The value of dual-time-point ^{18}F -FDG PET/CT for identifying axillary lymph node metastasis in breast cancer patients

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Objective: The sensitivity of 18-fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) for detecting axillary lymph node (ALN) metastases in breast cancer is reported to be low. Several studies have shown, however, that dual-time-point ^{18}F -FDG PET imaging provides improved accuracy in the diagnosis of certain primary tumours when compared with single-scan imaging. The purpose of this study was to assess whether the use of dual-time-point ^{18}F -FDG PET/CT scans could improve the diagnostic accuracy of ALN metastasis in breast cancer.

Method: The study included 171 breast cancer patients who underwent pre-operative ^{18}F -FDG PET/CT scans at 2 time-points, the first at 1 h after radiotracer injection and the second 3 h after injection. Where ^{18}F -FDG uptake was in the ALN perceptibly increased, the maximum standardised uptake values for both time-points (SUVmax1 and SUVmax2) and the retention index (RI) were calculated. Correlation between the PET/CT results and post-operative histological results was assessed.

Results: The performance of 1 h and 3 h PET/CT scans was equal, with sensitivity 60.3% and specificity 84.7%, in detecting ALN metastasis. Out of 171 patients, 60 had ALNs with increased ^{18}F -FDG uptake on 1 h or 3 h images. There was no significant difference in RI between the metastatic ALN-positive group and the node-negative group. The area under the receiver operating characteristic (ROC) curve for SUVmax1 was 0.90 ($p < 0.001$) and 0.87 for SUVmax2 ($p < 0.001$).

Conclusion: Dual time-point imaging did not improve the overall performance of ^{18}F -FDG PET/CT in detecting ALN metastasis in breast cancer patients.

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Axillary lymph node (ALN) involvement is the key prognostic factor in patients with breast cancer [1]. Accurate assessment of axillary node status is therefore essential for both predicting outcome and choosing a therapeutic plan. The most reliable and accurate procedure for the examination of ALN is standard axillary lymph node dissection (ALND). However, the complications associated with ALND, such as lymphoedema, numbness of the skin of the upper arm and impairment of shoulder movement, lead to decreased quality of life [2]. Moreover, a significant proportion of breast cancer patients, especially those with small tumours, are node negative [3, 4]. Therefore, a non-invasive modality for accurate staging of ALNs is needed to avoid unnecessary ALND.

^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) and ^{18}F -FDG PET/CT have a useful role in staging and therapeutic planning in breast cancer patients in that these modalities are used to identify unexpected metastasis and recurrence [5]. The sensitivity of ^{18}F -FDG PET for detecting ALN metastasis in breast cancer staging is, however, reported to be relatively low [6, 7]. Recently, immunohistochemistry and multistep section have improved the detection rate of axillary micrometastasis and the value of ^{18}F -FDG PET in axillary staging has become more uncertain [6, 8, 9].

Several studies have shown that ^{18}F -FDG uptake by malignant tumours increases for hours after injection [10, 11]. Thus, some investigators suggest advantages of using delayed PET or dual time-point PET images. In breast cancer, Boerner et al [12] reported that PET images made 3 h after ^{18}F -FDG injection showed higher tumour-to-non-tumour and tumour-to-organ ratios, and enhanced lesion detectability when compared with 1.5 h images.

The purpose of this study was to assess whether dual-time-point (1 h and 3 h) ^{18}F -FDG PET/CT scans could improve the diagnostic accuracy of ALN metastasis in breast cancer.

Methods and materials

Patient population

The population for this retrospective study consisted of 171 female patients (mean age, 50.1 ± 10.2 years; age range, 24–77 years) with breast cancer who had ^{18}F -FDG PET/CT scanning for pre-operative staging between December 2003 and May 2006. We excluded patients who received chemotherapy or radiotherapy before undergoing PET/CT scans. All of the patients had surgery that included either ALND or sentinel lymph node biopsy (SLNB) in addition to mastectomy within 4 weeks of the ^{18}F -FDG PET/CT scan. A total of 135 of the 171 patients received ALND, and 7 to 46 nodes were removed from each patient.

