wide range of variation in the sensitivity (39%-100%) and specificity (74%-100%) of PET-CT in the literature. In this study, the sensitivity was 75% and specificity was 75% for the primary tumor, and the sensitivity was 55% and specificity was 100% for the axillary lymph nodes. In our study, false positivity with PET-CT was also established in three out of 15 patients with pCR. Furthermore, out of the 20 patients with a complete response in PET-CT, 12 exhibited true positivity and 8 exhibited false positivity. There is no significant difference between the mean pretreatment $SUV_{max}$ values of the patients with or without pCR. However, there is a significant difference between the $SUV_{max}$ values between these two groups after NAC ($SUV_{max}$ breast 2.92 vs. 0.30, p=0.01; $SUV_{max}$ axilla 1.5 vs. 0.0, p=0.02).

Our study has several limitations. Firstly, since this was a retrospective study and the number of patients was low, its results should be interpreted with caution. In some studies, it was revealed that the $\Delta SUV_{max}$ measurements used to evaluate the metabolic response after NAC correlated with pCR. In our study, $\Delta SUV_{max}$ measurements were not performed. The association between the histological subtypes and pCR was not assessed because of the low number of patients in the subgroups. Finally, we did not attempt to analyze the relationship between $SUV_{max}$ and survival as the follow-up period of the study population was relatively short.

Consequently, no relationship between PET-CT $SUV_{max}$ values and demographical features of the patients could be established in LABC. However, it seems that there may be a relationship with certain histopathological prognostic factors. Moreover, there is a significant relationship between the post-treatment $SUV_{max}$ value and pCR. PET/CT may be useful in predicting the prognosis in NAC-subjected patients with LABC because none of the patients with a complete response in PET/CT exhibited recurrence. In order to support these results, there is a need for randomized prospective studies that involve a large number of patients and a longer follow-up period.

**Ethics Committee Approval:** This study was conducted according to the ethical standards of the University Ethical Commitee and the 1964 Helsinki Declaration.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

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

**Author Contributions:** Concept - N.Y., M.S.; Design - N.Y., M.B.; Supervision - N.Y., M.B.; Resources - N.Y., M.N.A.; Materials - N.Y., S.B.T.; Data Collection and/or Processing – N.Y., M.S.; Analysis and/or Interpretation - N.Y., M.S.; Literature Search - N.Y., M.N.A.; Writing Manuscript - N.Y., M.S.; Critical Review - N.Y., S.B.T.

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## References

1. Kumar A, Kumar R, Seenu V, et al. The role of 18F-FDG PET/CT in evaluation of early response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. Eur Radiol 2009; 19: 1347-57. [CrossRef]
2. Van der Hage JA, Van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001; 19: 4224-37. [CrossRef]
3. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. J Clin Oncol 2008; 26: 778-85. [CrossRef]
4. Smith IC, Heys SD, Hutcheon AW, et al. Neoadjuvant chemotherapy in breast cancer: Significantly enhanced response with docetaxel. J Clin Oncol 2002; 20: 1456-66. [CrossRef]
5. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998; 16: 2672-85. [CrossRef]
6. Chaturvedi S, McLaren C, Schofield A, et al. Patterns of local and distant disease relapse in patients with breast cancer treated with primary chemotherapy: do patients with a complete pathological response differ from those with residual tumour in the breast? Breast Cancer Res Treat 2005; 93: 151-8. [CrossRef]
7. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and longterm clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384:164-72. [CrossRef]
8. Ishiba T, Nakagawa T, Sato T, et al. Efficiency of fluorodeoxyglucose positron emission tomography/computed tomography to predict prognosis in breast cancer patients received neoadjuvant chemotherapy. Springerplus 2015; 4: 817. [CrossRef]
9. Koolen BB, Vrancken Peeters MJ, Aukema TS, et al. 18FFDG PET/CT as a staging procedure in primary stage II and III breast cancer: comparison with conventional imaging techniques. Breast Cancer Res Treat 2012; 131: 117-26. [CrossRef]
10. Ekmekcioglu O, Aliyev A, Yilmaz S, et al. Correlation of 18F-fluorodeoxyglucose uptake with histopathological prognostic factors in breast carcinoma. Nucl Med Commun 2013; 34: 1055-67. [CrossRef]
11. Groheux D, Giacchetti S, Moretti JL, et al. Correlation of high 18F-FDG uptake to clinical, pathological and biological prognostic factors in breast cancer. Eur J Nucl Med Mol Imaging 2011; 38: 426-35 [CrossRef].
12. Koo HR, Park JS, Kang KW, Han W, Park IA, Moon WK. Correlation between 18F-FDG uptake on PET/CT and prognostic factors in triple-negative breast cancer. Eur Radiol 2015; 25: 3314-21. [CrossRef]
13. Inoue T, Yutani K, Taguchi T, Tamaki Y, Shiba E, Noguchi S. Preoperative evaluation of prognosis in breast cancer patients by [(18)F]2-Deoxy-2-fluo-

