European Review for Medical and Pharmacological Sciences 2023; 27: 10008-10015

The predictive value, sensitivity, specificity, and accuracy of PET CT in the evaluation of axillary metastases in breast cancer

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Abstract. – OBJECTIVE: This study aims to evaluate the accuracy of preoperative 18F-FDG PET CT in detecting axillary lymph node (ALN) metastases in patients with breast cancer.

PATIENTS AND METHODS: A retrospective analysis was performed on the medical records of 114 patients who underwent PET CT for breast cancer between January 2017 and January 2020. Clinicopathological features and the relationship between lymph node metastasis were evaluated. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated based on the PET CT findings compared to histopathological results.

RESULTS: Among the 67 patients included in this study, 29 were identified as having no axillary involvement, while 38 showed axillary involvement according to preoperative PET CT. Of the 34 patients with histopathologically confirmed metastatic lymph nodes, 28 had PET CT-detected axillary involvement, while 6 did not. Similarly, among the 33 patients without histopathological evidence of lymph node metastasis, 23 had no axillary involvement according to PET CT, while 10 showed axillary involvement. The calculated values were as follows: sensitivity = 82.4% (67-92%), specificity = 69.7% (53-83%), positive predictive value = 73.7% (62-83%), negative predictive value = 79.3% (64%-89%), and accuracy = 76.1% (64-86%).

CONCLUSIONS: The results suggest that preoperative 18F-FDG PET CT, particularly p SUVmax, can serve as an independent prognostic factor for ALN metastasis in breast cancer patients. Therefore, it may be beneficial for preoperative risk stratification and personalized treatment planning.

Key Words:
Breast cancer, PET CT, Predictive value, Accuracy.

Introduction

Breast cancer is the most common cancer in women in the West and is the second leading cause of cancer-related deaths in women[1-4]. Management and prognosis of breast cancer depend on tumor size and grade, hormone receptor status, human epidermal growth factor receptor 2 (HER2) status, axillary lymph node (ALN) involvement, and metastatic spread. Among them, the most reliable predictor of survival is metastatic involvement of ALN[5,6]. Knowing the ALN status before treatment is important for patient management and treatment decision.

Axillary lymph node dissection (ALND) in breast-conserving surgery or during mastectomy; can lead to critical complications, such as lymphedema, pain, and limitation of movement. In order to prevent these complications, sentinel lymph node biopsy (SLNB) was applied to patients with early-stage breast cancer and clinically negative ALN (Cn-ALN).

Previous studies[7,8] have shown that SLNB alone is an adequate procedure in terms of disease-free survival, overall survival, and regional recurrence compared to ALND. However, SLNB may cause clinical morbidities[9,10]. Extra time and effort are spent during surgery for comprehensive pathological examination. In addition, false negative findings related to SLNB are a major concern, with an average of 8.4% to 4.6% to 16.7% in previous studies[11,12]. Therefore, it is necessary to determine an additional predictive significance of ALN metastasis to compensate for SLNB, especially for breast cancer with cN-ALN.

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The ALN evaluation plays an important role in staging breast cancer. It is an important predictor of survival and disease recurrence in patients[13]. It determines treatment and prognosis[14]. Axillary staging can also be used to monitor therapeutic response[2].

Integrated positron emission tomography/computerized 18F-fluorodeoxyglucose (18F FDG) tomography (PET CT) is widely used in clinical practice for staging, restaging, monitoring the therapeutic response, and evaluating prognosis in breast cancer patients[15,16]. However, there are not enough studies in the literature on how accurately we can detect ALN metastases in breast cancer preoperatively with PET CT.

In our study, we aimed to see how accurately we can predict axillary metastases with preoperative PET CT and to evaluate the predictive value of PET CT in detecting ALN metastasis.

Patients and Methods

This study complied with the guidelines of the Declaration of Helsinki and was reviewed and approved by the Medicine Ankara University Faculty Medicine Research Ethics Committee. The Human Research Ethics Committee Decision was taken. (Approval No: I2 – 153 – 21).

