¹⁸F-FDG PET/CT with Contrast Enhancement for Evaluation of Axillary Lymph Node Involvement in T1 Breast Cancer

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Abstract

Background ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography ((PET) safely predicts axillary status in patients with breast cancer, but is not sufficiently accurate in early breast cancer patients. This study analyzed the value of ¹⁸F-FDG PET/computed tomography (CT) with contrast enhancement in detecting axillary lymph node involvement in T1 breast cancer patients.

Methods Contrast-enhanced ¹⁸F-FDG PET/CT was performed within 20 days of surgery in 143 breast cancer patients with tumors ≤2 cm in size. The patients underwent either axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB), and histopathology reports were used to provide the definitive diagnosis against which the contrast-enhanced ¹⁸F-FDG PET/CT study results were compared.

Results The sensitivity, specificity, and negative and positive predictive values of contrast-enhanced ¹⁸F-FDG PET/CT in detecting axillary involvement were 70.0%, 92.2%, 88.8%, and 77.8%, respectively, in the entire series of 143 patients, with eight false-positive and 12 false negative results. The false-negative results were associated with the number of metastatic lymph nodes and the rate of FDG uptake.

Conclusion Contrast-enhanced ¹⁸F-FDG PET/CT cannot replace histologic staging using SLNB in patients with breast cancer, but ¹⁸F-FDG PET/CT increases the sensitivity for predicting axillary node metastasis, and allows for a selective approach to either ALND or SLNB, even in patients with T1 breast cancer.

Keywords Breast cancer · Axillary lymph node · FDG · PET/CT

Introduction

The most powerful predictor of recurrence and survival in women with breast cancer is axillary lymph node (ALN) status [1, 2]. ALN status is essential for decisions regarding systemic and locoregional treatment [2]. It has been suggested that detection of tiny foci of disease in ALNs may be important in determining prognosis and treatment. However, only 30% of women with an invasive breast tumor with a diameter of ≤20 mm have ALN metastasis [3]. Further, axillary lymph node dissection (ALND) may cause numbness of the arm, motor disturbances of the upper limb, and lymphedema, and decrease the long-term quality of life with mental health issues [4, 5]. Moreover, the effect of ALND on survival is unclear [6]. Clinical examination of the axilla and currently available imaging techniques are inaccurate for axillary staging [7]. Therefore, the role of ALND has shifted to an identification of prognosis-predictive factors, and a less invasive axillary staging procedure is required to replace ALND [8, 9]. In recent years, sentinel lymph node biopsy (SLNB) represents the standard of care for ALN staging in patients with early-stage, clinically node-negative breast cancer, as a less invasive alternative to ALND. Importantly, SLNB is also an invasive ALN staging method and there is no reliable non-invasive method of evaluation of lymph node status in patients with breast cancer.

Positron emission tomography (PET) using the glucose analogue, ¹⁸F-fluorodeoxyglucose (FDG), has been used for staging in a variety of human malignancies [10], and various studies have shown that PET/computed tomogra-

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phy (CT) is a sensitive and specific diagnostic tool for the detection of ALN metastases in breast cancer [11]. Compared with morphologic imaging methods, additional sites of tumor deposits, including lymph nodes, are detected owing to the higher glycolytic rate of cancer cells compared with normal cells. Several studies have investigated the significance of pre-operative staging of breast cancer by ^{18}F -FDG PET, but the sensitivity has generally been low, and various results have been obtained in the diagnosis of ALN metastases by ^{18}F -FDG PET [12–14]. ^{18}F -FDG PET alone cannot substitute for ALND and SNB, but the positive predictive value (PPV) is high with the accumulation of ^{18}F -FDG in ALNs [13], and detailed anatomic analysis has recently become possible using PET/CT, in which lymph nodes can be evaluated in fused PET and CT images. The combination of metabolic ^{18}F -FDG PET data with morphologic CT data through application of integrated ^{18}F -FDG PET/CT has been shown to further increase diagnostic accuracy [15].

The aim of this study was to determine whether or not pre-operative contrast-enhanced ^{18}F -FDG PET/CT can assess axillary status accurately in patients with T1 breast cancer.