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The ethical committee of our institution does not require patient consent for retrospective review of imaging studies.

Imaging

After the patients fasted for at least 6 hours, 370–555 MBq of ^{18}F -FDG was injected intravenously in the contralateral antecubital fossa or hand. If these sites were not approachable, ^{18}F -FDG was injected into the feet.

None of the patients had blood glucose levels exceeding 130 mg dl^{-1} before the injection. No intravenous contrast agent was used. A combined PET/CT inline system (Biograph DUO LSO; Siemens Medical Solutions, Knoxville, TN) was used to acquire all data. A full-ring PET scanner integrated with a dual-section helical CT scanner (Somatom Emotion; Siemens) acquired the co-registration of PET and CT images in one session. All patients underwent two sequential PET/CT scans (dual time-point) for pre-operative staging. The first scan, a whole-body image from orbitomeatal line to upper thigh, was performed 1 h after ^{18}F -FDG injection. 6 to 8 bed positions were used and the acquisition time was 2 min per bed position. All patients were in the supine position with their arms raised. CT scanning began at the orbitomeatal line and progressed to the upper thigh (30 mAs; 130 kV; slice thickness 5 mm) and PET imaging followed immediately over the same body region. The delayed PET/CT scan, which began approximately 3 h after ^{18}F -FDG injection, included just two bed positions in which only the thorax region was scanned. Patients were not allowed to have any food between the two scans. In the intervening time between the scans, patients rested in a separate room and were encouraged to drink water and void. Blood glucose was not checked again before the second scan unless severe hypoglycaemia was suspected. The CT data were used for attenuation correction, and images were reconstructed using the standard ordered subset expectation maximisation (OSEM two iterations, eight subsets) algorithm. The axial spatial resolution was 6.5 mm at the centre of the field of view.

Interpretation

All PET/CT images were reviewed at a workstation with fusion software (Syngo, Siemens) that provided multiplanar reformatted images and displayed PET images (either before or after attenuation correction), CT images and PET/CT fusion images. Two nuclear medicine physicians reviewed the PET/CT images and the interpretation was made visually. Two experienced nuclear medicine physicians interpreted the ^{18}F -FDG PET scans independently without knowledge of the pathological findings relating to the ALN. Any difference of opinion was resolved by consensus between the two physicians. If ^{18}F -FDG uptake was perceptible in the ALN, the case was interpreted as positive for metastasis. Conversely, if no ^{18}F -FDG uptake was perceptible in the axillary regions, the case was regarded as free of ALN metastasis. For semi-quantitative analysis, the maximum standardised uptake value (SUVmax) of ^{18}F -FDG was

measured from both the first (1 h) and second (3 h) sets of images (SUVmax1 and SUVmax2, respectively) by visually placing regions of interest (ROIs) around the ALNs that had perceptible ^{18}F -FDG uptake. If there were multiple nodes with perceptible ^{18}F -FDG uptake, the highest SUVmax was selected. The percentage change of SUVmax, designated as the retention index (RI), was calculated as follows: $(\text{SUVmax2} - \text{SUVmax1}) \times 100 / (\text{SUVmax1})$. All PET/CT results were correlated with the pathology results from the subsequent operation.

Statistical analysis

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) software (version 13.0). All of the quantitative values were expressed in terms of mean $\pm$ standard deviation (SD). An independent *t*-test was applied to compare the semi-quantitative parameters (SUVmax1, SUVmax2 and retention index (RI)) between the ALN-metastasis-positive group and the ALN-metastasis-negative group. The RI values were grouped as positive ($\text{SUVmax1} < \text{SUVmax2}$), no change ($\text{SUVmax1} = \text{SUVmax2}$) and negative ($\text{SUVmax1} > \text{SUVmax2}$). Receiver operating characteristic (ROC) analysis was performed to determine the best cut-off value for discriminating malignant lesions. A *p*-value of less than 0.05 was considered significant.

