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Assessment of multifocality and axillary nodal involvement in early-stage breast cancer patients using 18F-FDG PET/CT compared to contrast-enhanced and diffusion-weighted magnetic resonance imaging and sentinel node biopsy

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Abstract

Background: Non-invasive evaluation of the extent of axillary nodal involvement in early-stage breast cancer (ESBC) patients and accurate assessment of multifocality are both challenging. Few reports have explored whether 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) might be more useful than other diagnostic methods in these contexts.

Purpose: To prospectively evaluate the diagnostic utility of FDG PET/CT, contrast-enhanced, and diffusion-weighted magnetic resonance imaging (DCE-MRI and DWI), and sentinel lymph node biopsy (SNB), in detection of axillary metastatic lymph nodes in ESBC patients; and to explore the utilities of FDG PET/CT and DCE-MRI for identification of multifocality.

Material and Methods: Twenty-four female patients (mean age, 47 ± 9.9 years; range, 24–68 years) with ESBC underwent whole-body FDG PET/CT and breast MRI prior to operation. SNB and axillary lymph node dissection (ALND) were performed on all patients, as was mastectomy or wide local tumor excision. Histopathological findings served as the gold standard when evaluating either multifocality or axillary nodal involvement.

Results: The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy, of PET/CT and DCE-MRI, used to detect multifocality, were as follows: 67% *versus* 78%, 100% *versus* 53%, 100% *versus* 50%, 83% *versus* 80%, and 88% *versus* 63%. SNB afforded the highest sensitivity (93%) in terms of detection of axillary metastasis. The sensitivity, NPV, and accuracy of PET/CT were 67%, 62%, and 75% respectively, thus higher than the equivalent values of either DCE-MRI or DWI.

Conclusion: For assessment of multifocality in ESBC patients, highly specific results of PET/CT should be taken into account along with DCE-MRI findings. For evaluation of axillary nodal involvement, PET/CT has higher sensitivity, NPV, and accuracy values than DCE-MRI and DWI and may guide a surgical decision to proceed or not to SNB or ALND.

Keywords

Breast, magnetic resonance diffusion/perfusion, PET, magnetic resonance imaging (MRI)

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Introduction

Early-stage breast cancer (ESBC) patients are candidates for primary surgery if conventional diagnostic and clinical work-up reveal that such patients do not have distant metastases or an extensive lymphatic spread. Advanced imaging methods including 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) and brain magnetic resonance imaging (MRI), have traditionally not been used to assess such patients, because the frequency of distant metastases in ESBC is very low. However, the latter techniques have become increasingly applied in recent years (1).

The extent of multicentricity of all breast malignancies has been reported to be 14–47% (2). Achieving a reduction in the number of re-excisions and avoidance of local recurrence caused by residual disease remains challenging in ESBC patients. Dynamic contrast-enhanced MRI (DCE-MRI) has been suggested to afford optimal accuracy when used to detect multifocality and contralateral synchronous tumors (and also when used to accurately measure primary tumor size), compared to conventional imaging methods including mammography and ultrasonography (US). Breast DCE-MRI is often used when breast-conserving surgery is planned (3). Diffusion-weighted imaging, a magnetic resonance technique showing the restriction of the movement of water molecules in tumoral tissues, has been recently reported to be effective in the diagnostic work-up of breast cancer (4–7).

Axillary lymph node metastasis is an important factor for predicting both breast cancer recurrence and patient survival. In many previous studies, non-invasive imaging modalities – including US, FDG-PET, and MRI – proved to be inadequate when used in attempts to accurately gauge axillary involvement (8). Sentinel lymph node biopsy (SNB) has recently become a popular method used to accurately detect axillary nodal metastasis in a manner that is less invasive than axillary lymph node dissection (ALND). However, the false negative frequency of SNB data has been reported to be as high as 15% (8). Also, the procedure is invasive with associated complications and morbidity. On the other hand, it has been recently asserted that surgical approaches to the axilla, using either SNB or ALND to detect micrometastases or isolated tumor cells, did not compromise the overall survival of ESBC patients (3).