ro-D-glucosepositron emission tomography. J Cancer Res Clin Oncol 2004; 130: 273-8. [CrossRef]
14. Ueda S, Tsuda H, Asakawa H, et al. Clinicopathological and prognostic relevance of uptake level using 18F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging (18F-FDG PET/CT) in primary breast cancer. Jpn J Clin Oncol 2008; 38: 250-8. [CrossRef]
15. Schwarz-Dose J, Untch M, Tiling R, et al. Monitoring primary systemic therapy of large and locally advances breast cancer by using sequential positron emission tomography imaging with [18F]fluorodeoxyglucose. J Clin Oncol 2009; 27: 535-41. [CrossRef]
16. Tateishi U, Miyake M, Nagaoka T, et al. Neoadjuvant chemotherapy in breast cancer: prediction of pathologic response with PET/CT and dynamic contrastenhanced MR imaging-prospective assessment. Radiology 2012; 263: 53-63. [CrossRef]
17. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010; 28: 2784-95. [CrossRef]
18. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007; 25: 118-45.[CrossRef]
19. Higashi K, Clavo AC, Wahl R. Does FDG uptake measure proliferative activity of human cancer cells? In vitro comparison with DNA flow cytometry and tritiated thymidine uptake. J Nucl Med 1993; 34: 414-9.
20. Brock CS, Meikle SR, Price P. Does fluorine-18 fluorodeoxyglucose metabolic imaging of tumours benefit oncology? Eur J Nucl Med 1997; 24: 691-705. [CrossRef]
21. Buck AK, Schirrmeister H, Mattfeldt T, Reske SN. Biological characterisation of breast cancer by means of PET. Eur J Nucl Med Mol Imaging 2004; 31: 80-7. [CrossRef]
22. Kim BS, Sung SH. Usefulness of 18F-FDG uptake with clinicopathologic and immunohistochemical prognostic factors in breast cancer. Ann Nucl Med 2012; 26: 175-83. [CrossRef]
23. Berriolo-Riedinger A, Touzery C, Riedinger JM, et al. [18F] FDG-PET predicts complete pathological response of breast cancer to neoadjuvant chemotherapy. Eur J Nucl Med Mol Imaging 2007; 34: 1915-24. [CrossRef]
24. Inwald EC, Klinkhammer-Schalke M, Hofstädter F, et al. Ki-67 is a prognostic parameter in breast cancer patients: results of a large population-based cohort of a cancer registry. Breast Cancer Res Treat 2013; 139: 539-52. [CrossRef]
25. Urruticoechea A, Smith IE, Dowsett M. Proliferation marker Ki-67 in early breast cancer. J Clin Oncol 2005; 23: 7212-20. [CrossRef]
26. Mauri FA, Maisonneuve P, Caffo O, et al. Prognostic value of estrogen receptor status can be improved by combined evaluation of p53, Bcl2 and PgR expression: an immunohistochemical study on breast carcinoma with long-term follow-up. Int J Oncol 1999; 15: 1137-47. [CrossRef]
27. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007; 13: 4429-34. [CrossRef]
28. Lehmann BD, Pietenpol JA. Identification and use of biomarkers in treatment strategies for triple-negative breast cancer subtypes. J Pathol 2014; 232: 142-50. [CrossRef]
29. Koolen B, Peeters V, Wesseling J, et al. Association of primary tumour FDG uptake with clinical, histopathological and molecular characteristics in breast cancer patients scheduled forneoadjuvant chemotherapy. Eur J Nucl Med Mol Imaging 2012; 39: 1830-8.[CrossRef]
30. Wahl RL, Zasady K, Helvie M, Hutchins GD, Weber B, Cody R. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography -initial evaluation. J Clin Oncol 1993; 11: 2101-11. [CrossRef]