Results

Breast cancer was histologically confirmed by surgery in all of the 171 patients. Invasive ductal carcinoma was the most common type (Table 1). Metastatic ALNs were confirmed by pathology in 73 cases (42.7%). The 1 h and 3 h PET/CT images detected and missed the same numbers of malignant ALN cases. The sensitivity, specificity and accuracy of the 1 h ^{18}F -FDG PET/CT scans for detection of ALN metastases were 60.3%, 84.7% and 74.3%, respectively (Table 2). Of 59 cases with

Table 1. Clinical and pathological characteristics of the 171 female patients

Age (years)	
Mean	50.1 $\pm$ 10.2
Range	24–77
T stage	
T1	96
T2	70
T3	5
N stage	
N0	98
N1–3	73
M stage	
M0	168
M1	3
Histopathological tumour type	
Ductal carcinoma <i>in situ</i>	7
Invasive ductal carcinoma	155
Invasive lobular carcinoma	2
Medullary carcinoma	3
Mucinous carcinoma	3
Metaplastic carcinoma	1

Table 2. Performance of PET/CT in the detection of axillary lymph node metastasis

T stage	n	Confirmed ALN metastasis (n)	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
All	171	73	60.3	84.7	74.3	74.6	74.1
pT1	96	32	50.0	87.5	75.0	66.7	77.8
pT2	70	39	69.2	80.7	74.3	81.8	67.6
pT3	5	2	50.0	66.7	60.0	50.0	66.7

NPV, negative predictive value; PPV, positive predictive value; PET, positron emission tomography; ALN, axillary lymph node.

perceptible ^{18}F -FDG uptake in ALN on 1 h PET/CT images, 44 (74.6%) were confirmed to be metastasis-positive. Of the 112 cases without perceptible ^{18}F -FDG uptake in the ALN, 29 (25.9%) had node metastasis. The sensitivity of 1 h PET/CT was lower (50.0% *vs* 69.2%) but the specificity higher (87.5% *vs* 80.7%) for Stage T1 patients compared to Stage T2 patients.

One patient had ALN with perceptible ^{18}F -FDG uptake on only the 1 h PET images, and another patient had perceptible ^{18}F -FDG uptake only on the 3 h PET images. Both cases were pathologically proven to be benign lymph nodes. Therefore, both 1 h and 3 h PET/CT had the same number of false-positive cases, and their performances ended up being the same.

60 out of the 171 patients had ALN with perceptible ^{18}F -FDG uptake on either the 1 h or 3 h PET/CT images, and 44 of these 60 cases were positive for ALN metastasis upon pathological testing. The mean size of lymph nodes with perceptible ^{18}F -FDG uptake was 9.9 ± 2.2 mm (range: 4–18 mm). ^{18}F -FDG uptake was positive in lymph nodes of less than 5 mm in size in just 2 cases. The change in ^{18}F -FDG uptake over time, expressed as RI, is shown in Table 3. There was no significant difference in RI between the ALN-metastasis-positive and -negative groups ($p=0.262$).

The mean SUVmax1 of the ALN-metastasis-positive group was significantly higher than that of the metastasis-negative group (2.1 ± 1.1 *vs* 1.0 ± 0.4 , $p<0.001$); the mean SUVmax2 was also greater in the metastasis-positive group (2.5 ± 1.6 *vs* 1.1 ± 0.6 , $p<0.001$). The area under the ROC curve for SUVmax1 was 0.90 ($p<0.001$; 95% confidence interval (CI)=80.0–99.2%) and 0.87 for SUVmax2 ($p<0.001$; 95% CI=76.2–97.5%) (Figure 1). There was no significant difference, however, in the mean RIs of the ALN-metastasis-positive and -negative groups ($p=0.233$). The area under the ROC curve was 0.60 for RI, but the p -value was more than 0.05 ($p=0.242$; 95% CI=42.0–77.9%). The performances of the 1 h and 3 h PET/CT images according to several selected cut-off SUVs are shown in Table 4.