FDG PET/CT is not routinely used to evaluate ESBC patients although some reports have claimed that PET/CT can play a useful role in detecting unexpected distant metastases, with respectable specificity. Further, selective SNB scheduling based on FDG PET/CT imaging data might enhance the accuracy of SNB results and reduce the number of unnecessary invasive procedures (9–12).

In the present prospective study, we sought to analyze the possible contribution of FDG PET/CT in the preoperative evaluation of multifocality and axillary nodal involvement in patients clinically diagnosed with ESBC by comparing FDG PET/CT data with those derived from DCE-MRI, DWI, and SNB. Although our patient series was small, our present study is, to our knowledge, the first to compare the four modalities directly and prospectively in the same group of patients.

Material and Methods

Patients

Between January 2012 and March 2013, 24 consecutive patients with ESBC (diagnosed via clinical examination, US, and mammography of the breast and axilla) were prospectively enrolled in the present study. Invasive breast carcinoma was identified in each patient via either fine needle or core biopsy. All patients were female and the mean age was 47 ± 9.9 years (range, 24–68 years).

ESBC was defined as stage I or II disease, with T1- or T2-grade tumors and N0–N1 lymph node involvement, respectively. Patients with locally advanced or metastatic disease were excluded from the study. All patients underwent PET/CT and breast MRI examinations within a 2-week period and were operated upon within 1 month of diagnosis. The study was approved by our local Ethics Committee.

PET/CT examination

All patients underwent FDG PET/CT imaging using a high-resolution PET scanner fitted with an integrated 16-slice multidetector CT (Biograph PET/CT; Siemens, Chicago, IL, USA). Prior to FDG injection, blood sugar levels were measured in well-hydrated patients who had fasted for at least 4 h prior to their scheduled PET/CT sessions. FDG (296–703 MBq) was intravenously administered to patients whose blood sugar levels were below 150 mg/dL. After injection, patients were allowed to rest in a quiet comfortable room for 60 min to allow complete FDG biodistribution. Next, each patient emptied the urinary bladder and was instructed to assume a supine position on the PET/CT scanner bed. PET scans were acquired using seven to eight bed positions, with 3–4 min of total acquisition time per position, commencing from the vertex and proceeding to the upper thigh. PET/CT images were visually and semi-quantitatively assessed by two experienced nuclear medicine physicians who were not blinded to the findings of US, mammography, or biopsy. For semi-quantitative analysis, a region of interest was carefully drawn around any site of increased FDG uptake and the maximum standardized uptake value (SUVmax) of each lesion was used in calculation. The SUVmax values were not considered when multifocality and axillary nodal involvement were assessed; visual evaluation alone was performed. Both apparent and suspected FDG accumulations were considered to be positive.

MRI procedure

All MRI scans were obtained using a 1.5-T MR unit (Avanto; Siemens, Erlangen, Germany) fitted with a dedicated four-channel bilateral breast coil. Imaging commenced with acquisition of axial scout images. Next, conventional axial T1-weighted (T1W) (TR/TE), T2-weighted (T2W) (TR/TE), and TRIM and diffusion-weighted images (at b values of 50, 400, and 800 mm^2/s), were obtained. To obtain contrast-enhanced sequences, Gadobutrol (Gadovist, Bayer Schering Pharma AG, Berlin, Germany) was injected at a dose of 0.1 mmol/kg body weight. Six sequential fat-suppressed 3D T1W images were obtained both before and after injection of contrast medium, and pre-injection data were subtracted from post-injection information. MRI interpretation was performed by a single experienced radiologist who specialized in breast radiology. Both the morphological features of lesions, and the contrast-enhancement patterns, were evaluated; apparent diffusion coefficients (ADCs) were measured in the enhanced regions of lesions.

Operations and histopathology

Surgical treatment was either wide local excision of the tumor, or mastectomy, accompanied by SNB and ALND. Histopathological findings were regarded as the gold standard for assessment of multifocality and axillary node metastasis.

Statistical analysis

For assessment of multifocality, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of both FDG PET/CT and DCE-MRI data were analyzed by reference to the histopathological results. The same parameters were used to explore the diagnostic utilities of PET/CT, DCE-MRI, DWI, and SNB for detection of axillary nodal involvement, with the ALND test results being regarded as the gold standard.

