The role of ^{18}F-FDG PET/CT in the diagnosis of breast cancer and lymph nodes metastases and micrometastases may be limited

***Xuemei Zhang[1] MD,**
***Fengyu Wu[2] MD,**
Ping Han[1] MD
* *Xuemei Zhang and Fengyu Wu contributed equally to this work.*

1. Department of Surgery, Linyi People's Hospital, Linyi, Shandong, China
2. PET Centre and Nuclear Medicine, Affiliated Hospital of Medical College, Qingdao University, Qingdao, Shandong Province, China

Keywords: Breast cancer
- ^{18}F-FDG PET
- Distal metastases
- Axillary lymph nodes
-Micrometastases

Correspondence address:
Ping Han MD,
Department of Surgery,
Linyi People's Hospital,
Linyi, Shandong, China,
276000
E-mail: linyihp12@163.com
Tel: +0539-86-0539-8226999
Fax: +0539-86-0539-8226999

Received:
3 November 2014
Accepted revised:
5 December 2014

Abstract

Our aim was to evaluate the diagnostic accuracy of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in detecting primary invasive breast cancer (IBC) including invasive ductal breast cancer, invasive lobular breast cancer and axillary, internal mammary and supraclavicular lymph nodes metastases. *One hundred and sixty four patients* with operable IBC and clinically negative lymph nodes were recruited and analyzed retrospectively. All patients underwent ^{18}F-FDG PET/CT scan, the results of which were compared with histopathology of dissected axillary lymph nodes (ALN). All patients were followed-up annually by ultrasonography, mammography and/or CT or MRI for relapse and distant metastases. *Results showed that* the ^{18}F-FDG PET/CT scans were positive in 141/164 (86%) patients and negative in 23/164 (14%) patients. The sensitivity of ^{18}F-FDG PET was 86% (141/164). Diagnostic performance of PET was significantly correlated with primary tumor grades and size (P:0.003 and P:0.0007, respectively). The sensitivity, specificity, overall accuracy, positive predictive value, and negative predictive value of ^{18}F-FDG PET/CT in ALN staging (SUVmax cutoff at 2.0) were 46.3%, 91.1%, 79.8%, 63.3%, and 83.6%, respectively. The false negative and false positive rate was 54% (22/41) and 9% (11/123), respectively. No relapse and metastases were found in a follow-up period of 2.42±2.56 months in patients with FN micrometastases in ^{18}F-FDG PET scan. *In conclusion*, ^{18}F-FDG PET/CT was useful in detecting the primary invasive breast cancer and its distant metastases but had a limited value in the axillary, internal mammary and supraclavicular lymph nodes. False negative ^{18}F-FDG PET scan in case of micrometastases and of metastases in ALN indicated good prognosis.

Hell J Nucl Med 2014; 17(3): 177-183 *Published online: 22 December 2014*

Introduction

Breast cancer is the most common malignant tumor in women worldwide [1]. Imaging modalities such as ultrasonography (US), mammography and magnetic resonance imaging (MRI) are used in the initial diagnosis of breast cancer. Mammography is the most often used technique but it suffers from a number of limitations in clinical practice, including limited sensitivity-especially in breasts containing dense fibroglandular tissue [2]. Accurate evaluation of axillary lymph nodes (ALN) involvement is mandatory before treatment of primary breast carcinoma. Fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG PET) had the advantage of allowing chest, abdomen and bone to be examined in a single session [3] which has been expected to diagnose or evaluate patients with breast cancer and ALN involvement with sensitivity from 20% to 96% [4-13]. It is supposed that ^{18}F-FDG PET may have a role in assessing patients with internal mammary or supraclavicular nodes metastasis, which could substantially alter the management of many patients with breast cancer [4, 5, 14-16]. In this study we retrospectively evaluated the diagnostic efficacy of ^{18}F-FDG PET/CT in detecting invasive breast cancer (IBC) and ALN, internal mammary, supraclavicular nodes metastases and micrometastases.

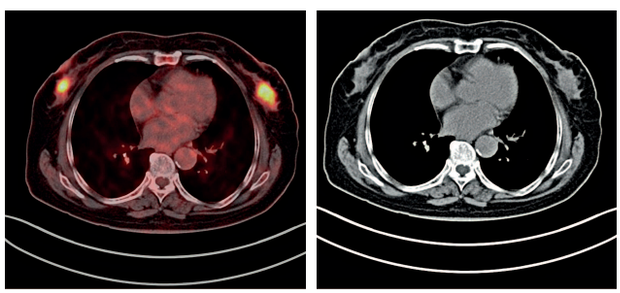
Patients and methods

Patients

From February 2006 to May 2012, 164 female patients with cytologically diagnosed IBC and clinically negative axilla were enrolled in the study. All patients had no preoperative radiation or chemotherapy. Patients with uncontrolled diabetes mellitus, evidence of systemic metastatic disease at presentation, active infections, serious organ dysfunction as suggested by Wahl et al (2004) [5] or distant metastases at diagnosis of breast cancer

and without operation were excluded. The median age of the patients was 45.3 years (21-70years). All patients underwent preoperative ^{18}F-FDG PET/CT examination. Follow-up examinations by ultrasonography, mammography, bone scan or CT or MRI were performed yearly in all patients to assess for recurrence and metastases.