Table 3. Retention index in ALN metastasis-positive and ALN metastasis-negative groups

Retention index	ALN metastasis	
	Positive	Negative
>0	30 (68%)	8 (50%)
≤0	14 (32%)	8 (50%)
Mean	0.2 ± 0.2	0.1 ± 0.3
Range	–0.25 to 0.6	–0.21 to 0.68
Total	44	16

ALN, axillary lymph node.

Discussion

The most important prognostic marker of survival in breast cancer patients is the state of axillary node metastasis. Thus, accurate axillary node staging is crucial for predicting prognosis and for guiding the selection of patients who need more aggressive local therapy or adjuvant systemic therapy.

ALND is the most accurate method for assessing ALN metastasis and also provides locoregional control of axillary disease. With such an invasive surgical staging method, however, the development of irreversible post-surgical complications is a major downside for the patient [2]. Although SLNB is less invasive and might be associated with less morbidity, the risk of complication still remains.

Only a minority of T1 breast cancer patients have lymph node metastases, although the rate of detection of micrometastasis has been increased by the recent use of thorough pathological examination. In a study by Van der Hoeven et al [9], 33% of T1 patients were node-positive histologically. This proportion agrees well with our findings, in which of 32 out of 96 (33.3%) T1-stage cases were node-positive. Thus, ALND might be unnecessary in the remaining majority of stage-T1 breast cancer patients. Furthermore, the survival advantage of ALND remains a matter of debate [13, 14]. Therefore, a non-invasive method to assess axillary nodal status accurately would be useful for sparing breast cancer patients from unnecessary ALND.

Cancer cells can have greater glucose metabolism than normal cells, and ^{18}F -FDG PET can often detect this difference in rates of metabolism before the lymph node is enlarged enough to be seen by anatomical imaging modalities [15]. Early studies with ^{18}F -FDG PET that showed promising results reported sensitivity and specificity of over 90% in the detection of ALN metastasis from breast cancer [16, 17]. In comparison to the introduction of more sensitive histological examination methods that have increased micrometastasis detection rate of [18]; however, ^{18}F -FDG PET has shown lower sensitivity for axillary nodal metastases. In recent studies, the sensitivity of ^{18}F -FDG PET ranged from 20% to 43% [6, 8, 9, 19]. Furthermore, because ^{18}F -FDG uptake is observed not only in tumours but also in inflammatory sites, distinguishing metastatic lymph nodes from reactive lymph nodes by ^{18}F -FDG PET is difficult.

^{18}F -FDG uptake in malignancy is observed to increase for several hours after injection. By contrast, such gradual ^{18}F -FDG uptake is rare in inflammatory lesions or normal tissues. Hamberg et al [11] found that Stage III lung cancers continue to accumulate ^{18}F -FDG for hours, and maximum accumulation was reached 5 h after

Figure 1. Receiver operating characteristic (ROC) curves for SUVmax1, SUVmax2 and retention index for the discrimination of metastatic axillary lymph node from a benign node. SUVmax, maximum standardised uptake value.

injection. Another study showed that ^{18}F -FDG uptake in high-grade sarcomas continued to increase until approximately 4 h after injection, whereas ^{18}F -FDG uptake in benign soft-tissue masses reached a maximum value within 30 min of injection [10]. In an experiment using a turpentine-induced inflammation model in rats, Yamada et al [20] reported that ^{18}F -FDG uptake in inflammatory tissue increased for a little longer, until 60 min post-injection, and then decreased gradually. The gradual ^{18}F -FDG uptake by a malignant tumour may be related to the relatively decreased expression of glucose-6-phosphatase rather than to increased hexokinase expression, resulting in a high hexokinase/phosphatase ratio relative to that of normal tissues [21]. Because of this difference in the time course of ^{18}F -FDG uptake between malignant and inflammatory tissues, a delayed PET scan is expected to show higher lesion-to-background ratio and thus improve diagnostic accuracy. In addition, a change of ^{18}F -FDG uptake is thought to be useful in differentiating malignant from benign lesions. Several studies have shown that dual time-point PET is helpful not only in differential diagnosis but also in identifying additional lesions in some tumour types [22–24]. In breast cancer, Kumar et al [25] reported that the change of SUVs over