Medical records of a total of 114 patients who underwent PET CT for breast cancer between January 2017 and January 2020 were evaluated retrospectively. Sixty-seven of 114 patients were included in the study and were operated for breast cancer in our clinic. Forty-seven patients were excluded from the study. Eleven patients underwent excisional biopsy before PET CT, 6 patients received neoadjuvant chemotherapy, 4 patients had secondary malignancies, 22 patients had distant metastatic disease, and 4 patients had missing data (Figure 1).

Preoperative PET CT scans of 67 patients diagnosed with histopathologically breast cancer were taken. The operated patients were evaluated into 3 groups: Group 1 SNLB + ALND, group 2 only SNLB, and Group 3 only ALND. Seventeen of these patients were premenopausal and 50 were postmenopausal. None of the patients received Neoadjuvant CT+RT.

Isosulfan blue was used in the SLNB technique. The periareolar region was massaged for 15 minutes after subcutaneous isosulfan blue injection. Sentinel lymph nodes (SLNs) from the axillary region was sent to pathology 15 minutes later. All SLNs were examined perioperatively (frozen section) and postoperatively (paraffin section). ALND was performed in all patients with positive macrometastatic SLN. In our study, isosulfan blue was used for SLNB because it is more accessible, cheaper, and has a higher sensitivity than radioisotope labeling, according to some studies[17].

According to the pathology reports, the patients were divided into two groups lymph node metastasis positive patient group and one lymph node metastasis negative patient group. ALN involvement results of preoperative PET CT and lymph node metastasis pathology results were compared and Sensitivity, Specificity, Positive predictive, Negative Predictive, and accuracy values of PET CT were calculated.

In addition, the relationship between lymph node metastasis and grade, progesterone receptor (PR), estrogen receptor (ER), HER2, lymphovascular invasion (LVI), and perineural invasion was also investigated in the study. Before the 18F-FDG-labeled PET CT application, the patients were fasted for at least 6 hours and the blood glucose level was less than 150 mg/dL. PET CT scan was obtained using Discovery STE PET/CT scanner (GE Healthcare, Ankara, AU, Turkey). All 18F-FDG PET/CT images were reviewed by experienced nuclear medicine physicians. Analysis; Performed using Advantage Workstation 4.3 (GE Healthcare, Chicago, IL, USA). The short axis diameter of the axillary lymph nodes was measured.

The maximum standard uptake value (SUVmax) was measured from the most prominent FDG uptake lymph node. Blood SUVmax was

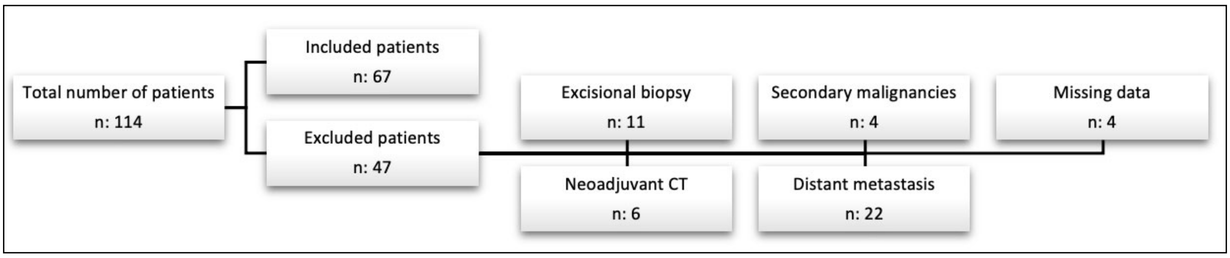

Figure 1. Included patients.

measured from the aortic arch. As a criterion for axillary lymph node metastasis, the SUVmax value measured from the lymph node was considered to be higher than the blood SUVmax value measured from the aorta.

