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Research Article

Value of FDG PET/CT in Predicting Pathologic Complete Response After Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer

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Abstract

Objectives: To investigate the importance of FDG PET/CT in predicting pathologic complete response (pCR) in primary breast lesions and axillary lymph nodes of patients with local, advanced breast cancer who were given neoadjuvant chemotherapy (NAC).

Methods: One hundred twenty-one patients who had FDG PET/CT and underwent surgery due to local, advanced breast cancer before and after NAC were involved in the study. SUVmax and SULpeak values before and after NAC were evaluated using FDG PET/CT and post-surgical responses were re-evaluated.

Results: Our study included 121 patients in total and 34 patients (28.1%) had a complete response in the breast, and 53 patients (43.8%) had a complete response in axillary lymph nodes. PostSUVmax and PostSULpeak values ≤1.15 and the activity presenting the pCR were controlled and the sensitivity and specificity were found as 61.8% and 61.8%, and 73.3% and 77.0%, respectively, for the breast ($p<0.001$ and $p<0.001$). The reduction rate (RR) of SUVmax >88% and the SULpeak (RR) >81% values and the activity presenting the pCR were controlled and the sensitivity and specificity were found as 80.0% and 81.8%, and 80.0% and 60.7%, respectively, for the breast ($p<0.001$ and $p<0.001$).

Conclusion: The decrease of SUVmax and SULpeak values detected between PET/CT studies before and after NAC were well correlated with the pathologic response. FDG- PET/CT has high sensitivity and specificity in the evaluation of treatment response rates in breast lesions of patients with breast cancer receiving NAC.

Keywords: Breast cancer, neoadjuvant chemotherapy, FDG Pet/CT, pathologic complete response

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Nowadays, neoadjuvant chemotherapy (NAC) has been a standard treatment in local, advanced breast cancer.[1] It is aimed to have both better cosmetic results by increasing the breast-preserving surgery rates and less morbidity by decreasing axillary lymph node dissection rates with the use of NAC, which also provides the oppor-

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tunity to evaluate chemo-resistance and predict survival.[2,3] Imaging before NAC should be performed to determine the spread of the disease. 18 fluorodeoxyglucose positron emission tomography/computer tomography (18F-FDG PET/CT) before NAC is an imaging method used with high sensitivity and specificity in breast cancer staging and the detection of remote metastasis.[4-7] Complete response rates after NAC in the breast and axilla may differ according to the tumour biology.[8] Discussions about the most available imaging for early detection of pathological complete response (pCR) are ongoing. Anatomical imaging methods [e.g. mammography, ultrasound, computer tomography (CT) and magnetic resonance imaging (MRI)] play a role in mainly assessing the changes in tumour size. However, their accuracies in predicting the response to neoadjuvant therapy are limited.[9]

For the measurement of change in tumour tissue, fluorine-18 fluorodeoxyglucose (18F-FDG) metabolism was recommended as an early determiner to cytotoxic therapy and a survival marker.[10-13] In 2009, the Positron Emission Tomography (PET) Response Criteria in Solid Tumours (PERCIST 1.0) was defined as a guide for evaluating the treatment response of 18F-FDG PET/CT systematically and in detail in patients with cancer.[14] In PERCIST, the peak standardized uptake value corrected for lean body mass (SULpeak) is chosen instead of the widely used maximum standardized uptake value (SUVmax). SUVlbm (referred to as SUL) is recommended because FDG uptake in adipose tissue is low, and glucose uptake assessed as SUVbw would be overestimated in patients with obesity.[15]

PERCIST encourages the recording of the percentage of change in tumour metabolism as a continuous variable with notation of the number of weeks since treatment began. The metabolic change was reported to be associated with clinical outcome in patients with several different types of cancer.[16] Complete metabolic response according to PERCIST 1.0 does not mean SULpeak to a decrease to zero. Complete metabolic response of the target lesion is defined as complete resolution of FDG uptake that is less than the mean SUL of the liver (background activity). Partial metabolic response shows a decrease of greater than or equal to 30% and of at least 0.8 SUL units between the most intense evaluable lesion at baseline and the most intense lesion at follow-up.[16]

We investigated the importance of 18F-FDG PET/CT in predicting pCR in primary breast and axillary lymph nodes of patients with local, advanced breast cancer who were given NAC, using both SUVmax values and SULpeak values according to PERCIST 1.0.

Methods

Patients

The data of three hundred and six patients who received NAC for breast cancer between 2012 and 2020 in the medical oncology clinic of the hospital were reviewed. One hundred twenty-one patients whose NACs were completed, who had 18F-FDG PET/CT before and after NAC, with available 18F-FDG PET/CT images were included in the study. One hundred eighty-one patients without 18F-FDG PET/CT before or after NAC and four patients who were out of follow-up while NAC treatment was ongoing were excluded from the study. Data on patient demographics, tumour histology, and assessments of tumours using metabolic response on 18F-FDG PET/CT imaging were collected. All patients were administered anthracycline and taxane-based chemotherapy (CT). Trastuzumab was applied topatients who were human epidermal growth factor receptor-2 (HER-2)-positive. After pertuzumab was approved in the neoadjuvant setting of breast cancer treatment in our country, we started to administer combination treatment of pertuzumab, trastuzumab and docetaxel. Follow-up PET/CT was performed in all patients 15 days after NAC treatment was finished to evaluate the treatment response.