Results

Primary tumors and multifocality

Tumor sizes were evaluated pathologically. Five lesions were of grade T1 (diameter range, 1–1.8 cm) and 19 of grade T2 (diameter range, 2.3–4 cm). T-stage was not changed after operation in any of the cases when compared to the measurements of DCE-MRI and PET/CT. Invasive ductal carcinoma was diagnosed in 19 patients (79%). Five patients were diagnosed with other types of invasive carcinomas; these were invasive lobular carcinoma ($n = 1$), invasive cribriform carcinoma ($n = 1$), invasive papillary carcinoma ($n = 2$), and invasive micropapillary carcinoma ($n = 1$). The mean SUVmax of all lesions was 7.4 ± 4.1 (range, 1.2–20.9).

Multifocality was pathologically evident in nine patients (38%). All six patients in whom multifocality was detected by PET/CT were also positive in pathological terms. One patient exhibited both multicentricity and multifocality in all four quadrants; this was also evident on MRI. Three patients yielded false negative results by PET/CT. On DCE-MRI, multifocality was observed in 14 patients, but seven were false positive; pathological analysis revealed fibrocystic changes in areas that had been defined as tumor foci. Two patients were false negative by MRI. The sensitivity, specificity, PPV, NPV, and accuracy of PET/CT and MRI for detection of multifocality were: 67 *versus* 78%, 100 *versus* 53%, 100 *versus* 50%, 83 *versus* 80%, and 88 *versus* 63%, respectively (Figs. 1 and 2).

Axillary nodal involvement

In 15 of 24 patients (63%), axillary nodal involvement was evident by pathological examination after ALND. Micrometastases were detected in two patients. The diameters of the lymph nodes in the other 13 patients were 0.5–3.5 cm. SNB, performed on each patient prior to ALND, discovered metastases in 14 patients, but in one patient a micrometastasis was not identified by SNB. Upon PET/CT examination, metastases to the axillary lymph nodes were evident in 11 patients, but one was a false positive. PET/CT did not detect metastases in five patients with axillary involvement. Two of these five patients had micrometastases and the involved lymph nodes of the remaining three patients were less than 1 cm in diameter. DCE-MRI and DWI also failed to detect these lymph node metastases. Upon data review, no positive indications were evident in the US or mammographic scans of these patients. DCE-MRI identified nine involved lymph nodes, but two of these were false positive. DCE-MRI yielded false negative results in eight patients. All six patients in whom DWI defined metastatic lymph nodes were truly positive. However, in nine patients, DWI did not detect