time was helpful in differentiating inflammatory lesions from malignant lesions. Another report on dual time-point PET showed that 3 h delayed PET images improved lesion detectability in breast cancer patients [12]. But few studies that evaluated the diagnostic role of dual-time-point PET for detection of regional lymph node metastasis have been reported. Ma et al [26] studied cervical cancer patients and reported enhanced sensitivity and specificity for paraaortic lymph nodes with the addition of 3 h delay ^{18}F -FDG PET scans. Another study of thoracic oesophageal cancer demonstrated improved performance of ^{18}F -FDG PET in local lymph node detection when dual time-point scans were used [27].

To our knowledge, there has been no evaluation of the usefulness of dual time-point PET in characterising ALN metastasis in breast cancer patients. In our study, the performances of the 1 h and 3 h PET/CT scans were identical in the detection of ALN metastasis, showing sensitivity of 60.3% and specificity of 84.7%. The 3 h PET/CT scan detected only one case that had no perceptible ^{18}F -FDG uptake on the 1 h scan, and this node was later confirmed to be negative for malignancy upon histological examination.

In addition, we computed the RI in 60 cases that showed perceptible ^{18}F -FDG uptake by ALN to see if the change in ^{18}F -FDG uptake with time can help differentiate metastatic from benign lymph nodes. A large proportion of ALN metastasis cases (68%) had a positive value for RI (Figure 2), but a significant percentage of node-negative patients (50%) also had positive RI value (Figure 3). Conversely, metastasis-positive ALNs can demonstrate negative RI values (Figure 4). So, RI was not a helpful tool in distinguishing between benign and metastatic ALN. ROC analysis for RI (95% CI = 42.0–77.9%) also demonstrated that this parameter was unsatisfactory for assessment of ALN metastasis. In addition, we examined whether the change in ^{18}F -FDG

Table 4. Performance of different cut-off values in the detection of axillary lymph node metastasis in cases with measurable standardised uptake value ($n=60$)

PET/CT criteria	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
SUVmax1 $\geq$ 1.0	90.9	62.5	83.3	87.0	71.4
SUVmax1 $\geq$ 1.1	80.6	87.5	88.3	95.1	73.7
SUVmax2 $\geq$ 1.1	88.6	68.8	83.3	88.6	68.8
SUVmax2 $\geq$ 1.2	86.4	81.3	85.0	92.7	68.4

NPV, negative predictive value; PPV, positive predictive value; PET, positron emission tomography.

Figure 2. A 52-year-old patient with a history of invasive ductal carcinoma of the right breast. (a) Focal ^{18}F -FDG uptake is present in right axilla (arrow) on 1 h positron emission tomography (PET), axial PET/CT fusion and coronal PET images (SUVmax1: 2.4). (b) The 3 h PET, axial PET/CT fusion and coronal PET images showed increased ^{18}F -FDG uptake (SUVmax2: 4.0). This axillary node was confirmed to contain a metastatic carcinoma. SUVmax, maximum standardised uptake value.

uptake in the primary tumour (RI of primary tumour) influenced the change in ^{18}F -FDG uptake in the ALN (RI of ALN). In cases where the RI of the primary tumour had a positive value, a large proportion of the ALN-positive group (50.8%) also showed a positive RI. The RI of the ALN tended to be helpful in distinguishing benign from metastatic nodes when the RI of the primary tumour had a positive value, but further study with a larger population is needed.