Materials and methods

Patients

Between May 2007 and June 2009, 143 women (mean age, 50.1 ± 9.6 years) with histopathologically confirmed breast cancer (tumors ≤ 2 cm in size) were included in this retrospective study. The histopathological subtypes were as follows: invasive ductal carcinoma [$n=118$ (82.5%)], invasive lobular carcinoma [$n=3$ (2.1%)], tubular carcinoma [$n=4$ (2.8%)], invasive micropapillary carcinoma [$n=3$ (2.1%)], metaplastic carcinoma [$n=3$ (2.1%)], medullary carcinoma [$n=2$ (1.4%)], mucinous carcinoma [$n=2$ (1.4%)], invasive cribriform carcinoma [$n=2$ (1.4%)], microinvasive carcinoma [$n=1$ (0.6%)], apocrine carcinoma [$n=1$ (0.6%)], mixed ductal/micropapillary carcinoma [$n=1$ (0.6%)], and ductal carcinoma in situ [$n=3$ (2.09%)]. In all patients, the ipsilateral axilla was assessed for lymph node metastases with SLNB, ALND, or both SLNB and ALND. We included 26 patients with diabetes mellitus. This was a retrospective study performed in accordance with the regulations of the local Ethics Committee.

Whole-body FDG PET/CT

Contrast-enhanced ^{18}F -FDG PET/CT was performed pre-operatively (mean, 5 ± 2.9 ; range, 1–20 days). Patients were required to fast for 6 h and had a pre-scan blood glucose

analysis to ensure a level <140 mg/dl. Patients received an intravenous injection of 370 MBq of ^{18}F -FDG in the arm contralateral to the primary breast tumor and rested quietly for 60–90 min after the injection. Each patient was positioned in the scanner with their arms above their head, and a scan from the mid-thigh to the skull base was performed in a VCT or DVCT PET/CT instrument (GE Medical Systems, Milwaukee, Wis., USA). Contrast-enhanced CT for attenuation correction was acquired before PET with 250 mA/s at 120 kV and 2 ml/kg of an iodinated contrast material (Pamiray 300, Taejoon Pharm, Korea) were administered with an automated injector at a flow rate of 2 ml/s. All images were reconstructed with a 3.75-mm slice thickness at 2.4-mm increments. After CT, a three-dimensional (3D) mode PET was performed, and iterative algorithms with two iterations and eight subsets were used for image reconstruction. Data were filtered (FWHM 5.0 mm) and corrected for scatter.

Image analysis

Two experienced nuclear medicine physicians interpreted the pre-operative studies. Diagnoses were made in consensus. Images were evaluated using an advanced Workstation (AW 4.4; General Electrics Healthcare). Scans were evaluated in three orthogonal planes (axial, coronal, and sagittal). The ipsilateral axillary fossa was evaluated for lymph node metastases. Image analysis was as follows: ^{18}F -FDG PET evaluation for any focally increased PET signal, then a morphologic evaluation was done. Images were considered positive if areas in the axillary basin took up more ^{18}F -FDG than the surrounding tissues. The criteria for abnormal lymph nodes on CT included a round, ovoid, or conglomerated shape with an enhancement pattern of contrast media. The sizes of the lymph nodes did not directly enter the final PET/CT finding criteria. In short, the ALNs were rated as positive if the lymph node had a round or ovoid shape with a higher FDG uptake than surrounding tissues and enhancement, regardless of the size (Table 1). The decision was empiric based on the long-term imaging experience of the two readers. Quantitative measurements, such as standardized uptake values on PET, were done in a concomitant manner only and were not used for decision-making.

Sentinel node biopsy

In all patients, the radioactive tracer ($^{99\text{m}}\text{Tc}$ phytate) was injected before surgery. Each single dose of $^{99\text{m}}\text{Tc}$ -phytate contained 7–10 MBq of $^{99\text{m}}\text{Tc}$ in a volume of 0.2 ml. Radiocolloids were intradermally injected into the subareolar area of the projection of the tumor. Immediately after injection, the areolar area was gently massaged for 5 min to

Table 1 Criteria for positive and negative axillary lymph node

		PET		
		Similar background activity	Increase than BG (mild uptake)	Hot
CT	Normal-clear fat hilum, bean shape	–	–	+
	Round or ovoid with contrast enhancement	–	+	+
	Conglomerate	+	+	+

increase lymphatic flow. Lymphoscintigraphy was performed with a large field of view dual-head gamma camera equipped with a low energy, high-resolution collimator (ECAM, Siemens, Germany). A 20% energy window with a 140 keV photopeak was used. Images were acquired from anterior and anterior-oblique views, starting 5 min after injection and up to 2 h later, if required. The skin projection of the first node (or nodes) taking up the tracer [defined as the sentinel lymph node (SLN)] was marked with a suitable pen while the patient was supine with the arm extended superiorly to the body.