18F-FDG-PET/CT Imaging

PET/CT examinations were performed after at least 6 hours of fasting in patients whose blood glucose levels were <180 mg/dL. After intravenous injections of 3.7 MBq/kg (0.1 mCi/kg) F18-FDG to all patients, the patients waited in a quiet room for 60 minutes. Then, the patients were imaged from vertex to mid-femur in the supine position using a PET/CT scanner that included a lutetium–yttrium oxyorthosilicate (LYSO) crystal for the PET component [GEMINI TF PET/CT (64 sections)]. A low-dose CT (120 kV; weight-based amperage range 80-60 mA) with oral contrast was performed for attenuation correction before the PET scan. Image thickness was 4 mm and a CT transmission map was generated for image fusion. PET emission data were acquired for 2 min in each bed position, with the patient in the same position as for the CT portion of the study. CT data were used for attenuation correction. PET data were reconstructed using a time-of-flight (TOF) reconstruction algorithm (OSEM TOF) using standard reconstruction settings; all images were reconstructed in a 144×144×144 image matrix and 4×4×4 mm^3 voxels.

Assessment of Tumour by the Metabolic Response

The images were re-evaluated by a nuclear medicine specialist who had 10 years' PET/CT experience and knew the breast cancer diagnosis, but who was un-

aware of the clinical and pathologic findings. The size of the primary tumour and the FDG-avid lymph nodes or lymphadenopathies were measured in two dimensions for referring to the longest dimension. For patients with multiple tumours or the presence of FDG-avid lymph nodes, tumours larger than 1 cm in at least one dimension and with the most intense 18F-FDG uptake were used for evaluation.

The attenuation corrected images were normalized for the injected activity and body weight. The SUVmax values were determined by drawing the region of interest (ROI) around the primary tumour with the most intense uptake on the transaxial slices and calculated using the following formula:

Measured activity concentration [Bq/mL] × body weight [kg] / injected activity [Bq]

Intensities of 18F-FDG uptake were quantified by calculating standardized uptake values corrected for lean body mass in a 1 cm^3 spherical volume of interest (VOI) from the hottest voxel (SULpeak) in the tumour and 3 cm^3 spherical volume of interest (VOI) in physiologic liver tissue for background activity normalisation. Normalisation by lean body mass (SUVLBM) formula was used:

Measured activity concentration [Bq/mL] × lean body mass [kg] / injected activity [Bq]

Lean body mass was calculated according to the following formula for women:[16]

(1.07 ×weight [kg]) −148 × (weight $[kg]^2$ / height $[cm]^2$)

Relative percentage changes of metabolic activity in tumour tissue and FDG-avid axillary nodes between SUVs at baseline (BL) and follow-up (FL) were calculated as response rate according to the following formula:

Response rate for SUVmax: 100 • [FLSUVmax – BLSUVmax]/BLSULmax

Response rate for SULpeak: 100 • [FLSULpeak – BLSULpeak]/BTLSULpeak

Response rate was analysed for their potential to predict histopathological response to chemotherapy.

Evaluation of Tumour Histology

Estrogen and progesterone hormone receptor levels in the Tru-cut biopsy samples of all patients involved in the study before NAC and their HER-2 statuses were reassessed. The haematoxylin and eosin (H&)-stained preparations of surgical resection samples of patients after NAC were retrieved from the archive and their histopathologic properties were reassessed by a pathologist. The response to NAC was classified according to the College of American Pathologists (CAP) 2018.

Statistical Analysis

The SPSS (version: 22.0. Armonk NY, IBM Corp. 2013) package was used for statistical analysis. The numerical variables between two independent situations were analysed using Student's t-test in the case of normal distribution and with the Mann-Whitney U test with non-normally distributed data. For a qualitative analysis, the diagnostic performance of 18F-FDG-PET SUVs and response rate percentage (%) for pCR detection, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were computed. The diagnostic power of 18F-FDG-PET was computed using the optimum SUVmax and SULpeak cut-off value and a semi-quantitative analysis provided by receiver operating characteristics (ROC) analysis. Results were determined using 95% confidence interval (CIs). The statistical significance level of alpha was set as $p<0.05$. Determiners related to pCR were reviewed using multivariate logistic regression analysis.

Results

The median age of the patients was 49 (range, 42-57) years. Out of the 121 patients, 120 had clinical disease stage III. Ninety-five (78.5%) patients were oestrogen receptor (ER)-positive, 78 (64.5%) were progesterone receptor (PR)-positive, and 14 (11.6%) were triple-negative. HER-2 overexpression/amplification was positive in 49 (40.5%) patients. Detailed demographic and clinical characteristics of the patients are shown in Table 1. The number of patients with a complete response in both the primary breast mass and axilla was 30 (24.8%).

Findings in Breast Lesions

Thirty-four of the total 121 (28.1%) patients had a complete response in the breast. The HER-2 positive sub-group had a 58.8% complete response rate and 33.3% lack of complete response rate ($p=0.01$). Patients with low levels of both average oestrogen receptors and progesterone receptors had more benefit from NAC ($p=0.02$ and $p=0.01$, respectively) (Table 1).

A significant decrease in breast diameter, SUVmax, and SULpeak median values were determined after NAC was completed ($p<0.001$, $p<0.001$, and $p<0.001$, respectively) using FDG-PET/CT findings (Table 2).

SUVs were evaluated using ROC analysis after NAC. The SUVmax cut-off value that best demonstrated pCR in the ROC curve analysis was found as 1.15 for PostSUVmax. pCR was seen in 61.8% of the total 41 patients with ≤1.15 PostSUVmax values ($p<0.001$). Using the ≤1.15 PostSUVmax value, 61.8% sensitivity, 73.3% specificity, 51.2% PPV, and 83.8% NPV were found for efficacy in evaluating pCR (Fig.

