Description of metastatic disease detected with PET/CT in recently diagnosed breast cancer and relapsed breast cancer after treatment

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Abstract: Purpose. Describe metastatic disease detected by PET/CT in breast cancer (BC), and evaluate the relative contribution of PET and CT analyzed separately. Patients and Method. We divided the patients with BC into two groups: 1) at staging, 2) relapsed after treatment, using PET/CT. We described the lesions found exclusively with PET and exclusively with CT. Results. The patients at staging (n=17) 88% show lymphadenopathies, 29% bone metastases (BM), 17% lung metastases, 17% hepatic metastases, and 11% other localizations. For relapsed patients (n=35) these percentages were 54%, 62%, 34%, 31% and 28%, respectively. CT detected more lung nodules and sclerotic bone lesions than PET. PET detected more lymphadenopathies, medullary bone and hepatic lesions than CT.

Introduction

PET/CT (Positron Emission Tomography/Computed Tomography) has been proven useful at staging and monitoring of breast cancer patients and it has been gradually incorporated into the different protocols and study algorithms for this disease\(^{(1)}\). The ability to detect distant nodal metastases with greater sensitivity than any other imaging method, and to explore the entire body at once, are its most recognized advantages. These qualities result in a greater number of detected lesions and a more extensive corporal field of study (whole body imaging), with earlier detection and in sites unsuspected with techniques of conventional imaging.
The aim of this paper is to describe the distant lymph node metastatic involvement detected with 18F-FDG PET/CT in patients with cancer breast, not only in patients at staging, but also those already treated and suffering a relapse, and to estimate the relative contribution of PET and CT, interpreted separately, in the detection of lesions.

Patients and methods

We selected results using 18F-FDG PET/CT performed on patients with a diagnosis of breast cancer, between January 2009 and December 2011, dividing them into two clinical groups: 1) patients at initial staging, recently diagnosed without treatment, and 2) already treated breast cancer patients, in which PET/CT showed a relapse (re-staging). The patients without affected lymph nodes or metastasis were excluded.

Protocol PET/CT: All of the PET/CT were performed on a Discovery STE 16 (GE), with CT acquisition for attenuation correction and localization, followed by 3D acquisition of metabolic imaging for the same field. The PET/CT charts comprised a field from the base of the skull to the front of the thigh, and were conducted 60 minutes after injection of 18F-FDG calculated according to kg of weight. The vast majority of the patients also underwent a CT scan of the chest, abdomen and pelvis on the same equipment, immediately after the acquisition of the PET/CT and before administration of the intravenous iodinated contrast. Each patient was interviewed to find out their history and to give instructions in preparation for the examination. This interview was conducted by a physician or medical technologist, based on availability. Before administering the iv dose of 18F-FDG, blood glucose was measured using a hemoglucotest on all patients, with a cutoff value of 200 mg/dl to be able to perform the examination. In cases of higher levels physiological serum was used for hydration and glycemia was monitored until it reached an appropriate level. Rapid insulin infusion was not required in any patient.

Semi-quantitative analysis: Uptake of affected nodes and distant metastases was assessed in each case, using the index SUVmax (Standardized uptake value maximum), which is obtained by plotting an area of interest on the lesion, with automatic calculation of the peak-voxel activity, resulting in a measure of activity per volume, corrected by the injected dose and patient weight\(^{(2)}\). We obtained the SUVmax index of each metastatic lesion, recording that which showed the greater uptake for each location (nodal, marrow, liver, etc).

Interpretation of the images: The images of PET and CT were evaluated separately by two expert observers, recording the presence of distant nodal metastatic lesions, visible with the corresponding method. The lesions of each organ or system were counted and characterized one by one. A number equal to or greater than 40 lesions per organ or system were considered “multiple” and recorded as 40 lesions in that organ. Then both observers analyzed the hybrid PET/CT study and the contrast-enhanced CT, comparing lesion to lesion and agreeing in the recording of false negatives for each technique. We defined “false negative” (FN) as a lesion visualized by one method (for example CT) but not by the other (in this case PET), corresponding to a FN of the second technique. For the comparative PET vs CT analysis of abdominal (liver, spleen, etc.) and ganglion lesions, only cases that were performed using contrast-enhanced CT, were included. Taking into account the complete hybrid study (PET/CT + CT with intravenous iodinated contrast) and the joint interpretation of both observers, the distant lymph node metastatic disease in the staging group and the re-staging group, was described. The “Gold Standard” to determine false negatives and positives was biopsy or monitoring of the lesions. “False positive” was defined as a suspicious lesion with PET or CT that was benign in the biopsy or resection. The detection of a second malignancy or second primary tumor was not considered false positive.