Statistical Analysis

First, all significant factors ($p < 0.05$) associated with ALN metastasis were confirmed in univariate analysis, and these important factors were evaluated to identify variables independently associated with ALN metastasis using multivariate logistic regression. We used c-statistics to evaluate the additional predictive value of pSUVmax for ALN metastasis. Statistical analyses were performed using SPSS (Statistical Package for Social Sciences) for Windows 20.0 (IBM Corp., Armonk, NY, USA). *p*-values < 0.05 were considered statistically significant.

Optimal cut-off values of tumor size for prediction of ALN metastasis were determined using pSUVmax (p-all SUVmax) for all patients and pSUVmax (p-subtypeSUVmax) for each molecular subtype using receiver operating characteristic (ROC) curve analysis (Figure 2).

Results

The median mean age of the patients was 56, and the age range was 26-86. The number of patients over the age of 45 was 51. Modified Radical Mastectomy (MRM) was performed in 31 of the 67 patients included in the study, Breast Conserving Surgery + Axillary Lymph Node Dissection (BCS + ALND) and 23 BCS + SLNB were performed.

The tumor size of 38 patients was in the range of 2-5 cm. The tumor histological type of 51 patients was invasive ductal carcinoma. Clinicopathological features and lymph node metastasis relationships of 67 patients included in this study are available in Table I and Table II.

According to preoperative PET CT, 29 of 67 patients did not have axillary involvement, while 38 had axillary involvement. The pathological diagnosis of 51 patients was invasive ductal carcinoma, and the pathological diagnosis of 6 patients was invasive lobular carcinoma. Ten patients had mixed tumors and other histopathological tumors. In pathological staging, it was stage I in 2 patients, stage II in 33 patients, and stage III in 32 patients. In the pathological examinations of the patients, estrogen receptor (ER) was negative in 10 patients and positive in 57 patients. Eighteen patients were progesterone receptor (PR) negative and 49 were positive. 43 patients were HER2 negative and 24 were positive.

While there was no lymphovascular invasion in the breast tumor pathology of 35 patients, there was a lymphovascular invasion in 32 patients. While 49 patients did not have a perineural invasion, 18 of them had a perineural invasion. In the histopathological examination, 33 patients did not have lymph node metastases, while 34 of them had lymph node metastases.

When the relationship between metastatic lymph

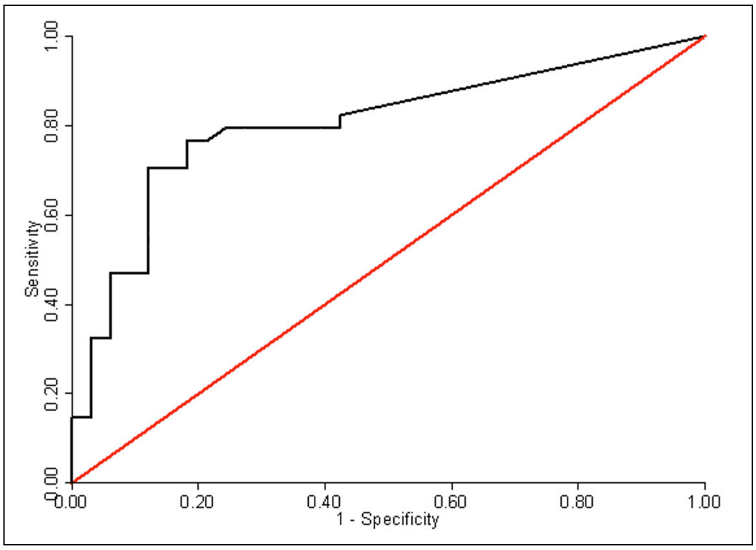

Figure 2. ROC curve.