One hundred and fifty patients had invasive ductal breast cancer (IDBC) and 14 invasive lobular breast cancer (ILBC). Three patients had bilateral breast cancers (see Figure 1), resulting in 167 axillary cases. The characteristics of patients including menopausal status, tumor and metastases characteristics, SUVmax, relapses etc, are listed in Table 1. The study was carried out after the hospital ethics committee approval and written informed consent from each patient with regard to ^{18}F-FDG PET/CT and the entry into the present study.



A B

Figure 1. A female patient at the age of 72 years had bilateral invasive ductal breast cancer (T2N1M0). A: ^{18}F-FDG-PET/CT showed the increased uptake in both bilateral soft tissue nodules in the breast. B: The CT image showed bilateral soft tissue nodules in the breast.

^{18}F-FDG PET imaging protocol

A PET/CT scan was carried out 2-5 days before surgery. The patients were fast (allowed to drink tap water) for a minimum of 6h before injection. Blood glucose level was measured in each patient to verify that blood glucose was less than 11.0mmol/L. Intravenous administration of 5.3MBq/kg±10% of ^{18}F-FDG was administered in the forearm opposite the primary breast tumor. After injection, patients stayed in the PET preparation room and rested for 1h. During the uptake phase we encouraged relaxation with no/minimal movements. Just prior to the end of the 1h uptake period, the patients emptied their urine bladder.

Image acquisition was performed using an integrated PET/CT system (Biograph, Siemens, Germany). Images were obtained one hour after injection from head basis to mid-thigh; 5-7 bed positions were acquired, for a total of 5,000,000 counts. Standard Protocol: Emission Time/Bed Position, 3min; attenuation correction, ^{137}Cs; Rotations/bed position. Attenuation-corrected images were reconstructed in transaxial, coronal and sagittal planes. CT scan was performed with a four-slice multidetector helical scanner. The emission images were reconstructed with the ordered subset expectation maximization implementation of iterative reconstruction (two iterations, 28 subsets). Attenuation-corrected emission data were obtained using the CT reconstructed with filtered back projection, a bilinear fit of attenuation coefficients and a Gaussian filter with 8mm full width at half maximum to match the PET resolution.

The ^{18}F-FDG PET/CT images were reviewed by two experienced nuclear medicine physicians. Images were considered positive for primary tumor if there was visually focal uptake in the breast and positive for ALN metastasis if its SUV_{max} was above 2.0. Semi-quantitative analysis was also performed in the primary IBC and the ALN. The interpreting physicians were blinded to any pathological findings of the IBC or of the ALN.

Surgery and pathology review

The size of the breast tumor was measured and tumors were classified according to the American Joint Committee on Cancer (AJCC) (edition 7) staging criteria: T1a-b (≤10mm), T1c (11-20mm), T2 (21-50mm), T3 (>50mm) [17]. The number, maximum size, nuclear grade, of the involved IBC and of the ALN metastases were also examined by histopathology. Histopathology examination of resected breast cancers and lymph nodes was used as reference to evaluate the ability of the ^{18}F-FDG PET/CT examination to detect primary tumor and axillary metastases. Pathologists were blinded to ^{18}F-FDG PET/CT interpretations.

Analysis of diagnostic performance

The diagnostic performances of ^{18}F-FDG PET/CT in detecting primary IBC and lymph node metastases was analyzed, based on the calculation of sensitivity [TP/(TP+FN)], specificity [TN/(TN+FP)], positive predictive value (PPV) [TP/(TP+FP)] and negative predictive value (NPV) [TN/(TN+FN)]. The overall accuracy was calculated as the percentage of all TP and TN cases out of the total number of cases [6].

Statistical analyses

All statistical analyses were performed with SPSS 10.0 statistical software. Independent t-test was used for the follow-up periods, and chi square test was used to establish the correlation between diagnostic performance and clinicopathological variables. Sensitivity, specificity PPV and NPV of ^{18}F-FDG PET imaging for primary IBC and ALN staging were analyzed using standard statistical analyses. All statistical tests were two-sided and statistical significance was set at the 5% level.

