The diagnostic value of PET/CT in recurrence and distant metastasis in breast cancer patients and impact on disease free survival

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Abstract  Aim of work: To detect the diagnostic value of PET/CT in breast cancer patients. We compared the performance of PET/CT with that of conventional imaging in detection of recurrence and distant metastasis and evaluated the impact PET/CT results have on disease free survival.

Materials and methods: We retrospectively studied 50 patients with breast cancer with clinical suspicion of recurrent or metastatic lesion and who underwent PET/CT and conventional imaging procedures. The imaging results were retrospectively compared with histopathology and clinical follow-up as a reference standard.

Results: PET/CT detected distant metastases with a sensitivity of 97% and a specificity of 93%. In contrast, the sensitivity and specificity of combined conventional imaging procedures were 75% and 73%, respectively, disease-free survival was significantly shorter in the 34 M1-PET/CT patients than in the 14 M0-PET/CT patients (log-rank \( P = 0.002 \)) also PET/CT detected recurrence in 1 patient with equivocal mammographic findings.

Conclusion: In breast cancer, PET/CT is superior to conventional imaging procedures for detection of recurrence, distant metastases and PET/CT can be used to improve prediction of the clinical outcome of breast cancer patients.

1. Introduction

Breast cancer is the most frequent malignancy in women. Follow-up for the early detection of recurrence is important because the 5-y survival of patients with disseminated disease is significantly shorter than that of those who have only regional disease. The availability of various new therapies for relapsing breast cancer makes early detection as well as determination of the extent of disease and its precise localization of utmost importance (1).
Improved screening and treatment strategies for breast cancer have contributed to a significant decrease in breast cancer-related mortality over the past 20–30 years. Breast conserving surgery (BCS) with radiation results in survival outcomes similar to those of mastectomy with local recurrence in the ipsilateral breast of 6–9% at 5 years and 14–20% at 20 years. Early detection of asymptomatic local recurrence via appropriate surveillance techniques, including breast imaging, improves long-term survival when compared to late symptomatic detection. Therefore sensitive, non-invasive, and cost-effective surveillance strategies to detect early local recurrence are necessary.

In breast cancer, the role of PET is not clearly defined. Several efficient imaging tools including mammography, magnetic resonance imaging (MRI), bone scans (BS) and CT scans are widely available, making the implementation of yet another modality a challenging process. Published data suggest that PET is not reliable in evaluating the primary tumor or accurately staging the axillary disease. In primary staging, PET has been shown to be inferior to conventional imaging because of its low accuracy and its association with noticeable numbers of false-negative results.

However, recent literature suggests that PET/CT is appropriate for restaging of breast cancer patients with documented or suspected recurrent breast cancer. It accurately detects abnormal extra-axillary lymph nodes, detects distant metastases, and often demonstrates recurrent and/or distant disease prior to conventional imaging modalities. Evaluation of breast cancer patients with 18FDG PET or 18FDG PET–CT allows for survey of the chest, abdomen and bones in a single examination with both anatomic and metabolic information useful in the staging, restaging and assessing for therapeutic response. In the setting of asymptomatic patients with rising tumor markers the use of PET/CT may result in early detection of disease and a significant change in management.

In a recent prospective study involving locally advanced or inflammatory breast cancer patients, 18FDG PET–CT outperformed conventional imaging for the detection of bone and liver metastasis as well as distant lymph node involvement leading to a change in clinical stage in 61 of 117 patients (52%) (4). NCCN guidelines suggest the following for staging evaluation of women with recurrent or metastatic breast cancer: diagnostic chest CT, bone scan, and radiographs of painful long bones or those with abnormal appearance. CT of the abdomen with or without the pelvis may also be considered for restaging. PET/CT is considered an optional modality in this setting and should be considered in situations where standard imaging results are equivocal or suspicious.