Table I. Clinicopathological properties of patients.

c	Total number	%
Age		
<45	16	23.8
>45	51	76.1
Operation type		
MRM	31	46.2
BCS+ ALND	13	19.4
BCS + SLNB	23	34.3
Tumor size		
<0.5 cm	1	1.49
0.5 cm-1 cm	4	5.97
1.1 cm-2 cm	17	25.3
2.1 cm-5 cm	38	56.7
>5cm	7	10.4
Histopathological type		
Ductal	51	76.1
Lobuler	6	8.9
Others (mixed)	10	14.9

nodes and variables was analyzed, 2 patients with grade I did not have lymph node metastasis histopathologically. Of the 33 patients with grade II, 16 had histopathologically no lymph node metastasis, while 17 had it. Of the 32 patients with grade III, 15 had histopathologically no lymph node metastasis, while 17 had it. Since there were only 2 patients in Grade I, Grade I and II were combined and analyzed. Since the Pearson-chi-square test result was p=0.71, no significant correlation between Grade and metastatic lymph node was found (Table I).

Five of 10 patients with ER (-) did not have lymph node metastasis histopathologically, but 5 had it. ER (+) While 28 of 57 patients did not have lymph node metastasis histopathologically, it was present in 29 patients.

Since the Fisher's Exact test result was p=1, no significant relationship was found between ER and lymph node metastasis (Table II).

While 9 of 18 PR (-) patients did not have lymph node metastasis histopathologically, 9 had it. While

Table II. Relationship of clinicopathological properties of patients and lymph node metastasis.

					p-value
Grade			**Lymph Node Metastase (+)**	**Lymph Node Metastase (-)**	
I	2	(2.99%)	0	2 (2.99%)	0.71
II	33	(49.2%)	17 (25.3%)	16 (23.9%)	
III	32	(45.7%)	17 (25.3%)	15 (20.4%)	
Preop PET axillary involvment			**Lymph Node Metastase (+)**	**Lymph Node Metastase (-)**	
+	38	(56.7%)	28 (41.8%)	10 (14.9%)	0.001
-	29	(43.2%)	6 (8.9%)	23 (34.3%)	
HER2			**Lymph Node Metastase (+)**	**Lymph Node Metastase (-)**	
-	43	(64.1%)	19 (28.3%)	24 (35.8%)	0.151
+	24	(35.8%)	15 (22.3%)	9 (13.4%)	
ER			**Lymph Node Metastase (+)**	**Lymph Node Metastase (-)**	
+	57	(85%)	29 (43.3%)	28 (41.8%)	1
-	10	(14.9%)	5 (7.45%)	5 (7.45%)	
PR			**Lymph Node Metastase (+)**	**Lymph Node Metastase (-)**	
+	49	(73.1%)	25 (37.3%)	24 (35.8%)	0.941
-	18	(26.8%)	9 (13.4%)	9 (13.4%)	
LVI			**Lymph Node Metastase (+)**	**Lymph Node Metastase (-)**	
+	32	(47.7%)	22 (32.8%)	10 (14.9%)	0.005
-	35	(52.2%)	12 (17.9%)	23 (34.3%)	
Perineural invasion			**Lymph Node Metastase (+)**	**Lymph Node Metastase (-)**	
+	18	(26.8%)	13 (19.4%)	5 (7.4%)	0.033
-	49	(73.1%)	21 (31.3%)	28 (41.8%)	
Histopathologically axillary met			**Mean Preop PET CT SUV**	***P value***	
+	34	(50.7%)	6.3	0.001	
-	33	(49.2%)	1.6		

a = Pearlson-chi-square test, b = Fisher's Exact test

24 of 49 PR (+) patients did not have lymph node metastasis histopathologically, 25 had it.

Since the Pearson-chi-square test result was p=0.941, no significant correlation between PR and metastatic lymph node was found (Table II). While 24 of 43 HER2 (-) patients did not have lymph node metastases histopathologically, 19 had it. While 9 of 24 HER2 (+) patients did not have lymph node metastasis histopathologically, 15 had it. Since the Pearlson-chi-square test result was p=0.151, no significant relationship was found between HER2 and metastatic lymph node (Table II).

Of the 35 patients without LVI, 23 had histopathologically no lymph node metastasis, while 12 had it. While 10 of 32 patients with LVI did not have lymph node metastasis histopathologically, 22 did.