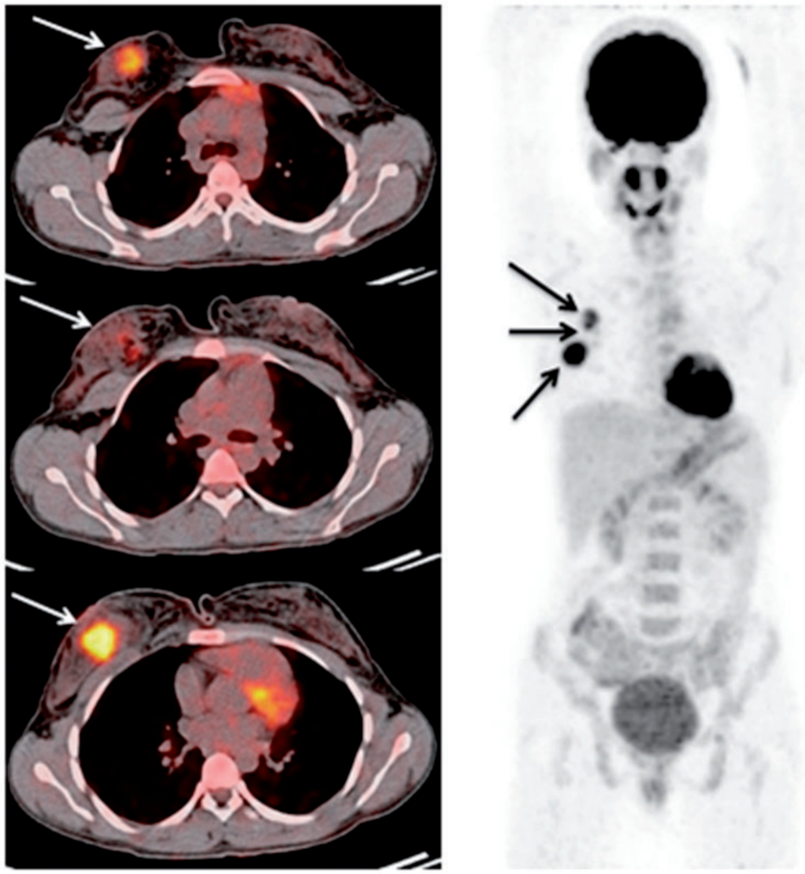

Fig. 1. PET/CT images of a patient with early-stage invasive ductal carcinoma of breast. Multifocality was observed (axial fused images on the left side and MIP image on the right side, arrows) and no metastatic lymph node was detected in the axilla in PET/CT. The findings were consistent with the pathology.

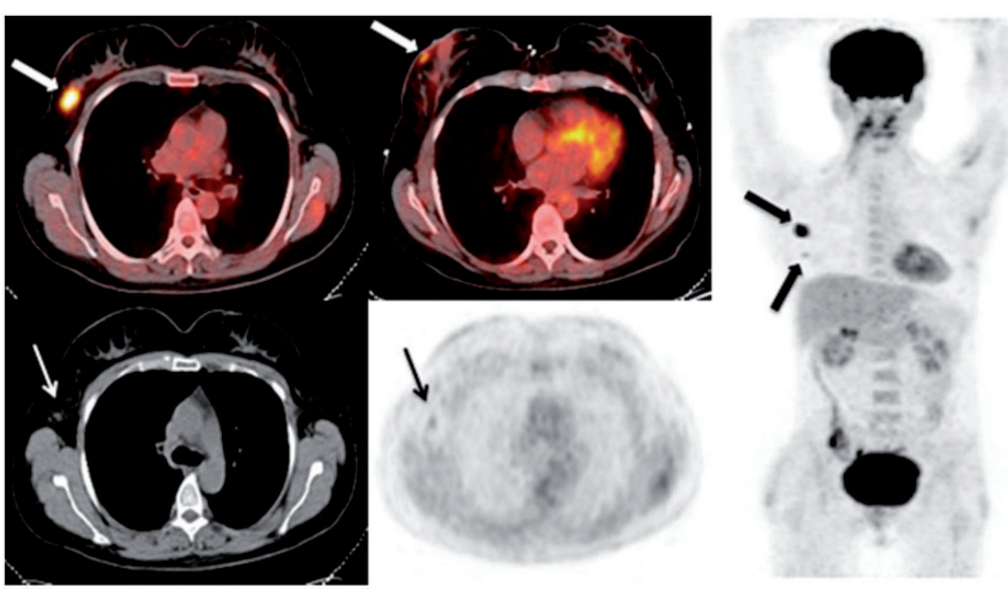

Fig. 2. Multifocal invasive ductal carcinoma in the right breast (upper row fused images and MIP image on the right side, thick arrows). In the right axilla there was a small lymph node with moderate FDG uptake that was evaluated as positive for metastasis (bottom row CT and PET images, thin arrows). Contrast-enhanced and diffusion-weighted MRI could not detect this lymph node, however pathology confirmed the metastasis.

Table 1. The diagnostic utilities of four methods in detecting axillary lymph node metastasis regarding the axillary lymph node dissection as the gold standard.

	Sensitivity	Specificity	PPV	NPV	Accuracy
SNB	93%	100%	100%	90%	96%
PET/CT	67%	89%	91%	62%	75%
DCE-MRI	47%	78%	78%	47%	58%
DWI	40%	100%	100%	50%	63%

DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; DWI, diffusion-weighted imaging; NPV, negative predictive value; PET/CT, positron emission tomography/computed tomography; PPV, positive predictive value; SNB, sentinel lymph node biopsy.

involved lymph nodes. By reference to ALND as the gold standard, the sensitivity, specificity, PPV, NPV, and accuracy of SNB, PET/CT, DCE-MRI, and DWI were as shown in Table 1 (Figs. 2 and 3).