Results

Patients' characteristics

Patients' clinical examination of the tumor, characteristics of metastases, of hormonal receptors and relapses are found in Table 1.

^{18}F-FDG PET/CT in the diagnosis of primary IBC and its correlation with clinicopathological variables

Out of the 164 patients with cytologically established IBC, ^{18}F-FDG PET/CT was positive in 141 (86%) patients and negative in 23 (14%) patients (Table 1). The sensitivity of ^{18}F-FDG PET was 86% (141/164).

False negative primary IBC were found by ^{18}F-FDG PET in patients with: low and high tumor grade (P:0.003 and 0.008), low tumor nuclear grade (P:0.003), positive lymphvascular invasion (P<0.001) negative estrogen receptors (P:0.000), positive and negative progesterone receptors (P:0.026 and 0.000), with increased tumor size (P:0.0007) etc, as shown in Table 2. Additionally, small breast cancer size (≤1cm) was found in 27 patients, 17 of which were ^{18}F-FDG PET FN. Three

of 36 multifocal primary IBC were not detected by ^{18}F-FDG PET/CT, (sensitivity, 92%).

Table 1. *Characteristics of the 164 patients, clinical examination of tumor, characteristics of metastases, hormonal receptors and relapses*

Variables	Number of patients (%) or median (range)
Menopausal status	
Pre-menopausal	62(37.8%)
Post-menopausal	102(62.2%)
Laterality of tumor	
Right	73(44.5%)
Left	88(53.6%)
Bilateral	3(1.8%)
pT-stage	
pT1mic/1a	9(5.5%)
pT1b	25(15.2%)
pT1c	93(56.7%)
pT2	35(21.3%)
pT3	2(1.2%)
pN	
pN0	123(75%)
pN1	29(17.7%)
pN2	9(5.5%)
pN3	3(1.8%)
Primary tumor size (cm, median range)	1.56(0.03-7)
Tumor diameter (cm)	
≤2	126(76.8%)
≥2 to 4	32(19.5%)
>4	6(3.6%)
Histology	
Invasive ductal carcinoma	150(91.5%)
Invasive lobular carcinoma	14(8.5%)
Nuclear grade	
Low	23(14.0%)
High	141(86.0%)
Overall grade	
Low	51(31.1%)
High	113(68.9%)
Estrogen receptor+	140(85.3%)
Unknown	2(1.2%)
Progesterone receptor+	120(73.2%)
c-erB-2(HER2)+	18(10.9%)
Lymphvascular invasion	52(31.7%)
multifocality+	36(21.9%)
Number of nodes examined	6.1(1-24)
Number of positive nodes (median, range)	3.28(1-21)
Number of micrometastatic ALN	5(2.74%)
Cases with metastatic ALN by pathology	41(25%)
SUVmax of the primary tumor (median, range)	3.23(0.6-18.7)
SUVmax of axillary uptake (median, range)	2.38(0.8-13.9)
Follow-up period in years (mean±SD)	2.42(2.56)
Relapses	3/164(1.8%)
Distant metastases	15/164(9.1%)

pT: pathological classification of the primary tumour; ALN: axillary lymph node; HER2: human epidermal growth factor receptor-2. SUV: standardized uptake value.

Table 2. *Correlation of ^{18}F-FDG PET/CT false negatives in detecting primary breast carcinomas and in ALN staging with clinico-pathological variables*

Clinico-pathological variables	N	No. of primary tumors with FN	No. of ALN with FN	P
Histology				
IDBC	150	21	19	NS
ILBC	14	2	3	NS
Grading				
Low	51	14	2	0.003
High	113	9	20	0.008
Nuclear grade				
Low	23	8	1	0.003
High	141	15	21	NS
pT1	127	21	12	NS
pT2 and pT3	37	2	10	0.000
Lymph vascular invasion+	52	1	13	<0.001
Lymph vascular invasion-	112	22	9	NS
Multifocality+	36	2	10	NS
Multifocality-	128	21	12	NS
Estrogen receptor+	140	22	21	NS
Estrogen receptor-	24	1	1	0.000
Progesterone receptor+	120	21	28	0.026
Progesterone receptor-	44	2	4	0.000
c-erB-2(HER2)+	18	1	1	NS
c-erB-2(HER2)-	146	22	21	NS

ALN: axillary lymph node; FN: false negative; IDBC: invasive ductal breast cancer; ILBC: invasive lobular breast cancer; pT: pathological classification of the primary tumour; HER2: human epidermal growth factor receptor-2; NS: non significant