Compared with the recent study by van der Hoeven [9], our study showed greater sensitivity of ^{18}F -FDG PET

(60.3% *vs* 28%), although the proportion of T1 tumours (56% *vs* 53%) and the diagnostic criteria were similar (presence of perceptible ^{18}F -FDG uptake was regarded as positive for metastasis). The results of our study suggest that combined PET/CT may improve sensitivity compared with PET alone, as the CT portion of PET/CT makes the exact localisation of ^{18}F -FDG uptake possible. Past reports showed greater accuracy with PET/CT compared with PET alone in primary breast cancer [28, 29]. With regard to the T stage, the sensitivity of PET/CT for ALN was lower in T1 breast carcinomas than in T2 or T3

Figure 3. A 53-year-old patient who was diagnosed with medullary carcinoma in upper outer quadrant of left breast. (a) The 1 h positron emission tomography (PET) and PET/CT fusion images show faint ^{18}F -FDG uptake (SUVmax1: 1.0) in left axilla (arrow). (b) In 3 h PET and PET/CT fusion images, the ^{18}F -FDG uptake in previous lesion becomes more discrete and intense (SUVmax2: 1.9). Axillary lymph node dissection showed no evidence of malignancy in this lymph node. SUVmax, maximum standardised uptake value.

Figure 4. Dual time-point positron emission tomography (PET)/CT images of a 35-year-old left breast cancer patient. (a) The 1 h coronal PET and PET/CT fusion images demonstrate mild nodular ^{18}F -FDG uptake (SUVmax1: 1.8) in left axilla (arrow). (b) In the 3 h PET and PET/CT fusion images, the intensity of this lesion is decreased (SUVmax2: 1.6). Metastasis in this node was confirmed by post-operative histological examination. SUVmax, maximum standardised uptake value.

tumour cases in our study; a few other studies have reported similar results of relatively low ^{18}F -FDG PET sensitivity for ALN metastasis in tumour stage T1 patients [17, 19, 30].

All of the 29 patients later recognised to be false-negative on PET/CT also had either pre-operative ultrasonography or MRI for axillary node staging. Of these 29 patients, none showed abnormal MRI findings or the ultrasonography finding was suspicious for ALN metastasis except in 1 patient.

Most patients underwent PET/CT after pathological confirmation of breast cancer. The time interval between biopsy of primary tumour and PET/CT ranged from 0 to 44 days. Fine needle aspiration biopsy was performed on 71 patients and core needle biopsy on 95. Five patients underwent biopsy at an outside clinic where the biopsy procedure was not documented. Inflammation following biopsy procedure could be a cause of false-positive ^{18}F -FDG uptake in the ALNs.

Dual time-point PET/CT increases the image acquisition time and workload in processing the data, as well as the radiation dose. Although it has been reported that dual time-point PET provides additional information on primary breast cancer, this may not be true for ALN. Our study suggests that additional delayed ^{18}F -FDG PET/CT imaging might not be necessary for axillary staging in breast cancer patients: dual time-point PET/CT scans improved neither the sensitivity nor the specificity of the imaging.

The first of this study's limitations is that we cannot be sure that the axillary nodes detected on the PET/CT were the actual ones dissected and reviewed on histology. We assumed that PET-positive axillary nodes were surgically removed because the lymph nodes with perceptible ^{18}F -FDG uptake were usually larger than those without. Second, we did not evaluate the value of dual time-point PET according to size of lymph node. Small lymph node metastases may not have been perceptible on ^{18}F -FDG PET/CT because of the known limited spatial resolution of PET/CT currently used in clinical practice. In fact, only two nodes of less than 5 mm in diameter were PET-positive.

Conclusion

Dual time-point PET/CT imaging, relative to single-scan imaging, does not improve the performance of ^{18}F -FDG PET/CT in detecting ALN metastasis in known breast cancer patients.

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