Table 1. Demographic and clinical characteristics of the study subjects

	All (n=121)	Completeresponse (+) (n=34)	Completeresponse (-) (n=87)	p
Age, years, Median (IQR)	49 (42-57)	48 (41-54)	50 (42-58)	0.59
ECOGPS status				0.63
0	106 (87.6)	29 (85.3)	77 (88.5)	
1	15 (12.4)	5 (14.7)	10 (11.5)	
Histopathology				0.23
Invasiveductal	111 (91.7)	30 (88.2)	81 (93.1)	
Invasive lobular	2 (1.7)	–	2 (2.3)	
Mixed lobular andductal	2 (1.7)	2 (5.9)	–	
Mucinous	2 (1.7)	1 (2.9)	1 (1.1)	
Micropapillary	3 (2.5)	1 (2.9)	2 (2.3)	
Others	1 (0.8)	–	1 (1.1)	
Grade				0.34
Grade 1	3 (2.5)	–	3 (3.6)	0.09
Grade 2	65 (53.7)	19 (55.9)	46 (54.8)	0.06
Grade 3	47 (38.8)	13 (38.2)	34 (40.5)	**0.02**
Unknown	3 (2.5)	2 (5.9)	1 (1.2)	**0.03**
Hormone status (+)	97 (80.2)	24 (70.6)	73 (83.9)	**0.01**
ER+,	95 (78.5)	23 (67.6)	72 (82.8)	**0.01**
Median ER rate (IQR)	80 (10-90)	45 (0-90)	80 (50-90)	0.50
PR+,	78 (64.5)	17 (50.0)	61 (70.1)	0.50
Median PR rate (IQR)	10 (0-60)	0 (0-30)	17 (0-70)	
HER-2 positivity	49 (40.5)	20 (58.8)	29 (33.3)	
Luminal/Non-luminal	10/39	5/15	5/24	
Triple-negative	14 (11.6)	5 (14.7)	9 (10.3)	
Clinical T				0.38
T1	38 (31.4)	11 (32.4)	27 (31.0)	
T2	71 (58.7)	22 (64.7)	49 (56.3)	
T3	6 (5.0)	–	6 (6.9)	
T4	6 (5.0)	1 (2.9)	5 (5.7)	
Clinical N				0.48
N1	2 (1.6)	1 (2.9)	1 (1.1)	
N2	98 (81.0)	29 (85.3)	69 (79.3)	
N3	21 (17.4)	4 (11.8)	17 (19.5)	
Clinical stage				0.31
Stage IIA	1 (0.8)	1 (2.9)	–	
Stage IIIA	95 (78.5)	28 (82.4)	67 (77.0)	
Stage IIIB	4 (3.3)	1 (2.9)	3 (3.4)	
Stage IIIC	21 (17.4)	4 (11.8)	17 (19.5)	
Surgery				0.59
Breastconserving	40 (33.1)	10 (29.4)	30 (34.5)	
Mastectomy	81 (66.9)	24 (70.6)	57 (65.5)	
Breast PostSUVs				
SUVmax ≤1.15	41 (33.9)	21 (61.8)	20 (23.0)	
SUVmax >1.15	80 (66.1)	13 (38.2)	67 (77.0)	<**0.001**
SULpeak ≤1.15	44 (36.4)	21 (61.8)	23 (26.7)	
SULpeak >1.15	76 (62.8)	13 (38.2)	63 (73.3)	<**0.001**
Breast RR (%)				
SUVmax RR ≤88	81 (66.9)	13 (39.4)	68 (79.1)	
SULVmax RR >88	38 (31.4)	20 (60.6)	18 (20.9)	<**0.001**
SULpeak RR ≤81	57 (48.7)	6 (17.6)	51 (58.6)	
SULpeak RR >81	60 (51.3)	27 (79.4)	33 (37.9)	<**0.001**

IQR: Interquartile range; ECOG PS: Eastern Cooperative Oncology Group performance status; ER: Estrogen receptor; PR: Progesterone receptor; HER-2: Human epidermal growth factor receptor-2; SUVmax: Maximum standardized uptake value; SULpeak: SUV normalized to body weight and lean body mass; RR: Reduction rate.

Table 2. Median tumor size and metabolic activityin baseline and follow-up after NAC

	Before NAC	After NAC	p
Breast tissue			
Size (mm)	27 (20-37)	10 (6-18)	<**0.001**
SUVmax	9.4 (6.3-12.9)	1.9 (0.9-2.8)	<**0.001**
SULpeak	8.8 (6.0-12.3)	1.6 (0.8-2.5)	<**0.001**
Axillary LAP			
Size (mm)	16 (10-20)	7 (5-9)	<**0.001**
SUVmax	5.5 (3.0-10.0)	0.5 (0.5-1.0)	<**0.001**
SULpeak	5.3 (2.9-9.5)	0.6 (0.5-1.0)	<**0.001**

NAC: Neoadjuvant chemotherapy; LAP: Lymphadenopathy; SUVmax: Maximum standardized uptake value, SULpeak SUV normalized to body weight and lean body mass.