In this retrospective study, we aimed to detect the diagnostic value of PET/CT in breast cancer patients. We compared the performance of PET/CT with that of conventional imaging in detection of recurrence and distant metastasis and examined the impact PET/CT results on survival.

2. Materials and methods

2.1. Patients

This retrospective study includes 50 eligible female patients with a history of breast cancer. This study was done from August 2011 to December 2013. The diagnosis was based on clinical examination, bilateral mammography and ultrasonography of the breast and axilla and it was biopsy-confirmed in all patients. All patients underwent conventional imaging studies and PET/CT to search for recurrence or distant metastases.

Exclusion criteria were patients whose information was incomplete or where PET/CT images were unavailable, other exclusion were diabetes mellitus, pregnancy, and patients younger than 18 year.

All patients gave written informed consent to review their medical studies according to ethics committee guidelines.

2.2. Treatment

Treatment consisted of neoadjuvant chemotherapy, followed by surgery, loco-regional radiotherapy, and hormonal therapy according to the subtype of breast cancer.

2.3. Follow up

For follow up: regular history, physical examination, and mammography were recommended, physical examinations should be performed every 3–6 months for the first 3 years, every 6–12 months for years 4 and 5, and annually thereafter. For women who have undergone breast-conserving surgery (mastectomy), a post-treatment mammogram should be obtained 1 year after the initial mammogram and at least 6 months after completion of radiation therapy. If indicated, a yearly mammographic evaluation should be performed. The use of complete blood counts, chemistry panels, bone scans, chest radiographs, liver ultrasounds, pelvic ultrasounds, computed tomography scans, [18F] fluorodeoxyglucose–positron emission tomography scans, magnetic resonance imaging, and/or tumor markers (carcinoembryonic antigen, CA 15-3, and CA 27.29) is not recommended for routine follow-up in an otherwise asymptomatic patient with no specific findings on clinical examination.

The follow up period ranged between 6 months and 36 months with a median of 14 months.

2.4. Methods

2.4.1. Conventional imaging

Conventional studies to detect recurrence or distant metastasis were performed according to routine practice in our institution and consisted of bone scanning, chest examination by X-ray and contrast enhanced CT scan and abdomeno-pelvic examination by ultrasonography or contrast-enhanced CT.

In this study, 14 patients had bone scan, 14 patients had chest radiography; 7 patients had CT of the chest; 2 of them had high resolution CT scan, 13 patients had abdominal ultrasound, and 12 patients had CT of the abdomen and pelvis. Conventional imaging was performed within 1 month preceding the PET/CT scan (mean, 14 days; range, 5–33 days).

2.4.2. PET/CT

All patients were imaged with a dedicated PET–CT scanner (Siemens, Biograph-2). All patients were fasted for at least 6 h before FDG injection. Fasting blood glucose level of less than 150 mg/dl was a requirement in all patients. The scan started 60 min after intravenous administration of 2.516 MBq (0.068 mCi/kg)
FDG, during this period, the patient was instructed to rest without talking. CT was performed from the skull base to pelvis by performing a scout view followed by a spiral CT with 80 mA, 140 kVp. No oral contrast was given, and water only was used to delineate bowel. Intravenous 130 ml of iohexol (Omnipaque 300 mg iodine/ml) was administered. On completion of CT, 2D PET emission data (4 min per bed position covering an axial FOV of 15.7 cm with a 3-slice overlap) were obtained. The total scanning time varied between 25 and 30 min for every patient. The CT, PET and PET/CT images were reconstructed in trans-axial, coronal and sagittal planes.

2.5. Image interpretation

A PET/CT scan is defined as positive for metastasis if there is abnormal FDG uptake greater than background in surrounding tissue and unrelated to physiologic sites of tracer uptake (e.g. bowel, myocardium), without a specific standardized uptake value (SUV) cut-off and a PET/CT scan is defined as negative if no 18F-FDG uptake. For residual hepatic or splenic lesion, abnormal uptake was defined as FDG accumulation greater than in the liver (8).