^{18}F-FDG PET/CT in ALN clinicopathological variables and staging

Involvement of ALN was detected in 41 (25%) of 164 patients at pathology who had a total ALN dissection following sentinel node biopsy (SNB). Four of the 164 patients, ALN (2.4%) contained micrometastases (≤2mm). Uptake in ALN was positive in 30 (18%) of the patients and negative in 134 (81.7%), (SUVmax cutoff at 2.0). Of these 30 ALN positive patients, 19 (40.5%) were true positive (TP), whereas 11 (59.5%) were FP. Of these 134 ALN negative patients, 22 were FN and 112 were TN. The FN and FP rate was 54% (22/41) and 9% (11/123), respectively (see Table 3). The sensitivity, specificity, overall accuracy, positive predictive value, and negative predictive value of ^{18}F-FDG PET/CT in ALN staging are shown in Table 4.

In these metastatic by pathology ALN, the maximum diameter and number of metastases are shown in Table 5. There was significant difference in the maximum diameter between patients with TP (1.17±0.59cm) and FN (0.76±0.65cm) ALN by ^{18}F-FDG PET (P:0.02). Metastatic involvement of ALN between patients with TP and FN ALN was not significant (Table 5). Additionally, in primary IBC and FN ALN by PET/CT, the SUVmax was 2.88±2.02, while in TP ALN by PET/CT the SUVmax was 4.9±4.38 (P:0.04).

***Table 3**. Axillary node staging by pathological diagnosis and ^{18}F-FDG PET (N=164)*

Pathological diagnosis	^{18}F-FDG PET/CT N+	N-	Total
pN+	19	22	41
pN0	11	112	123
Total	30	134	164

pN+: pathology for metastases-positive; pN0: pathology for metastasis-negative.

***Table 4**. Diagnostic performance of ^{18}F-FDG PET (SUVmax set at 1.5) in axillary lymph node staging*

Diagnostic parameters	^{18}F-FDG PET No	%
Sensitivity (%)	16/41	46.3
Specificity (%)	112/123	91.1
Overall accuracy	131/164	79.8
Positive-predictive value	19/30	63.3
Negative-predictive value	112/134	83.6

***Table 5**. Characteristics of axillary lymph nodes staging by ^{18}F-FDG PET/CT*

	Metastatic ALN by pathology	^{18}F-FDG PET/CT results of ALN TP	FN	FP	P
Maximum diameter (mean and ±SD)	0.94 (0.55)	1.17 (0.59)	0.76 (0.65)	1.48 (0.55)	0.02
Number of ALN involvement (mean and ±SD)	3.28 (3.27)	2.35 (1.79)	2.56 (2.23)		0.56
SUV (mean and ±SD)		2.95 (3.19)		1.59 (1.49)	0.04

ALN: axillary lymph node; TP: true positive; FN: false negative; FP: false positive.

The diagnostic performance of the PET/CT scan according to the size of ALN metastases is found in Table 6.

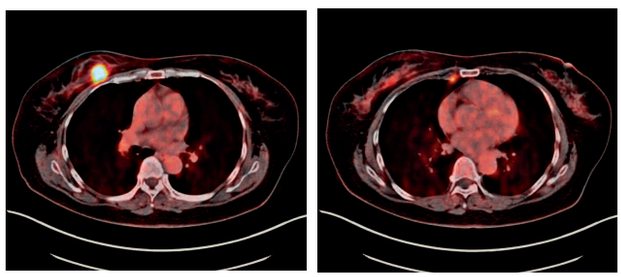
***Table 6**. Diagnostic performance of ^{18}F-FDG PET/CT findings according to the size of axillary lymph node metastases*

ALN size(mm)	^{18}F-FDG PET/CT results of ALN (N) N	TP(%)	FN(%)
≤2	4	0(0)	4(100)
2.1-5	13	3	10
5-10	8	4	4
>10	16	12	4
Total	41	19	22

^{18}F-FDG PET/CT in detecting internal mammary, supraclavicular lymph nodes and distant metastases

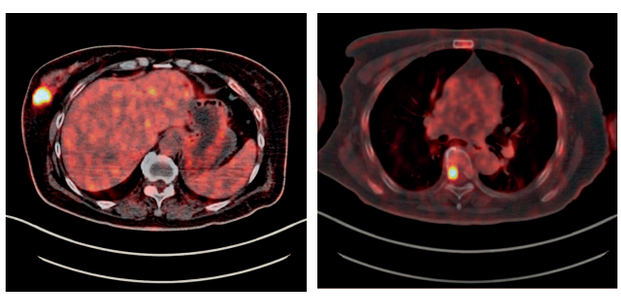
In one patient focally increased ^{18}F-FDG was found in the parasternal (SUVmax 2.3, Figure 2) and in another in the supraclavicular fossa (SUVmax 1.3), which were considered as suspicious of metastases. These two lesions were not verified by histological examination because SNB was free from lymph node metastases and surgery did not include resection of these lymph nodes groups. In a total of 9 internal mammary lymph nodes pathologically examined, 2/9 were metastatic by histopathology, while ^{18}F-FDG PET was FN.