Table 3. Multivariate logistic regression analysis of pCR of the study subjects

	OR	95% CI	p
Primary breast			
HER-2 positivity	2.964	1.213-7.238	**0.017**
HR positivity	0.420	0.150-1.178	0.099
Post-SUVmax≤1.15	5.550	2.268-13.577	<**0.001**
HER-2 positivity	3.135	1.261-7.792	**0.014**
HR positivity	0.476	0.165-1.370	0.169
RR%-SUVmax>88	5.659	2.274-14.084	<**0.001**
Axilla			
HER-2 positivity	4.878	2.118-11.237	<**0.001**
HR positivity	0.338	0.118-0.972	**0.044**
Post-SUVmax ≤0.55	0.274	0.114-0.654	**0.004**
HER-2 positivity	5.161	2.227-11.962	<**0.001**
HR positivity	0.397	0.141-1.116	0.080
RR%-SUVmax >86	2.226	0.952-5.203	0.065

pCR: Pathological complete responder; HER-2: Human epidermal growth factor receptor-2; HR: Hormone receptor; SUVmax: Maximum standardized uptake value; RR: Reduction rate; OR: Odd ratios; CI: Confidence interval.

1a). Similarly, the SULpeak cut-off value that best demonstrated pCR in the ROC curve analysis was found as 1.15 for PostSULpeak. Using the ≤1.15 PostSULpeak value, 61.8% sensitivity, 77.0% specificity, 47.7% PPV, and 82.9% NPV were found for efficacy in evaluating pCR (Fig. 1b).

The relationship of the ratio of SUV reductions before and after treatment with pCR was controlled. The SUVmax reduction rate (RR) cut-off value that best demonstrated pCR in the ROC curve analysis was found as 88% for SUVmax RR; 60.6% of 38 patients with SUVmax RR values >88% complied with pCR (p<0.001). Using the >88% SUVmax RR value, 80.0% sensitivity, 80.0% specificity, 52.6% PPV, and 84.0% NPV were found for efficacy in evaluating pCR (Fig. 2a). Likewise, the correlation of RR with pCR was controlled

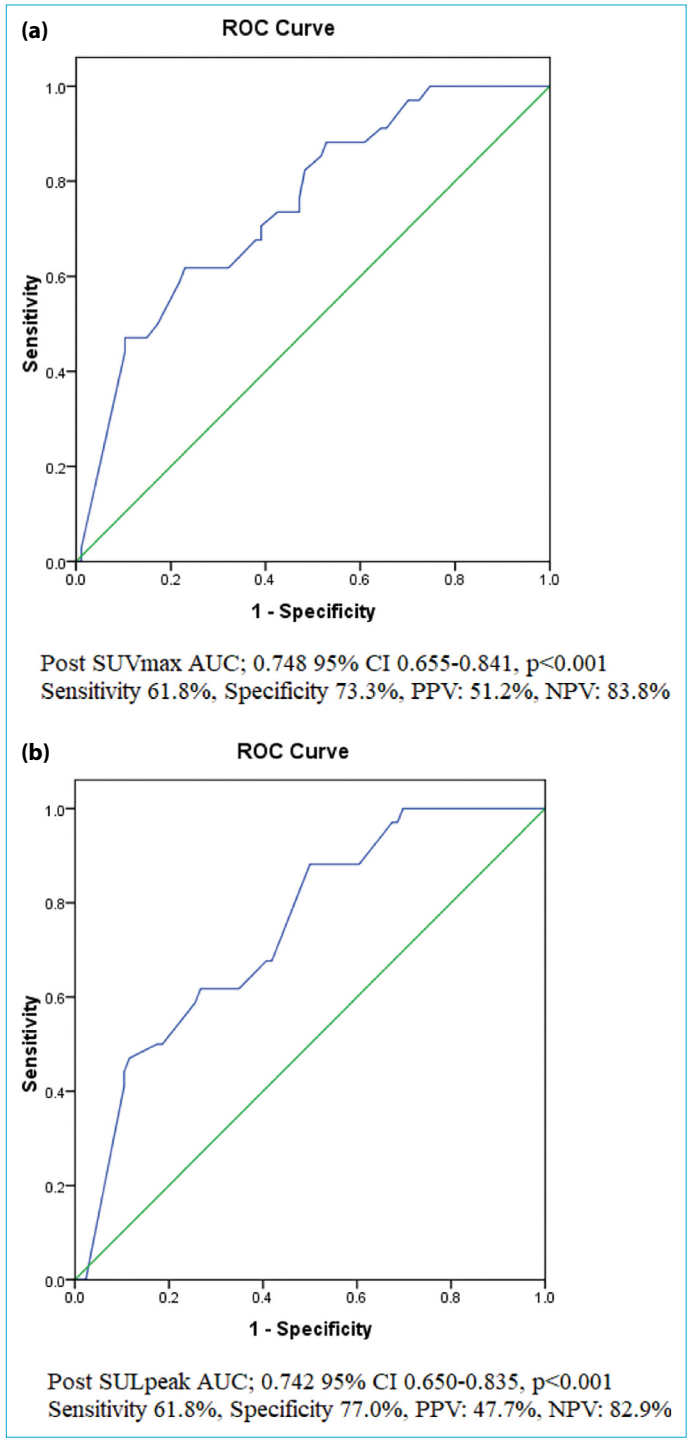

Figure 1. (a) Post SUVmax ROC curve: Suvmax best cut-off value, 1.15; to predict Complete responder **(b)** Post SULpeak ROC curve: SULpeak best cut-off value, 1.15; to predict Complete responder.

for SULpeak. The cut-off value that best demonstrated pCR was detected as 81% for SULpeak RR; 60.7% of 38 patients with SULpeak RR values >81% complied with pCR (p<0.001). Using the >81% SULpeak RR value, 81.8% sensitivity, 60.7% specificity, 60.7% PPV, and 81.8% NPV were found for efficacy in evaluating pCR (Fig. 2b)