2.6. Reference standard

The final diagnosis of recurrence or distant metastasis was made after histo-pathological analysis, clinical and imaging follow-up. In each case, we determined the indication for the scan, the result, concordance/discordance with other conventional imaging modalities and if the use of PET/CT had altered patient management.

2.7. Statistical analysis

Sensitivity, specificity, positive predictive value and negative predictive value were determined on the basis of number of patients, not number of lesions. Disease-free survival (DFS) (or recurrence-free survival) is defined as the time from randomization to the first of recurrence or relapse, second cancer, or death. DFS was measured in patients with and without distant metastases discovered on PET/CT, and comparisons between the 2 groups were assessed with using the Kaplan–Meier method and Log-rank test (log-rank $P = 0.002$). The analyses were performed using SAS version 9.1 (SAS Inc., Cary, NC).

3. Results

3.1. Patients and tumor characteristics

A total number of 50 female patients with a history of breast cancer were included in this study. The main indication for carrying out PET/CT scans was high clinical suspicion (signs or symptoms) of recurrence or distant metastasis. The age of patients ranged from 25 to 80 years with mean age being 50.85 years. Patient and tumor characteristics before PET/CT and conventional images are listed in Table 1. As regards the histo-pathological character of the tumor, 30 out of 50 patients (60%) had invasive ductal carcinoma.

Regarding treatment: surgery (modified radical mastectomy, lumpectomy and axillary lymph node resection for all patients), chemotherapy, and radiotherapy in 24 patients; surgery was followed by chemotherapy in 6 patients; surgery and radiotherapy were performed on 5 patients; surgery only was performed on 4 patients, and chemotherapy was performed on only 1 patient. Hormonal treatment with other lines of treatment had been administered to 10 patients.

Thirty-four (68%) out of 50 patients show positive estrogen receptor status while 32 patients (64%) show positive progesterone status.

Regarding tumor markers, 44 out of 50 patients (88%) showed an increased level of CA 15-3.

3.2. Value of PET/CT scan

Distant metastases were visualized on PET/CT in 35 patients (70%). Sites of distant involvement in the 35 patients included bone ($n = 15$), distant lymph nodes ($n = 6$), liver ($n = 7$), and lung ($n = 6$) Table 2. Additional chemotherapy was done for metastatic disease, some liver metastases were operated or treated by radiofrequency, and some bone lesions were treated by radiation therapy in the site of the lesion. In this study, PET/CT detected recurrence in 1 patient, this patient was referred for PET/CT scan because of elevated tumor markers and her mammography was equivocal (area of increased density). The patient showed increased FDG uptake in residual left breast tissue 2 years after left lumpectomy, a biopsy was performed and showed evidence of recurrence and the patient underwent mastectomy.

3.3. Comparison between PET/CT and conventional Imaging to detect distant metastasis in 35 patients with breast cancer

We compare the performance of both PET/CT and conventional imaging techniques to detect distant metastasis in 35 patients with breast cancer (Table 3).

For bone lesions, PET/CT detected bone metastases in 15 out of 35 patients. Bone scanning revealed metastases in 8 of these patients. Bone scanning could not detect lesion in 3 patients which was considered as false negative results, and showed false positive results in 4 patients with benign osteoarticular lesions.

The performance of PET/CT and conventional imaging in detecting distant extra-axillary lymph node metastases was evaluated separately at the supradiaphragmatic and infradiaphragmatic levels. Of 35 female patients; 4 showed supradiaphragmatic (cervical, mediastinal, or contralateral axillary) lymph node involvement on PET/CT. Contrast-enhanced CT missed mediastinal lymph nodes in 1 patient. Chest radiography did not detect involved lymph nodes in any patient. Two patients had PET/CT evidence of abdominal and pelvic lymph node involvement. Pelvic lesion in 1 patient disappeared with no therapy on a repeat CT study performed 3 months later and tumor markers returned to normal values and these findings represented an inflammatory process (false positive result). Among these 2 patients, conventional imaging was false-negative in the first (did not show the lesion) and false positive in the second like PET/CT.

