Original Article

Factors Affecting the Accuracy of ^{18}F-FDG PET/CT in Evaluating Axillary Metastases in Invasive Breast Cancer

K Kutlutürk, A Şimşek, A Çomak[1], F Gönültaş, B Ünal, E Kekilli[1]

Departments of General Surgery and [1]Nuclear Medicine, Inonu University, Turgut Ozal Medical Center, Malatya, Turkey

Abstract

Background and Aim: There are conflicting results of studies on accuracy of positron emission tomography (PET)/computed tomography (CT) for axillary staging. The aim of this study is to determine the factors affecting the efficacy of 18F-fluorodeoxyglucose (^{18}F-FDG) PET/CT in detecting axillary metastases in invasive breast cancer. **Materials and Methods:** Data of 232 patients with invasive breast cancer who underwent ^{18}F-FDG PET/CT examination before surgery between January 2013 and September 2017 were reviewed retrospectively. Histopathological examination of axillary lymph nodes (ALNs) was used as a reference to assess the efficacy of ^{18}F-FDG PET/CT in detecting axillary metastases. **Results:** While 134 (57.8%) patients had axillary metastases as detected in ^{18}F-FDG PET/CT scans, histopathologically axillary metastases were detected in 164 (70.7%) patients. The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of ^{18}F-FDG PET/CT in detection of axillary metastasis were 72.56%, 77.94%, 88.8%, 54%, and 74.1%, respectively. The false-negative and false-positive rates were 27.4% and 22%, respectively. In univariate analysis, patients' age, estrogen receptor positivity, higher ALN SUVmax, greater tumor size, and lymph node size determined by ^{18}F-FDG PET/CT were all significantly associated with accuracy of ^{18}F-FDG PET/CT for axillary metastasis. In multivariate analysis, tumor size determined by ^{18}F-FDG PET/CT and ALN SUVmax were independent variables associated with axillary metastasis. The accuracy of ^{18}F-FDG PET/CT for axillary metastasis was higher in patients with a larger tumor (≥19.5 mm) and a higher ALN SUVmax (≥3.2). **Conclusion:** ^{18}F-FDG PET/CT should not be routinely used for axillary staging, especially in patients with small tumors. It cannot eliminiate the necessity of sentinel lymph node biopsy. When it is used, both visual information and optimal cut-off value of axillary node SUVmax should be taken into consideration.

Keywords: *Axillary metastasis, breast cancer, positron emission tomography/computed tomography, sentinel lymph node, sentinel lymph node biopsy*

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Introduction

The most significant prognostic factor for patients with breast cancer is the status of axillary lymph nodes (ALNs).[1] Sentinel lymph node biopsy (SLNB) has become the standard care for patients with clinically and/or radiologically node-negative, early-stage invasive breast cancer.[2,3] When the sentinel lymph nodes (SLNs) are positive, standard treatment is to complete axillary dissection (AD).[4]

A variety of imaging modalities have been applied to evaluate axillary metastasis. Among them, 18F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) has

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Address for correspondence: Dr. K Kutlutürk, Department of General Surgery, Inonu University, Turgut Ozal Medical Center, Malatya, Turkey.
E-mail: kkutluturk@gmail.com

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the advantage of detecting metastasis in other parts of the body.[5] There are conflicting results of studies on accuracy of PET/CT for axillary staging. Some studies have claimed that PET/CT can select patients who need AD,[6,7] while others have doubt that it can accuretly identify axillary status.[8] These conflicting results raise the question of which factors affect accuracy of ^{18}F-FDG PET/CT for axillary metastasis. This study was conducted to determine the factors affecting the accuracy of ^{18}F-FDG PET/CT for axillary metastasis.

Materials and Methods

A retrospective examination was conducted on the records of 232 patients with invasive breast cancer who underwent ^{18}F-FDC PET/CT before surgery between January 2013 and September 2017. Patients with history of excisional biopsy, neoadjuvant chemotherapy, recurrent breast cancer, noninvasive types of breast cancer, or male sex were excluded from the study. Histopathologic examination of ALNs (SLNB and/or AD) was used as reference to evaluate the ability of ^{18}F-FDG PET/CT in detection of axillary metastasis.

Methylene blue was used in the identification of SLNs. All SLNs were examined peroperatively (frozen section) and postoperatively (paraffin section). Serial sectioning and/or immunohistochemical staining were also performed on SLNs that metastasis could not be detected by routine histopathological methods. AD was performed in all patients with positive macrometastatic SLN.

Tumor size was recorded by both pathological (pT) and clinical (cT; using ^{18}F-FDG PET/CT) measurement. The histological type of the tumor was classified into three types: invasive carcinoma of no special type (invasive ductal carcinoma), specified type, and mixed type. Histological grade was determined according to Modified Bloom–Richardson method. The limit value for the presence of hormone receptor was determined as 1%. Her2/neu amplification was considered positive if the Her2 receptor was stained 3+ and/or if the Her2 receptor was stained 2+ along with Her2/neu amplification determined by fluorescence *in situ* hybridization.

