Breast Cancer Res Treat (2014) 145:137–142
DOI 10.1007/s10549-014-2924-8

CLINICAL TRIAL

# Additional value of F-18 FDG PET/CT for initial staging in breast cancer with clinically negative axillary nodes

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Received: 5 March 2014 / Accepted: 17 March 2014 / Published online: 30 March 2014


**Abstract** The aim of this study was to evaluate the clinical impact of the preoperative $^{18}$F-FDG PET/CT in the initial workup of breast cancer with clinically negative axillary nodes. Whether the status of the clinical axillary nodal involvement can be considered a parameter for making a decision to omit the preoperative $^{18}$F-FDG PET/CT in the situation reported herein was also determined. A total of 178 patients who had newly diagnosed breast cancer and for whom the conventional diagnostic modalities showed no sign of axillary node metastasis were retrospectively enrolled in this study. All the patients underwent preoperative $^{18}$F-FDG PET/CT. The images and histologic results that were obtained were analyzed. $^{18}$F-FDG PET/CT detected primary lesions in 156 of the 178 patients, with an overall sensitivity of 87.6 %, and false negative results were obtained for 22 patients (12.4 %). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of $^{18}$F-FDG PET/CT in the detection of axillary nodes were 20.8, 86.9, 37.0, 74.8, and 69.1 %, respectively. Extra-axillary node metastasis was identified in two patients (1.1 %) who had internal mammary nodes. There was no distant metastasis, but coexisting primary tumor was detected in five patients (2.8 %). In total, the therapeutic plan was changed based on $^{18}$F-FDG PET/CT in seven (3.9 %) of the 178 patients, but considering only the cases confined to breast cancer, the change occurred in only two patients (1.1 %). $^{18}$F-FDG PET/CT almost did not affect the initial staging and treatment plan in breast cancer with clinically negative axillary node. If the axillary node is clinically negative in the preoperative workup of breast cancer, then $^{18}$F-FDG PET/CT can be omitted.

**Keywords** Breast cancer · Axillary node · Negative · F-18 FDG · PET/CT

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## Introduction

In breast cancer, accurate initial evaluation for the spread of the disease is important for prognostication and treatment selection [1]. For initial staging workup, many imaging modalities, such as chest plain radiography, mammography, breast ultrasonography (US), breast magnetic resonance imaging (MRI), and abdominal US or computed tomography (CT), are utilized [2]. $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) has been widely accepted in the oncologic clinical field and has particularly been shown to be a valuable tool in the evaluation of breast cancer. There have been many studies about the value of $^{18}$F-FDG PET or PET/CT in the preoperative evaluation of breast cancer [3–7]. These studies revealed that $^{18}$F-FDG PET or PET/CT is generally helpful but is particularly valuable in detecting extra-axillary nodal metastasis and occult distant metastasis in breast cancer. According to the National Comprehensive Cancer Network (NCCN) guidelines, $^{18}$F-FDG PET/CT is recommended in situations where the standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic diseases.

Today, due to the nationwide cancer screening program, the number of early-stage breast cancer cases has increased.

Moreover, among them, a significant number of patients have been diagnosed as having clinically negative axillary nodes through physical exam and conventional imaging modalities. As a node-negative status at diagnosis has commonly been associated with a favorable patient outcome, the prognosis of patients with breast cancer with clinically negative axillary nodes is predicted to be extremely good. Although the current guideline does not recommend $^{18}$F-FDG PET/CT in the evaluation for early-stage breast cancer, there have been many cases where this imaging study revealed unsuspected metastatic lesions regardless of cancer stage. Also, some studies that dealt with the performance of $^{18}$F-FDG PET/CT in early-stage breast cancer reported that this imaging modality had a role [8–12]. There has been no report, however, on the value of the preoperative $^{18}$F-FDG PET/CT in breast cancer with clinically negative axillary nodes, which is regarded as a disease with a very good prognosis.

The aim of this study was to evaluate the clinical impact of the preoperative $^{18}$F-FDG PET/CT in the initial workup of breast cancer with clinically negative axillary nodes. Whether the status of the clinical axillary nodal involvement can be considered a parameter for making a decision to omit the preoperative $^{18}$F-FDG PET/CT in the situation reported herein was also determined.