Discussion

In the present study, we explored the utility of PET/CT imaging to assess tumor multifocality and multicentricity, and axillary lymph node involvement in patients with ESBC.

Although the sensitivity of DCE-MRI was slightly higher than that of PET/CT in terms of multifocality detection, both the specificity and PPV of PET/CT were significantly higher than those of DCE-MRI. Accurate assessment of multifocal/multicentric disease can help a surgeon decide on the optimal type of resection required to ensure long-term disease-free survival. Conventional methods such as mammography and US may be inadequate when used to evaluate the exact size and degree of extension of a tumor in breast tissue. Breast MRI is now more frequently used for T-staging, and to define tumor multifocality and multicentricity, than was hitherto the case. One prospective study found that evaluation of MRI data triggered changes to the prior management plans of 44.4% of patients, and increased the number of mastectomies by 26.8% (2). Garami et al. conducted one of the few studies of a possible role for FDG PET/CT in evaluation of tumor extension, and reported that the PET/CT sensitivity in terms of detection of multifocality was significantly higher than those of the traditional diagnostic modalities as US and mammography, by 100% and 43.8%, respectively (11). In another study, PET/CT revealed previously unsuspected multifocal disease in seven of 70 patients (12). Our results emphasize that PET/CT affords a higher specificity, PPV, and accuracy, compared to DCE-MRI, when used to detect multifocal disease.

The utility of searching for axillary metastases in clinically node-negative ESBC patients remains controversial. The widespread introduction of mammographic screening programs has triggered detection of small tumors without lymph node involvement in more than 60% of patients (3). As ALND is associated with several well-known problems including lymphedema, pain, and limitation of shoulder movement, ALND has been replaced by SNB when patients considered to be node-negative after clinical and US examination are to be further evaluated. Several studies have validated the use of SNB compared to ALND (the gold standard) (3). In our present study, SNB afforded the highest sensitivity, specificity, PPV, NPV and accuracy, when used to detect axillary nodal metastasis, in agreement with the data of previous studies. SNB yielded a false negative result in only a single patient; a micrometastasis was found with the aid of ALND.

However, some recent studies suggest that surgical management of the axilla using either SNB or ALND does not affect the duration of either recurrence-free or overall survival of ESBC patients (3,13). Further, any prognostic significance of isolated tumor cells (ITCs) and micrometastases detected in ESBC patients is arguable. A recent study found that the 5-year disease-free survival rates did not differ significantly between node-negative patients and those with micrometastases and ITCs in the axillary lymph nodes (14). Thus, even SNB may be considered to be an ‘overtreatment’, considering the morbidity associated with this invasive procedure. Identification of a non-invasive and effective imaging method that enables accurate evaluation of axillary nodal status is needed for optimal treatment of ESBC patients.

In several studies of the utility of FDG PET/CT in detection of axillary nodal involvement in clinically node-negative patients, the sensitivity was in the range of 25–50%, similar to that of US used to detect axillary node metastases (9,15). In our present study, the sensitivity of PET/CT employed to detect axillary nodal metastasis was 67%. Although this figure is higher than most of those reported previously, the sensitivity remains low in comparison to that of SNB. In five patients in whom PET/CT axillary data were negative, two had micrometastases and the other three metastatic lymph nodes less than 1 cm in diameter. The low spatial resolution of PET became evident in such circumstances. However, upon comparison with two other promising imaging methods, DCE-MRI and DWI, PET/CT afforded the highest sensitivity, NPV, and accuracy values.