The patients fasted for at least 6 h before ^{18}F-FDG injection. Approximately 60 min after the injection of 0.1 mg/kg ^{18}F-FDG intravenously, anatomical imaging with CT (140 keV, 80 mA; Siemens, Knoxville, TN, USA) and then PET (Siemens Biograph mCTS (20)-3R) imaging was performed from vertex to the mid-thigh at PET/CT. Data were reconstructed by ordered subsets expectation maximization. Images on coronal, sagittal, and transverse axis were evaluated using software program (Syngo.via/VB10B software version/Siemens Medical Solutions Inc.). The CT data were acquired without contrast enhancement. Breast lesion and ALNs were evaluated visually first in PET and CT images. SUVmax of hypermetabolic breast lesion and SUVmax of hypermetabolic ALNs were automatically calculated through previously mentioned software.

Statistical analysis

Statistical Package of the Social Sciences 17.0 software was used for statistical analysis. The clinicopathological characteristics of the tumors were analyzed by Chi-square independence test and descriptive analysis. Data were expressed as *n* (%) and mean with standard deviation. The selection of variables for logistic model was started by Chi-square independence test and univariate logistic regression analysis. Significant variables were included in multivariate binary logistic regression analysis. Receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value of the tumor size and the SUVmax of the ALNs.

As this was a retrospective study, we did not apply for ethical committee approval. However, informed consent was obtained from all patients before ^{18}F-FDG PET/CT procedure.

Results

The mean age was 50.65 ± 12.35 years old; mean pT and mean cT were 3.4 ± 2.5 and 2.4 ± 1.9 cm, respectively. The mean SUVmax values of tumors and ALN were 11.18 ± 9.07 and 8.83 ± 7.1, respectively [Table 1]. SLNB was performed in 81 patients (34.9%), and AD was performed in 178 (76.7%) patients. Total mastectomy was applied in a majority (68.1%) of cases.

Axillary metastases were detected in ^{18}F-FDG PET/CT scans of 134 (57.8%) patients. In all, 164 (70.7%) patients had histopathologically proven axillary metastasis (micrometastasis in 14 cases). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy (OAA) of ^{18} F-FDG PET/CT in detection of axillary metastasis were 72.56%, 77.94%, 88.8%, 54%, and 74.1%, respectively. The false-negative (FN) and false-positive (FP) rates were 27.4% (45/164) and 22% (15/68), respectively. The rate of patients with micrometastasis in FN results was 24.2%.

In univariate analysis, older age, estrogen receptor positivity, higer ALN SUVmax, greater tumor size, and ALN size determined by ^{18}F-FDG PET/CT were all significantly associated with accuracy of ^{18}F-FDG PET/CT for axillary metastasis [Table 2]. In multivariate analysis, tumor size determined by ^{18}

F-FDG PET/CT and ALN SUVmax were independent variables associated with accuracy of ^{18}F-FDG PET/CT for axillary metastasis [Table 2].

Table 1: Patient's age and clinicopathological characteristics of the tumors

	Mean	Min–max	Median
Patient age	50.6±12.35	25–85	44
Tumor size determined by ^{18}F-FDG PET/CT (cm)	2.4±1.9	0.5–23.3	1.4
Tumor size pathologically determined (cm)	3.4±2.5	0.5–23	2.5
Tumor SUVmax	11.18±9.07	1.1–81.2	3.9
ALN size determined by ^{18}F-FDG PET/CT (cm)	1.65±0.87	0.20–5.6	1.2
ALN SUVmax	8.83±7.1	1.5–40.7	2.2

FDG: ^{18}F-fluorodeoxyglucose; PET: Positron emission tomography; CT: Computed tomography; ALN: Axillary lymph node

According to the ROC curve analysis, the optimal cut-off values of the tumor size determined by ^{18}F-FDG PET/CT and ALN SUVmax were 19.5 mm and 3.2, respectively [Table 3].