For the detection of liver metastases, the performance of PET/CT was compared with that of abdominal CT and
In total, in this series of 50 patients with breast cancer PET/CT detected all distant lesions evidenced by the combination of conventional imaging, except in 1 case (of small pulmonary nodule with septal thickening), also PET/CT showed additional unknown lesions in bone, distant lymph nodes, and liver. Distant metastases were visualized on PET/CT in 35 patients. Only 25 of these 35 patients (71%) had distant metastases in conventional imaging.

PET/CT was positive in 35 cases and negative in 15 cases of all 50 patients included in the study, there were 34 true-positive and 14 true-negative cases, 1 patient showed false negative result and 1 patient showed false positive result so PET/CT has a sensitivity of 97% and a specificity of 93%, positive predictive value 97% and negative predictive value 93% Table 4.

Conventional imaging procedures were positive in 25 cases and negative in 25 cases of all 50 patients included in the study, there were 18 true-positive and 19 true-negative cases, 5 patients showed false negative result and 6 patients showed false positive result so conventional imaging procedures had a sensitivity of 75%, and a specificity of 73%, positive predictive value 72% and negative predictive value 76% (Table 4).
provide an imaging tool with higher sensitivity and special resolution that could potentially replace conventional imaging in at least some aspects of breast cancer management (3).

Our study strongly supports the conclusions of previous studies that have shown that PET/CT is more accurate than conventional imaging for the detection of distant metastases (10,11).

In our study, PET/CT detected metastatic disease with a sensitivity, specificity, positive predictive value and negative predictive value of 97% and 93%, 97% and 93%, respectively. The diagnostic performance of PET/CT in our study is in line with the study of Aukema et al. (12) which included 56 patients with suspected locoregional breast cancer recurrence and distant metastasis. The sensitivity, specificity, positive and negative predictive values of PET/CT were respectively 97%, 92%, 95% and 94%.

The Chinese investigators also reported a similar conclusion that PET–CT is useful in the detection of recurrent and metastatic disease in breast cancer (13).

In our study, PET/CT has higher sensitivity and specificity than conventional imaging in the detection of distant metastases of breast cancer as conventional imaging procedures had a sensitivity of 75%, and a specificity of 73%, positive predictive value 72% and negative predictive value of 76% and this result agrees with the result of Niikura et al. (14) who performed a retrospective review which included 225 patients with primary breast cancer and compared the sensitivity and specificity of PET/CT and conventional imaging (CT, ultrasonography, radiography, and skeletal scintigraphy) for the detection of distant metastases and they concluded that, in the detection of such metastases, PET/CT was superior to conventional imaging in terms of both sensitivity and specificity.

In this study, we performed a detailed analysis for different metastatic locations. Bone is the most frequent site of distant involvement in breast cancer (15). In our study, all osseous metastases detected by bone scan were also detected by PET/CT. Seven additional cases were detected only by PET/CT and our results are in agreement with other recent studies (16,17).

However, in the present study, similar to the practice in most PET/CT centers, data were acquired from the mid-thigh level to the base of the skull, with the arms raised. Most of the skull, upper extremities, and lower extremities would not be included in the imaged field of view. On the other hand, whole-body bone scanning is a true whole-body method. So, some investigators advised performing bone scanning in addition to 18F-FDG imaging (3).

Regarding pulmonary parenchyma, PET/CT efficiently detected supra-centimetric pulmonary nodules. However, because of the partial-volume effect and respiratory movements, PET lacked sensitivity for smaller nodules, reporting of the CT part of the PET/CT examination obviously improved the sensitivity of PET/CT in comparison to stand-alone PET. However, free-breathing CT remains less efficient than standard diagnostic thoracic CT (10). In our study PET/CT missed a small metastatic nodule in 1 patient.