## Materials and methods

### Patients

From January 2010 to September 2013, 178 patients (mean age: 54.9 ± 9.8 years) who had newly diagnosed breast cancer as confirmed by fine needle aspiration or core need biopsy, and for whom the conventional diagnostic modalities, such as breast US or MRI, showed no sign of axillary lymph node metastasis, were enrolled in this study. All the patients underwent $^{18}$F-FDG PET/CT scan within two weeks before surgery. The patients with breast cancer who were diagnosed with excision or mammotome biopsy were excluded because of the volume reduction of the primary tumor. Mammography, breast and abdominal US, and chest X-ray were performed on all the patients, and most of the patients also underwent breast MRI.

All the patients had surgical treatment accompanied by sentinel node biopsy and/or axillary lymph node dissection. The chart and the medical data of each patient were reviewed retrospectively. All the subjects provided written informed consents.

### $^{18}$F-FDG PET/CT evaluation and image interpretation

All the $^{18}$F-FDG PET/CT examinations were performed using a Gemini 16 PET/CT (Philips, Cleveland, Ohio, USA) or a Discovery 710 PET/CT (General Electric Medical System, Milwaukee, USA) scanner. After fasting for at least 8 h, the patients were intravenously injected with 5.2 MBq/kg $^{18}$F-FDG. The serum glucose level prior to the radiotracer injection was less than 180 mg/dl in all the patients. PET/CT acquisition was started 60 min after the radiotracer injection. Helical CT scan was carried out with a rotation time of 0.5 s and at 120 kVp and 80–100 mAs, depending on the body weight, without an intravenous contrast agent. PET scan followed immediately, with the three-dimensional mode (7–9 beds, 2 min per bed). All the images were acquired from the skull base to the mid-thigh.

The PET/CT results were interpreted by two experienced nuclear medicine physicians using a dedicated workstation with custom software, first visually then semi-quantitatively, based on the maximum standardized uptake value (SUVmax). To calculate the SUVmax, a semi-automatically delineated spherical volume of interest was drawn over the primary breast cancer and abnormal focal $^{18}$F-FDG-avid lesion. A positive lesion was defined as a focal $^{18}$F-FDG-avid lesion higher than the mediastinal blood pool activity and related to the anatomical lesion on the corresponding CT.

### Histology

For all the primary breast cancer cases, histopathology was done as a routine management procedure using the surgically resected specimens. For the metastatic lesions, the histopathologic results were also used as the final standard. If tissue sampling was not possible or feasible, additional images or follow-up studies were used to evaluate the clinical significance of a positive lesion detected via $^{18}$F-FDG PET/CT.

### Statistical analysis

The correlation between the $^{18}$F-FDG avidity and the size of the tumor was evaluated using the SPSS software version 19.0 (SPSS Inc., Chicago, USA). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated using the standard methods. Statistical significance was defined as $p$ value $< 0.05$.

## Results

### Primary tumor

Invasive ductal carcinoma (IDC) was confirmed by histology in 145 patients (81.5 %), followed by ductal

**Table 1** Patient characteristics

| Characteristics | No. (%) |
|---|---|
| Age (years) | |
| Mean ± SD | 54.9 ± 9.8 |
| Range | 33–82 |
| Tumor size (cm) | |
| ≤1.0 | 38 (21.3) |
| >1.0, ≤2.0 | 70 (39.3) |
| >2.0, ≤5.0 | 64 (36.0) |
| >5.0 | 6 (3.4) |
| Axillary node metastasis | |
| Negative | 130 (73.0) |
| Positive | 48 (27.0) |
| Distant metastasis | |
| Negative | 178 (100.0) |
| Positive | 0 (0.0) |
| Histology | |
| Ductal | 145 (81.5) |
| Lobular | 11 (6.2) |
| DCIS | 12 (6.7) |
| Other | 10 (5.6) |
| FDG avidity of tumor | |
| Positive | 156 (87.6) |
| Negative | 22 (12.4) |
| Tumor SUVmax | |
| Mean ± SD | 6.2 ± 4.5 |
| Median | 4.8 |
| Axillary procedure | |
| SNB | 93 (52.2) |
| SNB + ALND | 71 (39.9) |
| ALND | 14 (7.9) |