The optimal cut-off values of the tumor size determined by ^{18}F-FDG PET/CT, which was 19.5 mm, corresponded approximately to the size of T1 tumor, which was 20 mm, so we rearranged the statistical analysis according to T-stage. T1 tumors constituted 46.98% of cases (n = 109). Axillary metastases were detected in ^{18}F-FDG PET/CT scans of 48 (44%) patients with T1 tumors. In this group, 67 (61.4%) patients had histopathologically proven axillary metastasis (micrometastasis in 8 cases). The sensitivity, specificity, PPV, NPV, and OOA of ^{18}F-FDG PET/CT in detection of axillary metastasis were 58.2%, 78.57%, 81.25%, 54%, and 66%, respectively. The FN and FP rates were 41.79% and 21.4%, respectively. About

Table 2: Univariate and multivariate analyses of the factors affecting accuracy of ^{18}F-FDG PET/CT for axillarymetastasis

Characteristic	Univariate analysis			Multivariate analysis	
	Accurate detection *n* (%)				
	(−)	(+)	(*P*)	(*P*)	OR
Patient age†			**0.036**		
Bilaterality (+)	4 (57.1)	3 (42.9)	**0.055**		
Lateralization			**0.291**		
Right	27 (22.9)	93 (77.1)			
Left	33 (28.9)	79 (71.1)			
Multifocality/multicentricity (+)	22 (25.6)	64 (74.4)	**0.94**		
Tumor histology			**0.138**		
NOS	45 (27.4)	119 (72.6)			
Specified	9 (17)	44 (83)			
Mixed	6 (40)	9 (60)			
Tumor grade			**0.224**		
Grade I	15 (38.5)	119 (72.6)			
Grade II	23 (25)	44 (83)			
Grade III	22 (24.7)	9 (60)			
Estrogen receptor (+)	56 (29.5)	134 (70.5)	**0.008**		
Progesteron receptor (+)	48 (28.6)	120 (74.1)	**0.127**		
Cerb 2 (+)	13 (21.7)	47 (78.3)	**0.382**		
Molecular subtype			**0.59**		
Luminal A	41 (28.7)	102 (71.3)			
Luminal B	13 (30.2)	30 (69.8)			
Triple-negative	4 (19)	17 (100)			
Her2-positive	0	16 (74.1)			
Largest tumor size determined by PET/CT†			**0.005**	**0.035**	**2.41**
Highest tumor SUVmax†			**0.079**		
Largest ALN size determined by PET/CT†			**0.017**		
Highest ALN SUVmax†			**0.001**	**0.001**	**2.14**

FDG: ^{18}F-fluorodeoxyglucose; PET: Positron emission tomography; CT: Computed tomography; OR: Odds ratio; NOS: Not otherwise specified; ALN: Axillary lymph node. †Continuous variable

Table 3: The logistic model in which tumor size and ALN SUVmax were included as categorical variables

Characteristic	*P*	OR	95% Confidence interval	
			Lower	Upper
Largest tumor size determined by ^{18}F-FDG PET/CT (<1.95 cm)	**0.010**	4.775	1.462	15.595
Highest ALN SUVmax (<3.2)	**0.000**	15.659	4.422	55.447

ALN: axillary lymph node; OR: Odds ratio; FDG: ^{18}F-fluorodeoxyglucose; PET: Positron emission tomography; CT: Computed tomography

32% of FN results were observed in patients with micrometastasis. When we excluded T1 tumors, the sensitivity, specificity, PPV, NPV, and OAA of ^{18}F-FDG PET/CT in detection of axillary metastasis were 81.6%, 76%, 93%, 51.3%, and 80.4%, respectively. The FN and FP rates were 18.3% and 24%, respectively. About 27.5% of FN results were observed in patients with micrometastasis.

We also analyzed the factors affecting false negativitiy and false positivity of ^{18}F-FDG PET/CT for axillary metastasis:

For false negativity

In univariate analysis, patients' age (P = 0.017), tumor size determined by ^{18}F-FDG PET/CT (P = 0.021), tumor histology (P = 0.004), estrogen receptor status (P = 0.002), progesterone receptor status (P = 0.017), tumor SUVmax (P = 0.008), and moleculer subtype (P = 0.26) were all significantly associated with false negativity of ^{18}F-FDG PET/CT for axillary metastasis. There was multicollinearity between molecular subtype and estrogen and progesterone receptor status (r_s = 0.732 and r_s = 0.58). Therefore, in multivariate analysis, two separate logistic models were made.

In the first model in which "molecular subtype" was not included, patients' age, tumor histology, estrogen receptor status, and tumor SUVmax were independent variables associated with false negativity of ^{18}F-FDG PET/CT for axillary metastasis. The older age, lower tumor SUVmax, mixed type histology, and positive estrogen receptor increased the likelihood of false negativity of ^{18}F-FDG PET/CT for axillary metastasis. In the second model in which "molecular subtype" was included, patients' age, tumor histology, molecular subtype, and tumor SUVmax were independent variables associated with false negativity of ^{18}F-FDG PET/CT for axillary metastasis. The older age, lower tumor SUVmax, mixed type histology, and Luminal A subtype increased, but HER-2-positive and triple-negative subtype decreased the likelihood of false negativity of ^{18}F-FDG PET/CT for axillary metastasis.