18F-FDG-avid mediastinal lymph node metastases are not rare in cases of locally advanced breast carcinoma or inflammatory carcinoma (16).

PET/CT was important in our study in detecting metastasis of extra-axillary nodal regions, such as supraclavicular, inter-mammary, and mediastinal lesions. Bernsdorf et al. (18) reported that PET/CT solely detected six cases of distant metastasis and 12 cases of extra-axillary LN involvement, in

**Table 3** Performance of PET/CT versus conventional imaging work-up to detect distant metastasis in 35 patients with breast cancer.

<table>
<thead>
<tr>
<th>Site</th>
<th>PET/CT</th>
<th>Bone scanning</th>
<th>Chest imaging (X-ray, contrast-enhanced CT)</th>
<th>Abdominal imaging (ultrasound or contrast enhanced CT)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>15</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>15</td>
</tr>
<tr>
<td>Extra-axillary LN</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Liver</td>
<td>7</td>
<td>–</td>
<td>–</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Lung</td>
<td>6</td>
<td>7</td>
<td></td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

**Table 4** Diagnostic performance of conventional imaging and PET/CT in 35 patients with breast cancer.

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>True negative</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>False positive</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>False negative</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>75%</td>
<td>97%</td>
</tr>
<tr>
<td>Specificity</td>
<td>73%</td>
<td>93%</td>
</tr>
<tr>
<td>PPV</td>
<td>72%</td>
<td>97%</td>
</tr>
<tr>
<td>NPV</td>
<td>76%</td>
<td>93%</td>
</tr>
</tbody>
</table>

**Fig. 1** Kaplan-Meier plot of disease-free survival for 34 female patients with positive PET/CT scan of metastasis versus 14 patients with negative PET/CT scan of metastasis.
comparison with the conventional imaging in early breast cancer above 2 cm and because they studied bone scan, abdomen ultrasonography, chest X-ray, and blood samples on conventional staging, they stated that PET/CT could be only diagnostic modality of the metastasis work up (18). In our patients, 4 out of 35 patients (11%) had lymph node involvement in the thorax. Lymph nodes larger than 1 cm were easily detected by enhanced CT in our study, as they were in others (14,16) however post-contrast CT scan missed the diagnosis in 1 patient with mediastinal lymph node and another patient with inguinal lymph node. The only false positive lesion with PET/CT was in the inguinal region which was proved by follow up to be due to an inflammatory process. In agreement with the recent report of Koolen et al. (16), chest radiography did not detect mediastinal lymph node metastases in any patient.

The liver is the main site of visceral breast cancer metastases; however, only little information is available regarding the detection of liver metastases with FDG-PET (15).

18F-FDG PET/CT had sensitivity for liver metastases similar to that of conventional imaging, PET/CT helped to classify doubtful findings on conventional imaging (angiomas and cysts), as also reported by Garami et al. (19). In this study PET/CT detected liver metastases in all 6 patients and showed a metastasis in an additional patient in whom ultrasonography was negative, and the case was confirmed by imaging follow-up. In 1 patient, PET/CT helped to settle doubtful findings on conventional imaging because liver ultrasonography was suggestive of metastasis (false-positive result) but PET/CT and MR imaging were negative. In our study, PET/CT detected recurrence in 1 patient, her mammography was equivocal (area of increased density). The patient showed increased FDG uptake in residual left breast tissue 2 years after left lumpectomy, a biopsy was performed and showed evidence of recurrence, our result agrees with the result of Manohar et al. (20) who analyzed the data of 111 patients who underwent FDG PET/CT and were suspected of having recurrent breast carcinoma and they concluded that F-18 FDG PET/CT is a very sensitive and specific imaging tool in detecting and restaging recurrent breast carcinoma. It can be a very useful imaging tool for restaging locoregional recurrences.