Abnormal ^{18}F-FDG uptake in the adrenal gland, the skeleton, the lung, etc was observed in 8 patients (see Figure 3).



A B

Figure 2. A female patient at the age of 53 years had invasive ductal breast cancer (T2N2M0). Fusion PET/CT imaging showed the increased uptake in the right breast (A) and in the right internal mammary lymph node (B) which indicated metastatic lesions.



A B

Figure 3. A female patient at the age of 67 years had invasive ductal breast cancer (TxNoM1). Fusion PET/CT imaging showed the increased uptake in the right breast (A) and in a thoracic vertrbra (B) which indicated metastatic lesions.

Follow-up for relapse and metastases of breast carcinoma

Follow-up data by ultrasonography, mammography, bone scan and MRI for relapse and distant metastases were available in 153/164 (93.3%) patients. Mean follow-up was 2.42±2.56 years in the entire patient population. Mean follow-up in the subsets of patients with negative and positive primary IBC in ^{18}F-FDG PET by visual analysis were 3.04±0.3 and 3.31±0.41, respectively (P:0.59). At the end of follow-up, no patient with ^{18}F-FDG PET negative IBC, FN ALN and with ALN micrometastases had developed relapse and distant metastases (Table 7).

Discussion

It has been reported that ^{18}F-FDG-PET/CT scan can detect

Table 7. *Relapse and metastases in patients with positive and false negative primary breast carcinoma and ALN all studied by ^{18}F-FDG PET/CT*

Relapse and metastases	Primary IBC		ALN		Micrometastatic ALN
	FN	TP	FN	TP	
Follow-up in years (mean±SD)	3.04±0.30	3.31±0.41	3.03±1.58	3.31±1.66	2.75±1.18
Relapse	0/23(0%)	3/141(2.2%)	0/22(0%)	1/19(5.2%)	0/4(0%)
Distant metastases	0/26(0%)	15/141(10.6%)	0/27(0%)	1/19(5.9%)	0/4(0%)

ALN: axillary lymph node; TP: true positive; FN: false negative; SD: standard deviation.

and evaluate patients with primary IBC with a sensitivity varying from 63% to 93% [4, 10-13]. It is of note that these studies were conducted in a relatively small patient group, varying from 15 to 86 patients, with a median tumor size not reported or varying from 1.6 to 2cm [10, 12-13]. Our study of 164 patients showed that ^{18}F-FDG PET/CT was useful in detecting distant metastases from breast cancer. ^{18}F-FDG PET/CT is more accurate than bone scan in detecting bone metastases [18]. However, 23/164 patients had FN results for primary breast cancer. Correlating ^{18}F-FDG PET/CT performance with the clinicopathological variables of our patients we noticed that the FN cases were observed in the moderate to low histological grade of IBC [6-9] and also in patients with no lymphvascular invasion and with negative progesterone receptors. The fact that we studied ductal and lobular BC together did not influence our results. We noticed no significant correlation of ^{18}F-FDG PET findings with the histological subtype, the size of the tumor or the multifocality of metastases. It was surprising that the majority of FN primary IBC were found in patients with breast cancer size ≤1cm (21/23). The ability of ^{18}F-FDG PET in detecting tumors smaller than 8-9mm in diameter was limited [2, 4, 19, 20] due to its limited spatial resolution [21]. Therefore, ^{18}F-FDG-PET is insufficiently sensitive to rule out small primary tumours [22]. The prone position may achieve higher lesion visualization as well as higher semiquantitative values in comparison with the standard suprine procedure in PET/CT studies [23]. Unfortunately, all patients in our study had the supine position in PET/CT studies which may have contributed to the FN cases.

In our study, we choose as ^{18}FDG PET positive a SUV cutoff of 2.0 in ALN which provides the best accuracy in identifying regional nodal metastases in patients with inflammatory breast cancer [24]. The role of ^{18}F-FDG PET in ALN staging was also limited, with a sensitivity of 46%, which was similar to the study by Hwang et al (2013) (44%) [25] but lower than that of Robertson et al (2011) (60%) [26]. A systematic review of 25 studies involving 2,460 patients indicated currently that the performance of ^{18}F-FDG PET was low, suggesting that for the assessment of ALN metastases surgical biopsy and histological assessment are indicated [27].