For false positivity

In univariate analysis, ALN size determined by ^{18}F-FDG PET/CT (P = 0.023) and ALN SUVmax (P = 0.003) were significantly associated with false positivity of ^{18}F-FDG PET/CT for axillary metastasis. In multivariate analysis, ALN SUVmax (P = 0.003, odds ratio = 0.534) was the only independent variable associated with false positivity of ^{18}F-FDG PET/CT for axillary metastasis. The higher ALN SUVmax decreased the likelihood of false positivity of ^{18}F-FDG PET/CT for axillary metastasis.

Discussion

A variety of imaging modalities have been applied to evaluate axillary metastasis. Among them, ^{18}F-FDG PET/CT has the advantage of detecting metastasis in other parts of the body.[5] The sensitivity, specificity, and accuracy of ^{18}F-FDG PET/CT for axillary metastasis were reported in a wide range – sensitivity: 20%–100%, specificity: 64%–97%, and accuracy: 73.2%–89.8%.[5-13] Consequently, some studies have claimed that PET/CT can select patients who need AD,[6,7] while others have questioned whether it can accurately identify axillary status.[8,9] The differences in results between these studies can be attributed to the population studied, the PET protocol, and the histopathological procedure applied.

Some authors have reported that lower sensitivity of PET/CT was restricted to micrometastasis.[5,14] The role of micrometastasis was not known in the prognosis of breast cancer. Crippa *et al*. have supposed that limitation of PET should be analyzed in relation to the size of metastasis.[5] They claimed that based on a study, only a few micrometastasis (6.7%) become clinically evident,[15] and the risk of axillary downstaging with PET might be acceptable, paticularly in patients with a low risk of axillay metastasis.[5] According to the study conducted by Greco *et al*., FN results were observed only in patients with micrometastasis.[16] In contrast to both studies, in this study the FN results were not restricted to micrometastasis. The FN rate was 27.4%, and only 24.2% of the FN results were observed in patients with micrometastasis. There might be more factors other than micrometastasis underlying the FN results of ^{18}F-FDG PET/CT in detection of axillary metastasis. In this study, the older age, lower tumor SUVmax, mixed type histology, positive estrogen receptor, and Luminal A subtype increased, whereas HER-2-positive and triple-negative subtype decreased the likelihood of false negativity of ^{18}F-FDG PET/CT for axillary metastasis.

There is not axillary metastasis in 75% of T1 and 55% of T2 tumors.[17] According to this study, the accuracy of ^{18}F-FDG PET/CT for axillary metastasis was lower in patients with tumors smaller than 19.5 mm. Compared

with larger tumors, in T1 tumors the sensitivity (58,2% vs 81.6%), PPV (81.25% vs 93%), and OOA (66% vs 80.4%) of ^{18}F-FDG PET/CT in detection of axillary metastasis were lower, but FN rate (41.79% vs 18.3%) was higher. If small size of the tumor reduces the accuracy of ^{18}F-FDG PET/CT for axillary staging, can ^{18}F-FDG PET/CT take the place of SLNB? It is known when the tumor size and grade decrease, and accuracy of SLNB increases.[18,19] It may be due to the decreased rate of axillary metastasis in small-sized and low-grade tumors.[20,21] The American Society of Breast Surgeons declared acceptable standarts for SLNB. They recommended that the identification rate for SLNB be 85% or higher and the FN rate be 5% or lower.[22] The FN rates of SLNB were lower than 2% in most of the studies.[23-25] The sensitivity, specifity, and NPV of SLNB were 97%, 99%, and 98% reciprocally.[26] SLNB has become the standard care for patients with clinically and/or radiologically node-negative, early-stage invasive breast cancer.[2,3]

Chung *et al*. reported that if the PET scan was interpreted only visually, FP results were higher.[15] They suggested that SUVmax should be calculated when PET performed for axillary staging.[15] They stated that even with the same protocol, SUVmax values vary among different centers by 10%–15%, and therefore each center should develop its own reference values.[15] In this study, the optimal cut-off value of the ALN SUVmax was 3.2, and the likelihood of accuracy of ^{18}F-FDG PET/CT for axillary metastasis was 15.6-fold higher in patients with ALN SUVmax higher than 3.2. We agree with Chung *et al*. that each center should develop its own reference cut-off values of the ALN SUVmax.

In conclusion, ^{18}F-FDG PET/CT should not be routinely used for axillary staging, especially in patients with small tumors. It cannot eliminiate the necessity of SLNB. The probability of FN results should be kept in mind also in patients with older age, lower tumor SUVmax, mixed type histology, positive estrogen receptor, and Luminal A subtype. When ^{18}F-FDG PET/CT is used, both visual information and optimal cut-off values of the ALN SUVmax should be taken into consideration.

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Conflicts of interest

There are no conflicts of interest.

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