Fig. 2  A female patient aged 52 years who underwent lumpectomy for infiltrating ductal carcinoma in the lower inner quadrant of the left breast. Despite several cycles of chemotherapy, the levels of tumor markers rose. Work-up for recurrent or residual disease included mammography, bone scan, and CT of the chest, abdomen, and pelvis, but the results were negative for recurrence. (A) Cranio-Caudal mammogram shows: mild increased density with no definite lesion could be seen. (B) Axial fused PET/CT image shows: focal area of increased uptake (white left arrow) in left breast. (C) Axial non contrast CT scan of the same patient shows multiple enlarged right axillary lymph nodes (white star) but coronal whole body fused PET/CT images (D) showed: no active uptake indicating nonspecific benign looking axillary lymph nodes. The uptake was present only in the site of previous lumpectomy.
Fig. 3  A female patient aged 43 years in whom infiltrating carcinoma of the left breast was diagnosed. Despite the patient undergoing left mastectomy and high-dose chemotherapy, the cancer progressed. 1 year after diagnosis, high resolution CT (HRCT) (A)-(C) scan showed evidence of a small-pleural based-metastatic nodule (9 mm) (white arrow) associated with mild septal thickening but coronal whole body fused PET/CT images (D) missed the nodule and the septal thickening.

Fig. 4  Lymphatic spread of breast cancer in a 40-year-old woman who underwent lumpectomy and axillary node dissection for infiltrating lobular carcinoma in the left breast. She received adjuvant chemotherapy and radiation therapy to the breast and axillary region. Two years after surgery, levels of tumor markers were elevated. (A) Post contrast CT scan of the pelvis shows small lymph nodes in the right inguinal region (white arrow) only but coronal whole body fused PET/CT images (B) show extensive enlarged inguinal lymph nodes on both sides, a finding suspicious for metastasis. The patient subsequently received inguinal radiation therapy in addition to chemotherapy.
The National Comprehensive Cancer Network 2012 does not recommend the use of PET/CT in clinical stage I, II, or operable III breast cancer as an option, suggesting its use when findings on conventional imaging are equivocal (6). PET/CT is a fairly recent technique, and the relationship between initial staging with PET/CT and survival has not yet been extensively studied (11).

Alberini et al. (21) followed a group of 42 patients with inflammatory carcinoma (median follow-up, 44 mo) (14). They found a trend toward longer survival for M0 than for M1 patients—a trend that nearly reached significance \( (P = 0.06) \). In another study which included 104 evaluable patients, they found a significantly longer disease-specific survival in the 64 M0-patients than in the 40 women with distant metastases evidenced by PET/CT 11. In our study Disease-free survival was significantly shorter in the 34 M1-PET/CT female patients than in the 15 M0-PET/CT female patients (log-rank \( P = 0.002 \), the median survival was 25 months for patients with metastasis and more than 60 months for no metastatic patients.

Our study has some limitations. First, it was a retrospective study. Second, not all of the patients underwent all types of conventional imaging. Third, histo-pathologic findings were not available for all patients with suspected distant metastases so we do not know whether or not the patient with false-negative PET/CT scan who did not undergo biopsy, actually had distant metastases.

5. Conclusion

From our study we can conclude that: PET/CT was superior to conventional imaging in the detection of distant metastases in patients with breast cancer and when we compare the overall diagnostic performance of PET/CT to other diagnostic conventional imaging procedures, we found that PET/CTA: had clinically relevant advantages in the detection of extra-axillary lymph node metastases particularly if the nodes were not enlarged. PET/CT also detected bone metastases with higher accuracy compared with bone scan. On the other hand, CT had distinct advantages in the identification of both small lung and liver metastases. Thus, combined PET/CT could replace the other conventional imaging procedures and detect recurrence and distant metastases in breast cancer patients.

Conflict of interest

We have no conflict of interest to declare.

References