The SLNB started with four subareolar injections of 2.5–3 cc of methylene blue dye (1% methylene blue; Laboratorio Farmacologico) using a 25-gauge needle. A handheld gamma detector (Neoprobe, Dublin, Ohio, USA) was used to transcutaneously detect spots of increased emission of ionizing radiation (hot spots). A skin incision was made directly above the hot spot. If blue-stained lymphatic vessels were detected, they were followed. A lymph node with afferent blue-stained lymphatic vessels was considered to be an SLN, as well as lymph nodes with radioactive emission of more than three times that of the surrounding tissues. All “blue” or “hot” lymph nodes were considered to be SLNs. Following breast surgery, a routine level I and II ALND was performed.

Gold standard

A histopathological workup of resected specimens was performed. In brief, SLNs were intra-operatively submitted for frozen section analysis. After removal of perinodal fatty tissue the SLNs were sectioned into 2-mm slices. Only the most suspicious slice was snap-frozen and one superficial cryostat section was examined histologically. Following standard fixation overnight and paraffin embedding, each block was cut into at least three serial sections in 500- μ m levels and stained with hematoxylin and eosin and an additional immunohistochemical study.

Statistical analysis

The following parameters for the detection of ipsilateral ALNs with enhanced ^{18}F -FDG PET/CT were calculated on

a patient-based analysis: sensitivity, specificity, accuracy, PPV, and negative predictive value (NPV). Correlations between lymph node metastasis and histologic factors were evaluated using a Pearson chi-square test and Fisher’s exact test. All statistical analyses were performed with SPSS 16.0 software (SPSS, Chicago, Ill., USA). All statistical tests were two-sided and statistical significance was set at the 5% level.

Results

The study included 143 women with breast cancer. The mean age was 50.1 ± 9.6 years (range, 24–78). Sixty-nine patients had right-sided breast cancer and 74 patients had left-sided breast cancer. The median tumor size was 1.4 ± 0.4 cm (range, 0.1–2.0 cm), of which 23 were ≤ 1 cm. The prevalence of ALN involvement on pathologic examination was 28.0%. Twenty-two of 143 tumors were from the internal quadrants of the breast, six of which (27.3%) had ALN involvement ($p > 0.05$). The breast tumors were not visualized by ^{18}F -FDG PET in four women (sensitivity, 97.2%) and the mean SUVmax for the overall tumors was 5.7 ± 4.2 . Histologically, 31.4% of the patients with invasive ductal carcinoma patients had ALN involvement; 12% of the other patient types had ALN involvement ($p < 0.05$).

Based on PET analysis, the cases had a similar uptake with surrounding tissues (mean of SUVmax = 0.7 ± 0.2) showed 10% metastasis, mildly increased compared with surrounding tissues (mean of SUVmax = 1.1 ± 0.6) showed 41.2% metastasis, and hot uptake (mean of SUVmax = 10.1 ± 5.6) showed 100% metastasis. Based on CT analysis, the cases showed a clear fat hilum with a bean-shape showed 7.6% (5/66) metastasis, contrast-enhanced round or ovoid shape showed 34.3% (22/64) metastasis, and all of the mass-like conglomerated lymphadenopathy had LN metastasis (13/13). Figure 1 shows the true positive PET/CT images of a 51-year-old patient with mild FDG uptake and a small round shape with enhancement in a right ALN (SUVmax: 1.2).

The sensitivity, specificity, NPV, and PPV of contrast-enhanced ^{18}F -FDG PET/CT for detecting axillary status were 70.0%, 92.2%, 88.8%, and 77.8%, respectively

Fig. 1 **a** PET and **b** CT image showed mild FDG uptake and small round with enhancement in right axillary lymph node (SUVmax: 1.2). Metastasis was confirmed by surgical lymph node biopsy and underwent breast conserving surgery with axillary lymph node dissection

(Table 2). Contrast-enhanced ^{18}F -FDG PET/CT detected axillary involvement in 28 of 40 patients (12 false negatives; Table 3) and correctly diagnosed 95 of 103 patients without axillary metastases.

The characteristics of the tumors in women with true-positive axillary PET/CT scans were compared with those in women with false-negative scans in order to define a subgroup of patients for whom ^{18}F -FDG PET/CT most reliably predicted axillary status (Table 4). The mean of SUVmax in ALNs in those with a true-positive scan was 6.2 ± 6.2 compared with 0.6 ± 0.1 in those with a false-negative study ($p < 0.01$). The mean number of metastatic ALNs in those with a true-positive scan was 7.1 ± 16.1 compared with 1.4 ± 1.2 in those with a false-negative study ($p > 0.05$). The mean SUVmax in primary tumors in those with a true-positive and false-negative study was 7.7 ± 4.9 and 5.5 ± 4.3 , respectively ($p > 0.05$). All of the false-negative axillary ^{18}F -FDG PET/CT scans were of the invasive ductal carcinoma type, two of which were micrometastases.