*SD* standard deviation, *DCIS* ductal carcinoma in situ, *FDG* fluorodeoxyglucose, *SUVmax* maximum standardized uptake value, *SNB* sentinel node biopsy, *ALND* axillary lymph node dissection

carcinoma in situ (DCIS) in 12 patients (6.7 %), invasive lobular carcinoma in 11 patients (6.2 %), and others in 10 patients (5.6 %) (Table 1). $^{18}$F-FDG PET/CT detected primary lesions in 156 of the 178 patients, with an overall sensitivity of 87.6 %. The sensitivity according to the size of the tumor was as follows: 60.5 % (23/38) in stages T1a and T1b, 90.0 % (63/70) in stage T1c, 100.0 % (64/64) in stage T2, and 100.0 % (6/6) in stage T3. The mean SUVmax of the lesions was 6.2 ± 4.5, and the median value was 4.8. There was a significant correlation between tumor size and SUVmax ($r = 0.73$, $p = 0.03$).

A false negative result was obtained for 22 patients (12.4 %). The median size of the 22 unidentified lesions was 0.8 cm, and the range was 0.4–1.8 cm. The postoperative histology revealed IDC in 14 patients, ILC in 3, DCIS in 3, and others in 2.

**Table 2** FDG-avid axillary nodes

| | Pathologic metastasis | Pathologic no-metastasis |
|---|---|---|
| PET positive axillary node | 10 | 17 |
| PET negative axillary node | 38 | 113 |

*Sensitivity* 20.8 %, *specificity* 86.9 %, *PPV* 37.0 %, *NPV* 74.8 %, *accuracy* 69.1 %

**Table 3** Additional findings on 18F-FDG PET/CT

| Additional finding | Number |
|---|---|
| Internal mammary node metastasis | 2 |
| Thyroid cancer | 4 |
| Ovarian cancer | 1 |

## Axillary nodes

Among the 178 patients, 93 (52.2 %) and 14 (7.9 %) patients underwent only sentinel lymph node biopsy (SNB) or only axillary lymph node dissection (ALND), and 71 patients (39.9 %) underwent both SNB and ALND (Table 1). Abnormal $^{18}$F-FDG-avid axillary nodes were detected in 27 of the 178 patients on $^{18}$F-FDG PET/CT, and the histology confirmed metastases in 48 patients (27.0 %) (Tables 1, 2). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of $^{18}$F-FDG PET/CT were 20.8, 86.9, 37.0, 74.8, and 69.1 %, respectively (Table 2). Forty-three of the 48 metastatic axillary nodes were identified by SNB, and the other five axillary nodes were revealed only by ALND. There were micrometastatic axillary nodes in 12 of the 48 patients, and $^{18}$F-FDG PET/CT did not detect any micrometastatic axillary node.

## Extra-axillary nodes or distant organ metastasis

$^{18}$F-FDG PET/CT showed extra-axillary node metastasis in two patients (1.1 %) (Table 3; Fig. 1). These two patients had internal mammary node metastases, which were confirmed by the histology. There was no distant metastasis in the preoperative imaging studies, including $^{18}$F-FDG PET/CT and follow-up evaluation.

Incidental abnormal $^{18}$F-FDG-avid lesions were detected on $^{18}$F-FDG PET/CT in five of the 178 patients (2.8 %), consisting of thyroid cancer ($n = 4$) and ovarian cancer ($n = 1$) (Table 3, Fig. 1).

## Change in therapeutic plan

In total, the therapeutic plan was changed based on $^{18}$F-FDG PET/CT in seven (3.9 %) of the 178 patients; the field