Since the Pearlson-chi-square test result was p=0.005, a significant relationship was found between LVI and metastatic lymph node (Table II).

Twenty-eight of 49 patients without perineural invasion had histopathologically no lymph node metastasis, while 21 had it. While 5 of 18 patients with perineural invasion did not have lymph node metastasis histopathologically, 13 had it.

Since the Pearlson-chi-square test result was p=0.033, a significant correlation was found between perineural invasion and metastatic lymph node (Table II).

Twenty-three of 29 patients without axilla involvement in preoperative PET-CT, did not have lymph node metastasis histopathologically, while 6 of them had it. Ten of 38 patients with axilla involvement in preoperative PET-CT, did not have lymph node metastasis histopathologically, while 28 had it. Since the Pearlson-chi-square test result was p=0.001, a significant correlation was observed between preoperative PET CT axilla involvement and metastatic lymph node (Table II). The mean PET SUV axilla was 1.6 in 33 patients without metastatic lymph nodes histopathologically, while the mean PET SUV axilla in 34 patients with histopathologically metastatic lymph nodes was 6.3. When it was examined whether there was a difference in terms of pre-op PET SUV axilla values, the result was p=0.001, so a significant difference was accepted (Table III).

While 28 of 34 patients with histopathologically metastatic lymph nodes had PET CT axilla involvement, 6 did not have PET CT axilla involvement. There was no axillary involvement in PET CT in 23 out of 33 patients who had not metastatic lymph nodes histopathologically, whereas 10 patients had axillary involvement in PET CT.

According to these results, sensitivity, specificity, positive predictive value, and negative predictive value were found as follows: sensitivity = 82.4% (67-92%), specificity = 69.7% (53-83%), positive predictive value 73.7% (62-83%), negative predictive value = 79.3% (64%-89%) and accuracy = 76.1% (64-86%), respectively. (Table III).

Discussion

In our study, we aimed to see how accurately we can predict axillary lymph node metastasis of breast cancer with PET CT before the operation and to evaluate the sensitivity, specificity, predictive value, and accuracy of PET CT in detecting axillary metastasis. In our study, a significant correlation was found between preoperative PET CT axilla involvement and histopathologically metastatic lymph nodes.

Table III. Sensitivity, specificity, accuracy, positive predictive value, negative predictive value, 18F- FDG PET-CT.

Histopathologically axillary met			Preop 18F- FDG PET-CT Axillary involvment	
			(+)	(-)
+	34	(50.7%)	28 (41.8%)	6 (8.2%)
-	33	(49.2%)	10 (14.9%)	23 (34.3%)
Sensitivity			82.4% (67 - 92)	
Specificity			69.7% (53 - 83)	
Positive Predictive Value			73.7% (62 - 83)	
Negative Predictive Value			79.3% (64 - 89)	
Accuracy			76.1% (64 - 86)	

It has been shown in this study and other studies that a combined PET CT scan is more successful in detecting axillary lymph node metastasis than other morphological imaging studies[18,19]. ALN involvement is a guide for prognosis, staging, and treatment in breast cancer management[20]. The common initial route of spread for breast cancer is through the axillary lymph nodes, and the incidence of ALN metastases increases with larger tumors. Lymph node status is the strongest independent prognostic factor in breast cancer and remains the most important feature in defining the risk category. There is evidence that overall survival decreases as the number of positive nodes increases[21]. A clear determination of whether the ALN is malignant or benign by means of radiological imaging provides an accurate staging. Successful staging influences prognosis and survival by providing the right treatment plan. Various imaging modalities have been used to interpret axillary metastases. Of these methods, 18F-FDG PET CT can detect metastases in other parts of the body[12,22]. However, there are studies showing that even 18F-FDG PET CT for the full diagnosis cannot replace SLNB or ALND for the axilla[13]. In the literature, 18F-FDG PET CT range for lymph node metastasis in breast cancer – sensitivity: 20%-100%, specificity: 64%-97%, and accuracy: 73.2% - 89.8%[23]. In our study, we obtained sensitivity (82%), specificity (69%), positive predictive value (73%), negative predictive value (79%), and accuracy (76%) values. These findings are generally consistent with the existing literature. Ahmed et al[24] reported the mean rate of positive HER2 expresion as 42% in their study, while we also found the positive HER2 expression in our patients at the rate of nearly 45%. Some studies suggest that PET CT is sufficient to make a decision to perform axillary dissection. However, some studies[25,26] question whether PET CT is sufficient to decide for axillary dissection.