Discussion

The clinical use of ^{18}F -FDG PET for staging is being investigated for many human tumors, including breast cancer [10, 11, 16]. For nodal staging, Bombardieri et al.

[17] found that ^{18}F -FDG PET was superior to $^{99\text{m}}\text{Tc}$ -sestamibi or ^{111}In -pentetreotide scintigraphy. Other authors compared ^{18}F -FDG PET with CT and obtained sensitivity, specificity, and diagnostic accuracy values of 85%, 90%, and 88% compared with 54%, 85%, and 73%, respectively [18]. In previous comparisons of diagnoses of axillary metastasis by pathologic diagnosis and ^{18}F -FDG PET, the sensitivity of diagnosis by ^{18}F -FDG PET ranged from 46% to 95%, the specificity ranged from 66% to 100%, the PPV ranged from 62% to 100%, and the NPV ranged from 73% to 99% [11, 13, 19–21]. The diagnostic accuracy was different depending on the staging. In stage I and II patients, the sensitivity and specificity was 45% and 57%, respectively, which was relatively low compared with stage III and IV patients (83.3%) [19]. Previous studies indicate that ^{18}F -FDG PET is not sufficiently sensitive in the detection of lymph node metastases, particularly in early breast cancer patients with limited disease spread to the axilla. ^{18}F -FDG PET/CT added incremental diagnostic confidence to PET of patients and regions, and is preferable to PET in the diagnosis of breast cancer [22]. Ueda et al. [23] reported the utility of ^{18}F -FDG PET/CT for axillary staging; the diagnostic accuracy was 83%, with 58% sensitivity and 95% specificity. A recent study involving PET/CT was reported for pre-operative axilla, and included 137 patients with a mean tumor size of 1.8 ± 0.1 cm. The overall sensitivity and specificity of ^{18}F -FDG PET/CT in predicting axillary metastasis were 77.1% and 100%, respectively [24]. Although ^{18}F -FDG PET/CT alone still cannot replace invasive approaches for axillary staging, but may extend the indication for SLNB.

In this investigation, contrast-enhanced ^{18}F -FDG PET/CT appears to be insufficiently exact for ruling out metastatic lymph nodes in early breast cancer patients. The diagnostic accuracy was higher than other studies involving patients with early breast cancer, but the false negative rate (12 of 40 patients [30%]) was too high and the risk benefit ratio requires an ALNB. The most likely explanation for the low sensitivity observed in the current study would be a low tumor burden in the axilla due to

Table 2 Diagnostic performance of ^{18}F -FDG PET/CT for axillary lymph node metastasis and node positive rates according to the PET/CT results

PET/CT Biopsy	Positive	Negative	Total
Positive	28 (77.8%)	8 (22.2%)	36
Negative	12	95	107
Total	40	103	143

Sensitivity=70% (28/40), specificity=92.2% (95/103), positive predictive value=77.8% (28/36), negative predictive value=88.8% (95/107).

Table 3 Characteristics of 12 patients with false-negative results (*IDC* invasive ductal carcinoma)

Patient number	Age	DM	Cell type	LN number	Tumor uptake (SUVmax)	Tumor size	LN uptake (SUVmax)	LN size (mm)
1	46		IDC	1	3.6	1.6	0.7	11.1
2	48		IDC	1	1.2	0.7	0.6	11.1
3	41	Y	IDC	1	3.5	1.2	0.6	8.9
4	44		IDC	1	4.2	2	0.4	12.2
5	39		IDC	2	6.3	1.8	0.7	9
6	58		IDC	1	1.4	1.9	0.6	10.7
7	35		IDC	1	5.6	1.8	0.5	6.2
8	52		IDC	1	6.6	2	0.4	6.3
9	53		IDC	1	14.2	1.7	0.6	11.6
10	53	Y	IDC	5	2.1	1.1	0.6	11
11	39		IDC	1	3.7	1.3	0.5	10.3
12	43		IDC	1	13.9	1.8	0.8	16.7

involvement of early stage breast cancer. Indeed, in several studies of patients with clinically node-negative breast cancer, the sensitivity of ^{18}F -FDG PET for detection of ALN metastases ranged from 25% to 50% [21, 25, 26].