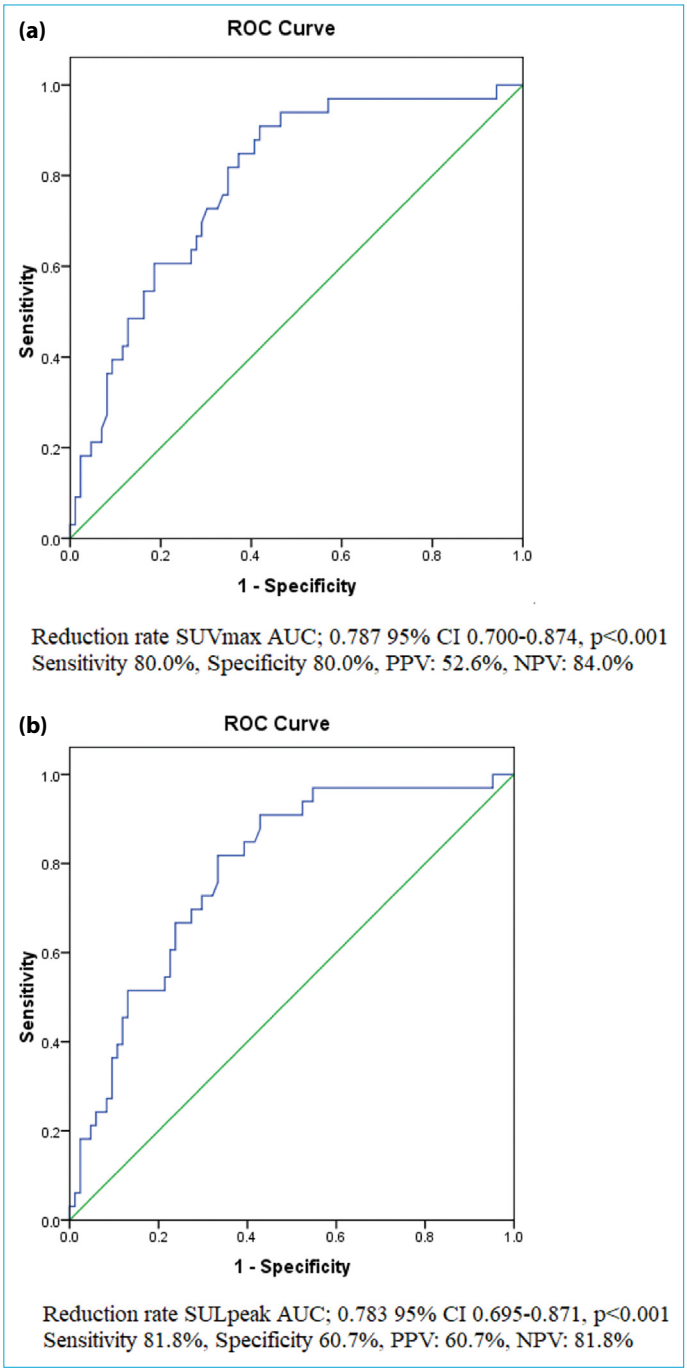

Figure 2. (a) Post SUVmax Reduction rate ROC curve: bestcut-off value, 88%; to predict Complete responder. **(b)** Post SULpeak Reduction rate ROC curve: bestcut-offvalue, 81%; to predict Complete responder.

Two different models were performed using multivariate logistic regression analysis to evaluate the parameters that most affected pCR. In the first model, ≤1.15 post SUVmax (p>0.001) with HER-2 positivity was found as significant by means of the relationship with pCR (p=0.017). In the second model, a decrease of RR SUVmax by more than 88% (p<0.001) and HER-2 positivity (p=0.014) were detected as the most important parameters related to pCR (Table 3).