The FN rate (53%, 22/41) in ALN staging in our study was higher than that of other studies: 4.94% (4/81) by Greco et al (2001) [28], 18.89% (17/90) by Zornoza et al (2004) [29] and 20% by Schirrmeister et al (2001) [4]. These FN results may be due to the small size of the ALN [5, 30, 31]. In our study, 14/22 ALN with FN PET/CT findings had shown metastases of less than 5mm. Undetectable ^{18}F-FDG uptake in more than half of the patients with ALN metastases less than 5mm (16/27) was expected [32, 33]. Fortunately, ^{18}F-FDG PET/CT allows for a selective approach to diagnose metastases either in ALN or SLN, even in patients with T1 breast cancer [34]. A recent study suggested that PET with point spread function reconstruction may improve spatial resolution in detecting nodal metastases of ≤7 mm [35].

Furthermore, ^{18}F-FDG PET scan did not detect ALN metastases in 5 of 12 patients with ILBC, which, as is known, are stromal rich cancers [29]. The FN ^{18}F-FDG PET/CT findings were often found in patients with positive lymphvascular invasion, multifocal tumor and high tumor staging which was inconsistent with previous reports [14].

Undetectable ALN metastases were more often observed in patients with significantly lower mean SUVmax in primary breast cancer, as had been previously reported [29]. The FP ^{18}F-FDG PET/CT lymph nodes may be due to the imaging threshold cutoff [31], or the reactive lymphadenopathy caused by previous breast biopsy [14]. The FP results were more often found by other researchers in patients with large primary tumors (T2 and T3) than with small tumors (T1) [9], which was also confirmed by our findings. Additionally, the significantly more FP ALN metastases found in patients with negative estrogen and progesterone receptors may be related to the hormone receptor status of primary breast cancers. Therefore, due to the high number of FP findings, the ^{18}F-FDG PET/CT scan cannot replace axillary dissection in ALN staging [22].

As suggested, ^{18}F-FDG PET/CT may have a role in assessing patients with internal mammary node or supraclavicular node metastases, which are often clinically occult and poorly visualized by conventional modalities including ultrasonography and could substantially alter the management of these patients [4, 5, 14-16]. Another study indicated that ^{18}F-FDG PET/CT has a highly positive predictive value for internal mammary metastases in clinical stage III breast cancer [36]. In our study, two focal ^{18}F-FDG uptakes in the parasternal and supraclavicular fossa were detected as suspicious of metastases but histological evaluation was not performed because patients had no ALN involvement. On the contrary, the histologically established metastases in two of nine internal mammary lymph nodes were not detected by ^{18}F-FDG PET/CT. Thus, our results indicated that ^{18}F-FDG PET played a limited role in determining the internal mammary lymph nodes involvement which does not agree with other researchers reporting that ^{18}F-FDG PET/CT can evaluate the in-

ternal mammary chain [29]. The efficacy of ^{18}F-FDG PET/CT in assessing the supraclavicular nodes involvement remains unknown.

Finally we tried to study the relation of ^{18}F-FDG PET/CT scans with prognosis of IBC patients. At the end of the follow-up period, no relapse or metastases were found in patients with ^{18}F-FDG PET/CT negative primary IBC, which indicated a relatively good prognosis. The mean SUVmax of the primary breast cancer was significantly higher in patients with a recurrence than in those who remained disease-free. A high primary tumor SUVmax on ^{18}F-FDG PET/CT has been reported as an independent factor associated with worse disease-free survival in patients with primary IDBC [37].

The clinical significance of microscopic lymph nodes involvement not detected by ^{18}F-FDG PET/CT was also analyzed by follow-up for relapse and distant metastases. Our results indicated that ALN metastases which were not visualized by ^{18}F-FDG PET/CT seemed to have little clinical significance to indicate relapse or distant metastases. Furthermore, no difference was found by others in ALN metastatic recurrence rate in women with negative ALN or negative ALN micrometastases after a median follow-up of 42 months [38]. Another study with a mean follow-up of 4.9 years showed that the distant recurrence rates for SNB-negative, and for SNB-positive tumor cells and micrometastases were: 6%, 8%, 14%, and 21%, respectively [39].

In conclusion, our study showed that ^{18}F-FDG PET/CT scan was useful in detecting the primary invasive breast cancer and its distant metastases but could not accurately stage the axillar, the internal mammary and the supraclavicular nodes. Primary breast cancer lesions, micrometastases and ALN metastases not visualized by ^{18}F-FDG PET seemed to indicate a better prognosis.

The authors declare that there are no conflicts of interest.