Previous studies suggested that PET/CT plays a role in guiding axillary sampling and, if PET data were positive, SNB might be omitted, and ALND immediately scheduled (16). The accuracy of selective SNB and

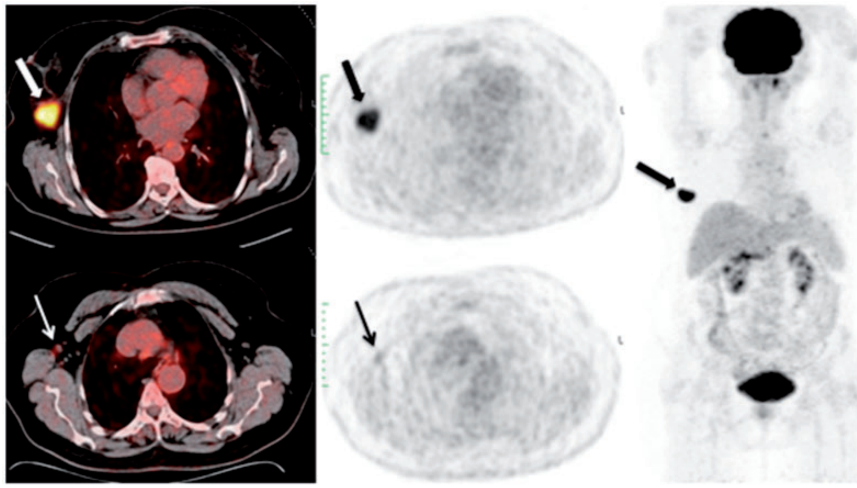

Fig. 3. False positive of PET/CT. The primary lesion was detected on the outer part of right breast (upper row axial fused and PET images and on the right side MIP-image, thick arrows). A lymph node with mild FDG uptake about 1 cm in diameter was reported as metastatic (bottom row axial fused and PET images, thin arrows), however there was no evidence of metastasis to the axillary lymph nodes in pathology.

additional non-sentinel node biopsy tests, based on FDG PET/CT findings, was 98.2% in one study (9).

A large meta-analysis of studies using FDG-PET, PET/CT, or MRI to (separately) assess axillary nodal involvement showed that the mean sensitivity of MRI was significantly higher than that of FDG-PET. However, no study has yet directly compared two imaging methods using the same group of patients, and the MRI techniques used in earlier reports varied (for example, in terms of the contrast material employed) (17). In another study reviewing data on patients with T1-stage breast cancer who had undergone preoperative US, DCE-MRI, and FDG PET/CT, DCE-MRI afforded the highest sensitivity when used to detect axillary involvement. However, the observed differences in sensitivity were not significant, and PET/CT afforded the highest specificity, PPV, and accuracy (18). Some of our results differ from those of previous studies. Not only the specificity, PPV, NPV, and accuracy, but also the sensitivity, of DCE-MRI, was lower than those of PET/CT (47% *vs*. 67% for sensitivity, respectively).

DWI is an emerging technique used to discriminate benign from malignant lesions. In a very recent study, the sensitivity, specificity, and accuracy of DWI were 100%, 83.3%, and 93.6%, respectively (all higher than those afforded by US), for detection of axillary node metastasis in breast cancer patients (5). Heusner et al. performed one of the few studies comparing the utilities of FDG PET/CT and DWI in the same group of patients. Twenty patients with breast cancer underwent whole-body PET/CT and whole-body DWI. DWI was highly sensitive but rather unspecific when used to identify whole-body tumor involvement (6). Our results were quite different. We expected DWI to exhibit high sensitivity but poor specificity; we in fact observed the opposite. The most likely reason may be that the low tumor cell burden in the lymph nodes of our ESBC patients rendered DWI-mediated detection difficult.

The principal limitation of our study was the small number of patients. Statistical analysis would (obviously) become more robust if larger numbers of ESBC patients, examined using the various imaging modes that we have discussed, were analyzed. Also, the use of contrast-enhanced fully diagnostic PET/CT might improve the detection sensitivities of both multifocality and axillary small lymph node metastases.

In conclusion, when ESBC multifocality is to be explored, DCE-MRI does indeed offer a slightly better sensitivity than FDG PET/CT. However, the specificity of the former modality is rather poor, being less than half that of PET/CT. Thus PET/CT data should be considered before aggressive surgery is scheduled. In terms of evaluation of axillary nodal status, SNB remains the most sensitive and accurate means of detecting axillary lymph node metastasis in ESBC patients. However, of the available non-invasive imaging methods, we suggest that FDG PET/CT is more sensitive and accurate than both DCE-MRI and DWI in this regard, and FDG PET/CT data can guide a decision to schedule selective SNB and/or ALND.

Conflict of interest

None declared.

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