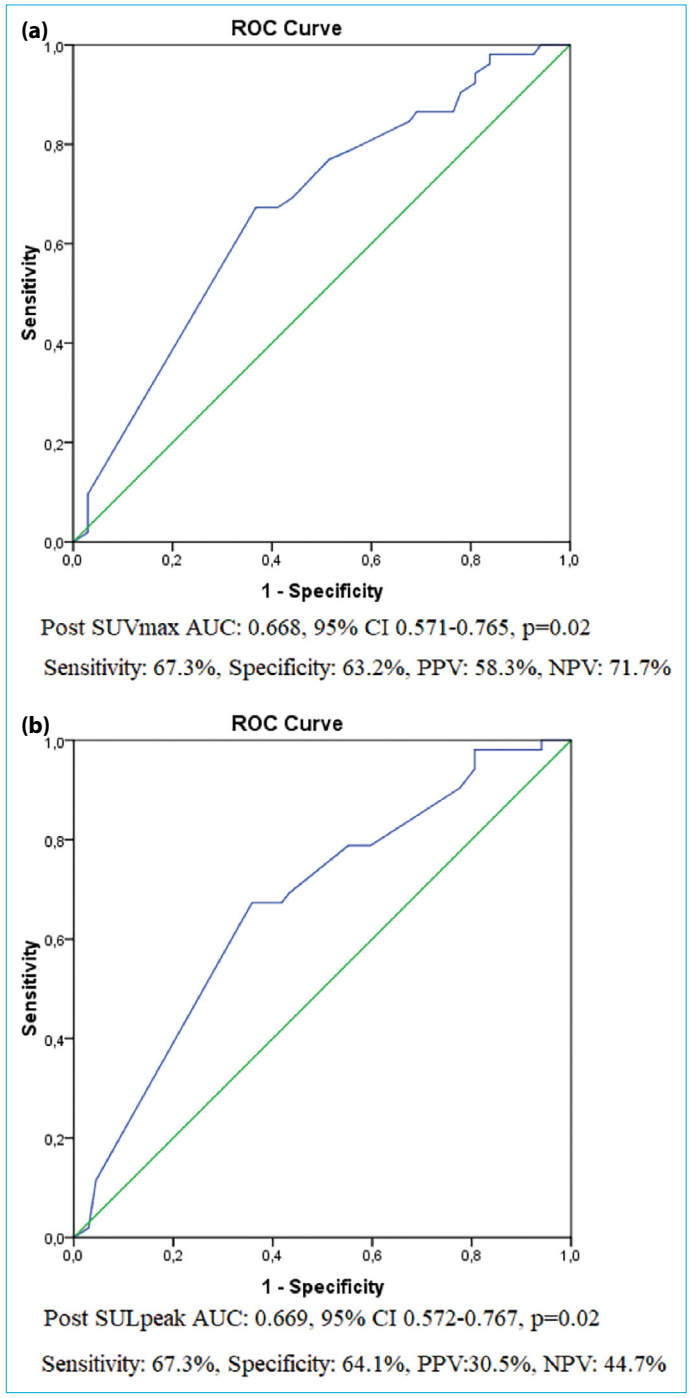

Figure 3. (a) Post SUVmax ROC curve: SUVmax best cut-off value, 0.55; to predict complete responder for axilla. **(b)** Post SULpeak ROC curve: SULpeak best cut-off value, 0.55; to predict complete responder for axilla.

Findings in FDG-avid Axillary Lymph Nodes

Fifty-three of the total 121 (43.8%) patients had a complete response in the axilla. Similarly, the HER-2 positive subgroup and the subgroup with low average ER levels had more benefit from NAC, whereas the subgroup with lower average PR levels did not reach statistical significance (p<0.001, p=0.001, and p=0.05, respectively).

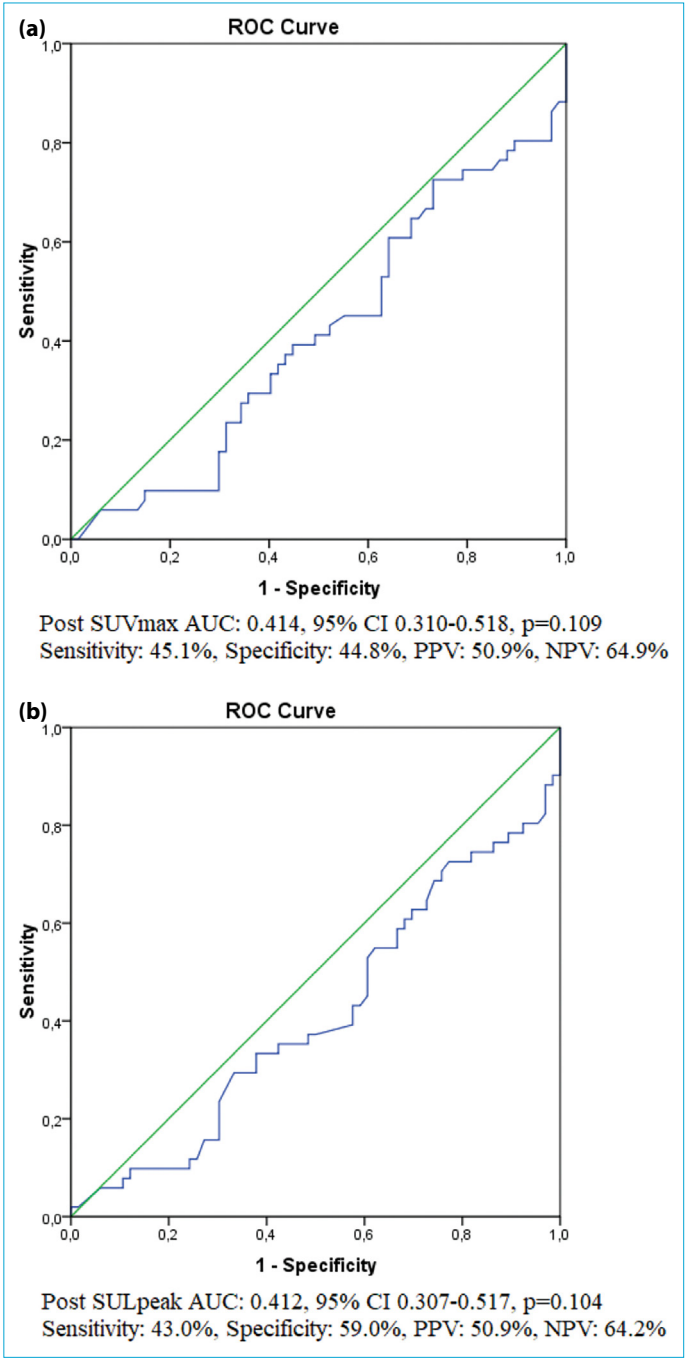

Figure 4. (a) Post SUVmax reduction rate ROC curve: best cut-off value, 86%; to predict complete responder for axilla. **(b)** Post SULpeak reduction rate ROC curve: best cut-offvalue, 85%; to predict complete responder for axilla.

Again, similar to the results obtained for the breast, significant reductions in axillary lymph node diameter, SUVmax, and SULpeak median values were maintained in follow-up PET/CT after NAC (p<0.001, p<0.001, and p<0.001, respectively) (Table 2).