Bibliography

1. Fan L, Strasser-Weippl K, Li JJ et al. Breast cancer in China. *Lancet Oncol* 2014; 15(7): e279-89.
2. Yutani K, Shiba E, Kusuoka H et al. Comparison of FDG-PET with MIBI-SPECT in the detection of breast cancer and axillary lymph node metastasis. *J Comput Assist Tomogr* 2000; 24(2): 274-80.
3. Groheux D, Giacchetti S, Delord M et al. ^{18}F-FDG PET/CT in staging patients with locally advanced or inflammatory breast cancer: comparison to conventional staging. *J Nucl Med* 2013; 54(1): 5-11.
4. Schirrmeister H, Kühn T, Guhlmann A et al. Fluorine-18 2-deoxy-2-fluoro-D-glucose PET in the preoperative staging of breast cancer: comparison with the standard staging procedures. *Eur J Nucl Med* 2001; 28(3): 351-8.
5. Wahl RL, Siegel BA, Coleman RE et al. Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: a report of the staging breast cancer with PET Study Group. *J Clin Oncol* 2004; 22: 277-85.
6. Guller U, Nitzsche EU, Schirp U et al. Selective axillary surgery in breast cancer patients based on positron emission tomography with 18F-fluoro-2-deoxy-D-glucose: not yet. *Breast Cancer Res Treat* 2002; 71: 171-3.
7. Kelemen PR, Lowe V, Phillips N. Positron emission tomography and sentinel lymph node dissection in breast cancer. *Clin Breast Cancer* 2002; 3: 73-7.
8. Veronesi U, De Cicco C, Galimberti VE et al. A comparative study on the value of FDG-PET and sentinel node biopsy to identify occult axillary metastases. *Ann Oncol* 2007; 18: 473-8.
9. Taira N, Ohsumi S, Takabatake D et al. Determination of indication for sentinel lymph node biopsy in clinical node-negative breast cancer using preoperative ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging. *Jpn J Clin Oncol* 2009; 39(1): 16-21.
10. Walter W, Scheidhauer K, Scharl A et al. Clinical and diagnostic value of preoperative MR mammography and FDG-PET in suspicious breast lesions. *Eur Radiol* 2003; 13(7): 1651-6.
11. Heinsich M, Gallowitsch HJ, Mikosch P et al. Comparison of FDG-PET and dynamic contrastenhanced RM in the evaluation of suggestive breast lesions. *Breast* 2003; 12(1): 17-22.
12. Rieber A, Schirrmeister H, Gabelmann A et al. Pre-operative staging of invasive breast cancer with MR mammography and/or FDG-PET: boon or bunk? *Br J Radiol* 2002; 75(898): 789-98.
13. Marshall C, Mustafa S, Wheatley DC et al. A comparison of ^{18}F-FDG gamma camera PET, mammography and ultrasonography in demonstrating primary disease in locally advanced breast cancer. *Nucl Med Commun* 2004; 25(7): 721-5.
14. Ueda S, Tsuda H, Asakawa H et al. Utility of ^{18}F-fluoro-deoxyglucose emission tomography/computed tomography fusion imaging (^{18}F-FDG PET/CT) in combination with ultrasonography for axillary staging in primary breast cancer. *BMC Cancer* 2008; 8: 165.
15. Veronesi U, Valagussa P. Inefficacy of internal mammary nodes dissection in breast cancer surgery. *Cancer* 1981; 47(1): 170-5.
16. Fortin A, Larochelle M, Laverdière J et al. Local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy. *J Clin Oncol* 1999; 17: 101-9.
17. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; 17(6): 1471-4.
18. Rong J, Wang S, Ding Q et al. Comparison of ^{18}FDG PET/CT and bone scintigraphy for detection of bone metastases in breast cancer patients. A meta-analysis. *Surg Oncol* 2013; 22(2): 86-91.
19. Kumar R, Chauhan A, Zhuang H et al. Clinicopathologic factors associated with false negative FDG PET in primary breast cancer. *Breast Cancer Res Treat* 2006; 98(3): 267-74.
20. Danforth DN Jr, Aloj L, Carrasquillo JA et al. The role of ^{18}F-FDG-PET in the local/regional evaluation of women with breast cancer. *Breast Cancer Res Treat* 2002; 75(2): 135-46.
21. Uematsu T, Kasami M, Yuen S. Comparison of FDG PET and MRI for evaluating the tumor extent of breast cancer and the impact of FDG PET on the systemic staging and prognosis of patients who are can didates for breast-conserving therapy. *Breast Cancer* 2009; 16(2): 97-104.
22. Escalona S1, Blasco JA, Reza MM et al. A systematic review of FDG-PET in breast cancer. *Med Oncol* 2010; 27(1): 114-29.
23. Vidal-Sicart S1, Aukema TS, Vogel WV et al. Added value of prone position technique for PET-TAC in breast cancer patients. *Rev Esp Med Nucl* 2010; 29(5): 230-5.
24. Carkaci S, Adrada BE, Rohren E et al. Semiquantitative analysis of maximum standardized uptake values of regional lymph nodes in inflammatory breast cancer: is there a reliable threshold for differ entiating benign from malignant? *Acad Radiol* 2012; 19(5): 535-41.
25. Hwang SO1, Lee SW, Kim HJ et al. The Comparative Study of Ultra sonography, Contrast-Enhanced MRI, and ^{18}F-FDG PET/CT for Detecting Axillary Lymph Node Metastasis in T1 Breast Cancer. *J Breast Cancer* 2013; 16(3): 315-21.
26. Robertson IJ1, Hand F, Kell MR. FDG-PET/CT in the staging of local/regional metastases in breast cancer. *Breast* 2011; 20(6): 491-4.
27. Peare R, Staff RT, Heys SD. The use of FDG-PET in assessing axillary lymph node status in breast cancer: a systematic review and meta-analysis of the literature. *Breast Cancer Res Treat* 2010; 123(1): 281-90.
28. Greco M, Crippa F, Agresti R et al. Axillary lymph node staging in breast cancer by 2-fluoro-2-deoxy-D-glucose-positron emission to mography: clinical evaluation and alternative management. *J Natl Cancer Inst* 2001; 93(8): 630-5.
29. Zornoza G, Garcia-Velloso MJ, Sola J et al. ^{18}F-FDG PET comple mented with sentinel lymph node biopsy in the detection of axillary involvement in breast cancer. *Eur J Surg Oncol* 2004; 30(1): 15-9.
30. Avril N, Dose J, Jänicke F et al. Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. *J Clin Oncol* 1996; 14(6): 1848-57.
31. Raylman RR, Kison PV, Wahl RL. Capabilities of two- and three-di-