In the present study, the 12 false-negative axillary PET/CT scans were analyzed to seek an explanation for these results and to look for factors associated with the accuracy of axillary PET/CT. Breast cancer with a low tumor burden, such as micrometastasis or SN-only metastasis, and low FDG uptake tend to cause false negative scans. Failure to detect macrometastases may result from the low metabolic rate of tumor, which is an intrinsic tumor characteristic, such as size and grade [13, 27, 28]. The majority of those not detected are at stage pT1 [20]. Guller et al. [25] reported a sensitivity of 29% and van der Hoeven et al. [21] a sensitivity of 25% for ^{18}F -FDG PET. In addition, it was related to the number of lymph nodes involved. In the previous study, ^{18}F -FDG PET had a limitation in its ability to detect metastases in single, rather than multiple ALNs. Ten of 12 patients in our study had single node involvement. Samson et al. [29] found no study in which ^{18}F -FDG PET was capable of determining the number of affected lymph nodes (information that is very useful when deciding upon the use of radiotherapy). Clinical studies have demonstrated the prognostic value of FDG uptake: tumors with higher FDG uptakes appear to be more aggressive and to develop faster [30–32]. We found that, even if carcinomas with high SUVs often have axillary

metastases, there was a high degree of SUV overlap in carcinomas with and without axillary metastases. As a result, it was impossible to establish a useful SUV cut-off value for the management of patients referred for ALND. There was only one false-negative result in more than five lymph nodes affected. The patient had type 2 diabetes (tumor size, 1.1 cm). Patients with type 2 diabetes mellitus have inadequate insulin receptors leading to an inability of insulin to bind to receptors causing an increase in blood glucose. Several studies have reported that increased blood glucose levels lead to decreased tumor uptake of ^{18}F -FDG [33, 34].

By performing ALND as a primary procedure in cases where there were positive ^{18}F -FDG PET/CT results, 28 patients were spared unnecessary SLNB in this study.

The detection of micrometastases in these lymph nodes was limited by the spatial resolution of ^{18}F -FDG PET [25]. This limitation has become particularly clear since the introduction of better pathologic examination techniques for SLNB (immunohistochemical staining and multistep sectioning) that have increased the rate of detection of axillary micrometastases and led to considerable upstaging. In a comparative study of ^{18}F -FDG PET and SLNB in 71 women with T1 N0 breast cancer, Crippa et al. [35] reported six false-negative results with SLNB and lymphoscintigraphy, whereas ^{18}F -FDG PET failed to detect 11 cases of ALN involvement. There is currently no technique that does not entail an intrinsic risk of downstaging axillary

Table 4 Characteristics of true-positive and false-negative pathologic lymph nodes

	Mean of SUVmax in lymph nodes	Mean of SUVmax in tumor	Mean number of metastatic lymph nodes
True-positive	6.5±6.2	7.7±4.9	7.1±16.1
False-negative	0.6±0.1	5.5±4.3	1.4±1.2
<i>p</i>	0.00005	0.173	0.07

status; even SLNB has a small false-negative rate in almost all studies. The most sophisticated imaging modality will never provide the same information as ALND. Greco et al. [36] suggest that only a few axillary micrometastases become clinically evident during such follow-up, and further analysis of these patients revealed that these axillary relapses had no major impact on overall survival. There is, however, uncertainty about the clinical significance of microscopic lymph node involvement. Current data suggest no difference in axillary recurrence rates in women with negative SLN or SLN micrometastases.

A limitation of this study was that in approximately one-half of the patients, the “gold standard” consisted of SLNB alone and not ALND. It is not clear that the suspected lymph nodes on enhanced ^{18}F -FDG PET/CT are the same ones proven on pathologic assessment, especially due to the number of lymph nodes at surgery being more numerous than those seen on the previous imaging study. The previous investigation also reported that ^{18}F -FDG PET/CT has a limitation in determining the number of affected lymph nodes. In this study, there was inconvenience with the elongation of scan time per bed and a delayed PET scan would increase sensitivity. Further progress in the development of ^{18}F -FDG PET/CT scanners may improve the diagnostic performance in the near future due to a higher spatial resolution, and thus detectability of smaller lymph node metastases.

Conclusion

Although incapable of replacing SLNB or ALND, contrast-enhanced ^{18}F -FDG PET/CT can select candidates for SLNB instead of ALND, even in early breast cancer. When using ^{18}F -FDG PET/CT as a pretest, patients with early breast cancer may safely undergo SLNB. Such an approach may avoid futile ALNDs and associated morbidity. The next generation PET/CT scanners with higher spatial resolution may further increase the diagnostic value of ^{18}F -FDG PET/CT for lymph node staging.

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