The SUVmax cut-off value that best demonstrated pCR after NAC was found as 0.55 for the axilla. PCR was seen in 30.5% of the total 59 patients with ≤0.55 PostSUVmax values for the axilla (p<0.02). Using the ≤0.55 PostSUVmax value, 67.3% sensitivity, 63.2% specificity, 58.3% PPV, and 71.7% NPV were found for efficacy in evaluating pCR (Fig. 3a). Similarly, the SULpeak cut-off value that best demonstrated pCR in the ROC curve analysis was found as 0.55 for PostSULpeak. Using the ≤0.55 PostSULpeak value, 67.3% sensitivity, 64.1% specificity, 30.5% PPV, and 44.7% NPV were found for efficacy in evaluating pCR (Fig. 3b).

The relationship of the pretreatment and posttreatment SUVs RR with pCR was also controlled for the axilla. The SUVmax RR cut-off value that best demonstrated pCR in the ROC curve analysis was found as 86% for the SUVmax reduction ratio. When pCR demonstrating activity of ≥86% SUVmax RR values was controlled, the sensitivity was 45.1% and specificity was 44.8% (Fig. 4a). Likewise, the correlation of decrease ratios between pretreatment and posttreatment SULpeak with pCR was controlled. The cut-off value that best demonstrated pCR of SULpeak was detected as 85%. When pCR demonstrating activity of ≥85% SUVmax RR values was controlled, the sensitivity was 43.0% and specificity was 59.0% (Fig. 4b).

In the first model made for determining the parameters that most affected pCR for the axillary lymph node, post SUVmax ≤0.55 (p<0.004) with HER-2 positivity and hormone receptor positivity were found as significant using the relationship with pCR (p<0.001 and p=0.044, respectively). In the second model, HER-2 positivity (p<0.001) was found as the most important parameter through the relationship with pCR (Table 3).

Discussion

Dissection of the primary mass and lymph nodes is required for the optimum local control and evaluation of treatment response after NAC. Obtaining pCR as a result of NAC in breast cancer both increases survival and provides an opportunity for less invasive surgery (especially lymph node dissection); therefore, postoperative complications, mainly lymphoedema risk, are prevented to a large extent.[18-20] The NAC-associated clinical response rate is 70% and the pCR rate is 13-26% in breast cancer.[21,22] In our study, pCR was found as 24.8%, also in good agreement with the literature.

FDG PET/CT has been widely accepted in staging, relapse/metastasis detection and restaging, prognostic determination, and for breast cancer with heterogeneous tumour biology.[23] Though a joint evaluation guideline is not yet present in clinical practices of breast cancer for evaluating response to neoadjuvant therapy, MRI and FDG PET/CT examinations have remained in the forefront.[24] In

our clinics, FDG PET/CT is used for staging for patients in whom NAC will be used. FDG PET/CT use in evaluating the response to NAC has gradually increased.

F18-FDG PET/CT is a non-invasive diagnostic technique that measures glucose use- related metabolic activity in tumour tissue via FDG uptake measurement.[25] In breast cancer, different quantitative parameters that show the FDG involvement levels in tumours, mainly SUV values, may correctly predict the pathologic response during the evaluation of treatment response.[26-28] It was suggested that SUVmax and SULpeak values differed less with respect to the observer and they were more sensitive in histopathologically distinguishing treatment-responsive and unresponsive tumours.[29] In our study, we used two different, quantitative, metabolic parameters to demonstrate treatment response. In all patients involved in the study, SUVmax and SULpeak values were used as SUV measurement methods in both breast and axillary lymph nodes before and after NAC. Use of PERCIST SULpeak is recommended in the literature for treatment response in other solid tumours. We found no statistically significant difference in the evaluation of treatment response between SUVmax and SULpeak measurements in the breast cancer group; the cut-off values obtained by both methods and sensitivities and specificities were found equivalent and the SUVmax and SULpeak values were not superior to each other. The RR percentage cut-off for SULpeak was found relatively lower than the cut-off found for SULmax (81% vs. 88%), which would be taken into consideration in treatment response according to PERCIST.

Many studies investigated interim PET/CT based pathological response prediction in early cycles of NAC referring encouraging results in sensitivity and accuracy.[9,27,28,30,31] In a meta-analysis of 17 studies that involved 781 patients and investigated the power of FDG PET and FDG PET/CT in determining the neoadjuvant treatment response, FDG PET/CT was shown to be 84% sensitive (95% CI: 0.80-0.88) and 71% specific (95% CI: 0.67-0.76).[25] A newer meta-analysis, evaluating the prognostic significance of FDG PET and FDG PET/CT both for interim response (during NAC in 12 studies) and posttreatment response (completed NAC in 10 studies) in breast cancer patients, meta-analytically pooled hazard ratios (between 0.20-0.31) for disease free and overall survival were not significantly different for interim or post-treatment PET scans. Both courses of time, FDG PET or FDG PET/ CT based evaluation of the metabolic response to NAC provide accurate risk stratification and support for risk- adapted therapeutic management in HER2+ or triple-negative subtypes which are known to be FDG-avid, but also in hormone receptor-positive tumours.[32] In our study design we evaluated metabolic based response prediction after completion of NAC in terms of changes in SUVmax and SULpeak metabolic parameters. Cut-off values in SUVmax RR (>88%) and SULpeak RR (>81%) revealed 80% and 81.8% sensitivity rates, 80% and 60.7% specificity rates respectively.