mensional FDG-PET for detecting small lesions and lymph nodes in the upper torso: A dynamic phantom study. *Eur J Nucl Med* 1999; 26: 39-45.
32. Vranjesevic D, Filmont JE, Meta J et al. Whole-body ^{18}F-FDG FDG-PET and conventional imaging for predicting outcome in previously treated breast cancer patients. *J Nucl Med 2002*; 43(3): 325-9.
33. van der Hoeven JJ, Hoekstra OS, Comans EF et al. Determinants of diagnostic performance of [F-18] fluorodeoxyglucose positron emission tomography for axillary staging in breast cancer. *Ann Surg* 2002; 236: 619-24.
34. Kong EJ, Chun KA, Cho IH et al. ^{18}F-FDG PET/CT with Contrast Enhancement for Evaluation of Axillary Lymph Node Involvement in T1 Breast Cancer. *Nucl Med Mol Imaging* 2010; 44(3): 170-6.
35. Bellevre D, Blanc Fournier C, Switsers O et al. Staging the axilla in breast cancer patients with ^{18}F-FDG PET: how small are the metastases that we can detect with new generation clinical PET systems? *Eur J Nucl Med Mol Imaging* 2014; 41(6): 1103-12.
36. Seo MJ, Lee JJ, Kim HO et al. Detection of internal mammary lymph node metastasis with ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with stage III breast cancer. *Eur J Nucl Med Mol Imaging* 2014; 41(3): 438-45.
37. Jo JE, Kim JY2, Lee SH1 et al. Preoperative ^{18}F-FDG PET/CT predicts disease-free survival in patients with primary invasive ductal breast cancer. *Acta Radiol* 2014; Nov. 18, pii: 0284185114556929. [Epub ahead of print].
38. Langer I, Marti WR, Guller U et al. Axillary recurrence rate in breast cancer patients with negative sentinel lymph node (SLN) or SLN micrometastases: prospective analysis of 150 patients after SLN biopsy. *Ann Surg* 2005; 241(1): 152-8.
39. Reed J, Rosman M, Verbanac KM et al. Prognostic implications of isolated tumor cells and micrometastases in sentinel nodes of patients with invasive breast cancer: 10-year analysis of patients enrolled in the prospective East Carolina University/Anne Arundel Medical Center Sentinel Node Multicenter Study. *J Am Coll Surg* 2009; 208(3): 333-40.

Vincent van Gogh (1853-1890): Head of a skeleton with a burning cigarette (1885-1886). Oil on canvas. Van Gogh Museum, Amsterdam.