On the other hand, Greco et al[26] suggested that SNLB and ALND can be avoided in case of a negative PET scan of the axilla. In our study, when the data obtained outside of our purpose were evaluated statistically, no significant relationship was found between grade and lymph node metastasis. However, in one study, a strong correlation was found between histological grade and the presence of axillary metastases[27]. We think that this finding in our study is due to the low number of grade I patients and, therefore, we made an analysis after combining grade I and II patients.

In our study, a significant relationship was found between LVI and axilla metastasis. When similar studies were screened, we found that in many studies, a correlation between lymphovascular invasion and lymph node metastasis in breast cancer was observed[28-30].

LVI has proven to be the strongest independent predictor of nodal involvement, and the grading system for lymph vessel tumor embolism is a very useful histological grading system by IDCs to predict lymph node metastasis[31]. In another study[21], both univariate and multivariate analyses identified LVI as an important predictor of ALN involvement.

In our study, the relationship between perineural invasion and axillary metastasis was found to be statistically significant. This has also been mentioned in some previous publications in the literature[32,33].

In our study, all patients who underwent neo-adjuvant chemotherapy were excluded from the analysis, as the surgical specimen would not be representative of the initial lymph node status after chemotherapy. If these advanced breast cancer patients undergoing neo-adjuvant chemotherapy are included in the study, the sensitivity and specificity of 18F-FDG PET CT to detect ALN metastasis may increase because most of these patients will have a higher tumoral and nodal FDG uptake.

Limitations

Our study has, nonetheless, some limitations. First, since the study is retrospective, it has selection bias and is a single-institution retrospective study. Another limitation was that multivariate analysis of each molecular subtype was not possible due to the relatively small number of participants. More multicenter-controlled prospective studies with larger patient groups are needed to clarify the predictive value of 18F-FDG PET CT for ALN metastasis in patients with breast cancer.

Conclusions

In conclusion, pSUVmax in preoperative 18F-FDG PET CT is an independent prognostic factor for ALN metastasis in patients with breast cancer. Therefore, it is believed that 18F-FDG PET-CT may be beneficial for preoperative risk stratification and optimal personalized treatment planning in patients with breast cancer.

Ethics Approval

Approval was obtained from the Ethics Committee of the Faculty of Medicine Ankara University (Ethics Committee No./Date: Ankara University Clinical Research Ethics Committee Approval No: I2 – 153 – 21).

Informed Consent

Informed consent was obtained from all participants included in the study.

Authors' Contribution

Ozhan Cetindag contributed to the design of the study, data collection and analysis, interpretation of the results, and writing of the manuscript. Gokhan Avsar contributed to the design of the study, data collection and analysis, interpretation of the results, and writing of the manuscript. Musluh Hakseven contributed to the design of the study, interpretation of the results, and writing of the manuscript. Rıza Deryol contributed to the design of the study, interpretation of the results, and writing of the manuscript. Suleyman Caglar Ertekin contributed to the analysis, interpretation of the results, and writing of the manuscript. Duru Karasoy contributed to data collection, analysis and interpretation of the results. Aydan Eroglu contributed to the design of the study, data collection and analysis, interpretation of the results, and writing of the manuscript. Sancar Bayar contributed to the design of the study, data collection and analysis, interpretation of the results, and writing of the manuscript. All authors have read and approved the final version of the manuscript.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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