In a prospective study of 104 patients with local, advanced breast cancer, the decrease of SUV after chemotherapy was 73%, the positive predictive value was 45%, the decrease of SUV after chemotherapy was 73%, and the negative predictive value was 90%.[33] They found lower sensitivity rates for FDG PET by applying a threshold SUV of 1.5 and 2.0 but highest specificity among all imaging modalities.[33] In 30 of 130 female with breast carcinoma achieving pCR after NAC completion, the ROC curves of the posttreatment SUVmax and pre – post SUVmax change to predict pCR revealed a cutoff of 1.3 and 80%, respectively.[34] However, in our study, a statistically significant difference was detected in the SUVmax and SULpeak values before and after neoadjuvant therapy and the pCR after completing the chemotherapy regimens ($p<0.001$ and $p<0.001$, respectively). For the decrease 88% of SUVmax value in the primary mass with respect to baseline, the PPV was 52.6% and NPV was 84.0% ($p<0.001$). For the decrease 81% of SULpeak value in the primary mass with respect to baseline, the PPV was 60.7% and NPV was 81.8% ($p<0.001$). Even though a cut-off value was not well specified in studies designed on this topic for SUVmax and SULpeak values, in our study, values ≤1.15 found using ROC analysis measured in the breast after NAC had 61.8% and 61.8% sensitivity and 73.3% and 77.0% specificity for detecting pCR.

The sensitivity of PET/CT in FDG(+) axillary lymph nodes is relatively low during the staging step of detecting axillary lymph node metastasis, the most important parameter in determining prognosis and life duration in breast cancer; however, specificity is high.[35] Yet, for patients with FDG (-) axilla sensitivity with PET/CT in the detection of small lymph nodes, early axillary involvement and micrometastases is low and diagnostic accuracy is less than in other methods such as ultrasonography (USG).[36,37] ALND is recommended instead of SLND in PET/CT positive axillary disease because of the high specificity of PET/CT, thus SLND is more prominent in patients with axilla-negative disease.[35,38] In our study, we detected 67.3% and 67.3% sensitivity, and 63.2% and 64.1% specificity in the axilla in detecting pCR ratios in patients with ≤0.55 SUVmax and SULpeak values after NAC using ROC analysis ($p=0.02$ and $p=0.02$, respectively). In addition, when the relationship of pCR with rate of decrease of SUVmax and SULpeak values before and after treatment was controlled, sensitivity was 45.1% and 43.0%, respectively, and specificity was 44.8% and 59.0%, respectively, for pCR demonstrating activity of ≥86% for SUVmax RR and ≥85% for SULpeak ($p=0.109$ and $p=0.104$, respectively). PET/CT can prevent unnecessary surgeries

because axillary sentinel lymph node sampling will be preferred instead of axillary dissection after NAC when axillary PET becomes negative, even though sensitivity and specificity of FDG PET/CT were low in terms of demonstrating axillary lymph node involvement after NAC in patients with a complete metabolic response (SUV <1).

We also know that FDG PET/CT and MRI, the most frequently used imaging methods in the evaluation of neoadjuvant therapy response, present different response rates with respect to different tumour subtypes.[27,39,40,41] In patients who were administered neoadjuvant therapy, the pCR rate was obtained at a higher rate in HER-2–positive and triple-negative tumours compared with a hormone-receptor-positive group. In the patients with triple- negative and hormone positive-HER-2 negative tumours, pCR rates and the change in SUVmax were correlated; however, in patients who were HER-2–positive, pCR rates were correlated with absolute SUVmax.[27] In our study, pCR rates in the breast and axilla were analysed separately and both axillary and breast pCR rates were found higher in the breast and axillary HER-2–positive group than in the hormone-positive group when pCR rates were analysed according to the subtypes (p=0.01 and p<0.001, respectively). On the other hand, the pCR rates in triple-negative tumours did not reach statistical significance in either the breast or axilla (p=0.50 and p=0.619, respectively).

The facts that our study was performed retrospectively on a limited number of patients, each with heterogeneous tumour characteristics, are among the factors that limit our study. However, although our study was retrospective, the single centre SUVmax and SULpeak values were re-evaluated in basal examinations before treatment and in control examinations after treatment on PET/CT images taken under similar conditions by an experienced nuclear medicine specialist who knew the breast cancer diagnosis but was unaware of the pathologic findings. Similarly, all pathology blocks were re-evaluated by an experienced pathologist. The change in SUV values and cut-off values for therapy response, which is most frequently used in daily practice, was documented for both lymph nodes of the breast tumour and the axilla.

Conclusion

The decrease between SUVmax and SULpeak values between preNAC and postNAC was found to be correlated with the pathologic response in our retrospective study. The SUVs cut- off value for breast was 1.15 and the same value for axillary lymph node was 0.55. The value that may contribute to the literature was defined in this way. HER-2–positive and triple- negative subtypes most frequently responded to NAC, also observed in FDG-PET/CT findings. FDG-PET/CT has high sensitivity and specificity in the evaluation of treatment response in patients with breast cancer receiving NAC. Safer breast-preserving surgery can be performed in patients after NAC using FDG-PET/CT findings, but a complete metabolic response in the axilla after NAC demonstrates low diagnostic sensitivity and specificity rates for metastasis detection. This should be evaluated as an important finding that affects therapy management. Detailed prospective studies in which the effects of axillary metabolic response on clinical management and prognosis in terms of axilla-preserving approaches are required.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital with approval number of 514/194/18. (27.01.2021).

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