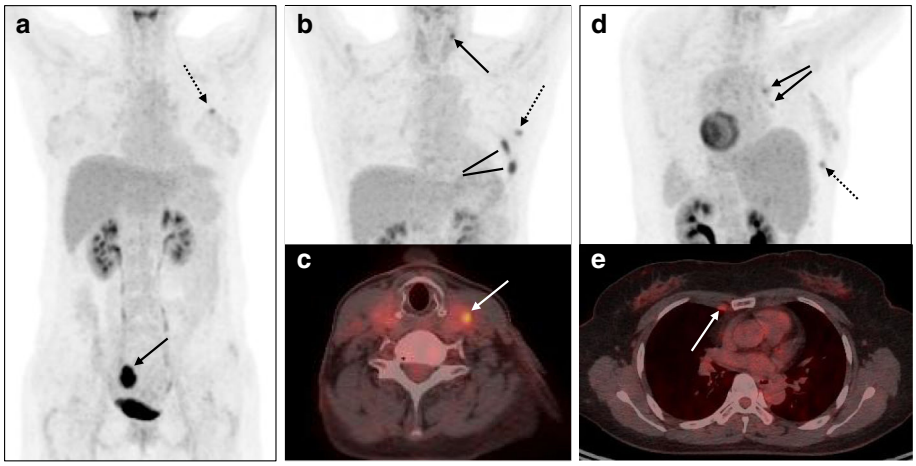


**Fig. 1** $^{18}$F-FDG PET/CT images of the patients with breast cancer. The maximum-intensity projection (MIP) (**a**, **b**) and the corresponding fusion image (**c**) showed the primary tumor of the breast (*dotted arrows*) and the coexisting malignancies (*solid arrows*) in the *right* ovary (**a**) and *left* thyroid gland (**b**, **c**). There was acute fracture in the *left* 6th and 7th ribs, showing hypermetabolism below the *left* breast tumor (*solid lines*, **b**). A *right* breast tumor (*dotted arrow*) and the metastatic nodes of the *right* internal mammary area (*solid arrows*) were also revealed in the MIP (**d**) and in the corresponding fusion image (e)

of radiation therapy was changed in two patients due to the nodal metastasis of the internal mammary area, and additional operations were done (thyroidectomy and ovariectomy) in five patients. Considering only the cases confined to breast cancer, change of therapeutic plan occurred in two patients (1.1 %) with metastasis in their internal mammary nodes.

## Discussion

Based on the recent guidelines, such as the NCCN guideline, the use of $^{18}$F-FDG PET/CT as a routine evaluation is not recommended in early-stage breast cancer. There is still a debate, however, about the value of $^{18}$F-FDG PET/CT in such situation [8–12], and it was reported that $^{18}$F-FDG PET/CT had a role in the staging of early-stage breast cancer. Garami et al. [12] reported that $^{18}$F-FDG PET/CT was able to assess the tumor size and axillary node metastasis more accurately than the traditional diagnostic imaging, and was also able to detect distant metastasis. Nevertheless, preoperative $^{18}$F-FDG PET/CT scanning in all the early-stage breast cancer situations cannot be justified because the absolute benefit was unclear. In breast cancer, axillary nodal involvement was generally considered a parameter of prognosis and tumor chronology [13]. Thus, it was thought that clinical axillary nodal involvement could be a simple and reliable decision-making factor for omitting preoperative $^{18}$F-FDG PET/CT in breast cancer.

In the present study, the overall sensitivity of $^{18}$F-FDG PET/CT in detecting primary tumor was 87.6 %, which was slightly lower compared to that reported by the previous studies [4, 7, 11, 12]. Such studies pointed out that the accuracy of $^{18}$F-FDG PET/CT was affected by the tumor size. This finding was in close agreement with that of this study. $^{18}$F-FDG PET/CT detected all the primary tumors larger than 2 cm in size, whereas only 60.5 % of the tumors smaller than 1 cm were revealed. Also, the SUVmax and tumor size were significantly correlated ($r = 0.73$, $p = 0.03$). Despite the improvement of the sensitivity and resolution of the recent PET/CT system, there still existed a problem in the detection of small lesions in breast cancer. As in the present study, it is likely that the tumor size of breast cancer with negative axillary nodes is small. In this study, breast US or MRI was able to identify all the primary tumors. Although it could not be said that the overall sensitivity of $^{18}$F-FDG PET/CT is not good, it was shown not to be good enough to replace the conventional methods of detecting primary tumors in breast cancer without axillary node involvement.

The presence of axillary node metastasis is an important factor for correct staging and for making an appropriate breast cancer therapeutic plan. Even though the axillary node was clinically negative, metastatic axillary nodes were confirmed in 48 cases (27.0 %) through pathology, which was similar to the results of the previous studies [8, 14]. In this study, $^{18}$F-FDG PET/CT detected metastatic axillary nodes in ten subjects (20.8 %), which were not identified in the conventional study. This result suggested the possibility that $^{18}$F-FDG PET/CT is a valuable method compared with the conventional exams, but its 20.8 % sensitivity and 86.9 % specificity were still too low to make it a reliable method. Especially, $^{18}$F-FDG PET/CT

could not detect any micrometastatic axillary node because of the small volume of tumor cells to be detected. Several studies reported that because $^{18}$F-FDG PET/CT has high specificity and a positive predictive value, the patient with $^{18}$F-FDG-avid axillary nodes should have ALND rather than SNB [4, 5, 7, 14]. In the present study, however, the specificity and positive predictive value were not very high (86.9 and 74.8 %, respectively). A possible explanation of this is that the present study involved relatively many cases of early tumor stage below T1c, and micrometastatic nodes. Among the patients who performed SNB only or SNB followed by ALND (164/178, 92.1 %), SNB identified all the metastatic axillary nodes. This result indicates that $^{18}$F-FDG PET/CT has limitations in detecting axillary node metastasis, and that SNB cannot be omitted in breast cancer with clinically negative axillary nodes.

Extra-axillary nodal status or distant metastasis are very crucial factors in determining the appropriate treatment plan in breast cancer, and many studies reported that $^{18}$F-FDG PET/CT showed value in assessing the disease status [5, 7, 15, 16]. In this study, metastatic nodes of the extra-axillary area were detected in two patients (1.1 %) via $^{18}$F-FDG PET/CT. The patients had metastatic nodes in the internal mammary area, which led to a change in nodal staging from N0 to N2, and additional radiation therapy was conducted, including the field of IM nodes. There was no distant metastasis, however, in all the cohorts of this study. The previous studies reported that $^{18}$F-FDG PET/CT identified IM nodal metastasis in 25 % of the patients, including those with stage I–IV breast cancer [15] and 8–10 % of the patients with early-stage breast cancer [11, 17]. Also, distant metastasis was detected at the diagnosis in range of 8–14 % in locally advanced breast cancer [5], and 5–8 % in early-stage breast cancer [4, 11, 12]. This study indicated that extra-axillary diseases, including distant metastasis, are extremely rare in patients with breast cancer with clinically negative axillary nodes. Although $^{18}$F-FDG PET/CT showed good performance in the detection of extra-axillary lesions even in early-stage breast cancer, the clinical impact was thought to be small due to the rarity of the disease.

In the present study, the treatment plan was changed by adding $^{18}$F-FDG PET/CT in seven (3.9 %) of the 178 patients with breast cancer with clinically negative axillary nodes. Two patients, as mentioned earlier, had metastasis of the extra-axillary nodes, and five patients had synchronous cancers (four had thyroid cancer and one had ovary cancer) and subsequently underwent an additional operation. It is well known that cancer patients have a high incidence of other primary malignancies [18]. It was true that $^{18}$F-FDG PET/CT gave a definite benefit to these five patients by detecting the coexisting primary tumor in the earlier stage. Considering only the cases confined to breast cancer, however, the treatment was changed in only two patients (1.1 %) who had metastasis of the extra-axillary nodes. Several studies showed an $^{18}$F-FDG PET/CT-modified treatment plan in breast cancer, and treatment modification in 8–16 % of the study subjects even in early-stage breast cancer [10–12]. This study revealed that the frequency of change of treatment plan was very low in breast cancer even if $^{18}$F-FDG PET/CT was added to the preoperative workup.

Although there is still a debate on the role of preoperative $^{18}$F-FDG PET/CT in early breast cancer, considering all the factors mentioned above, it seems that $^{18}$F-FDG PET/CT had no significant value as a preoperative study in breast cancer with clinically negative axillary nodes. It was thought that in the situation of the clinically negative axillary nodes, the conventional breast US or MRI and SNB are sufficient preoperative methods for evaluating the primary tumor and axillary node, respectively, and $^{18}$F-FDG PET/CT can be skipped because of the rarity of extra-axillary metastasis. It is difficult to set a factor as a criterion for skipping any test in a clinical situation, but the clinical status of the axillary nodes can be a factor for deciding whether to perform $^{18}$F-FDG PET/CT in the preoperative evaluation of breast cancer or not. Further study is needed, however, to validate this as the present study had limitations. Several factors can affect the $^{18}$F-FDG avidity of a tumor [19], but in this study, not all the histopathologic factors were evaluated. As the dominant patients had breast cancer with IDC, however, the histologic type was relatively homogeneous.

In conclusion, the study results revealed that $^{18}$F-FDG PET/CT almost did not affect the initial staging and treatment plan in breast cancer with clinically negative axillary nodes. Thus, if the axillary nodes are clinically negative in the preoperative workup of breast cancer, then $^{18}$F-FDG PET/CT can be omitted.

**Acknowledgments** This work was supported by the Dong-A University research fund.

**Conflict of interest** The authors declare that they have no conflict of interest

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