Confirmation of metastatic lesions: All primary breast tumors were biopsied and/or removed, with available histopathology in all cases. The node histologic correlation was possible only in cases with axillary clearance and/or targeted resection. In the case of extensive axillary involvement and/or multiple distant metastases, confirmation of the malignant nature of the lesions was carried out indirectly by observing a response to treatment or progression with PET/CT, CT or MRI monitoring. In cases of a single suspected metastasis lesion with PET/CT, this was always biopsied and/or resected, or followed-up with image controls to determine its nature.

Data analysis: We described the distribution and number of distant lymph node lesions detected by PET/CT (full hybrid study), both in the staging group and in the re-staging group. We performed a simple comparative study of both techniques (PET and CT) for the detection of nodal involvement and distant metastases, determining false negatives per patient and number of lesions for each technique, as mentioned previously.

Statistical analysis: Although this study is essentially descriptive, we used some statistical tests such as the t-test to compare SUVmax indexes between different lesions, and Chi squared to evaluate contingency tables.
Results

Description of metastatic disease

Staging patients (n = 17, average age 54 years, range 29-69 years) where 70% correspond to ductal carcinoma and 30% to lobular carcinoma. PET/CT showed an 88% of nodal involvement, 29% bone metastases (MO), 17% pulmonary (MP), 17% liver (MH) and 11% in other locations (OL). High concordance (p <0.0001, contingency coefficient: 0.51) in the axilla, was found between PET/CT results and the histopathologic findings in those cases where axillary dissection was performed, showing 35 true positive nodes using PET, 37 true negatives with PET, 20 false negative with PET (16 of those micrometastasis) and 1 false positive PET (Table I).

In the 36 monitored patients with suspected recurrence (re-staging), 66% corresponded to ductal histological tumors and 34% to lobular. Finally one patient was not counted in this group after it was found that the inguinal and membrane lymphadenopathies hypercaptation visible with PET/CT originated from a history of chronic inflammation, corresponding to a false positive with PET. The PET/CT in this group (n = 35, mean age 54 years, range 34-82 years) showed 54% nodal relapse, 62% MO, 34% MP, 31% MH, 8% adrenal and 28% OL. One patient with node hypercaptation in the operated breast, which was suspected of being a local recurrence with PET, was histologically confirmed as fat necrosis.

The distribution frequency of metastases in both clinical groups is shown in Table II.

PET vs CT analyzed separately

Staging Patients: Of the 75 hypermetabolic lymph nodes detected by PET, only 47 were positive in the CT, with 29 FN for the technique (Sensitivity of CT: 61.8%). Most of the FN in the CT corresponded to small ipsilateral axillary lymph nodes (n: 26) (Figure 1). One false positive for the CT was observed in ipsilateral axilla.

Of the 76 bone metastases present in five patients, PET detected 71 lesions and the CT 69 lesions, with 5 FN of PET in one patient (4 sclerotic and one lytic lesions), and 7 FN of the CT in two patients, both with spinal cord lesions (Figure 2).

Of the 81 liver metastases present in three patients, PET detected them all, and the CT 80, with one FN in the latter technique.

Regarding the 44 pulmonary metastasis, PET presented eight FN in three patients, no FN for the CT. The lesions not visualized with PET corresponded to small nodules, less than 6 mm.

Restaging patients: Of the 148 suspect lymph nodes on PET, 90 were abnormal on the CT (Sensitivity of CT: 60.8%). The CT false positives occurred mainly in the pulmonary hila (n: 17), lower cervical region (n: 12) and mediastinum (n: 10). One CT false positive occurred in a cervical lymphadenopathy, which was not resected but evolved as benign.

Of the 535 bone metastases in 22 patients, PET detected 529 (6 FN in one patient with sclerotic lesions) and the CT 454 (81 FN in eight patients with 70 being medullar lesions and 11 incipient lytic lesions).

Of the 137 liver metastases, PET did not detect 3 in one patient, and CT did not detect 2 in two patients (Figure 3).

Regarding the 195 lung metastases found, PET did not detect 14 in four patients, and CT did not

Table I. FDG PET vs histopathology in resected axillary lymph nodes in breast cancer patients undergoing axillary dissection.

<table>
<thead>
<tr>
<th>PET</th>
<th>+</th>
<th>-</th>
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<td>Histopathology</td>
<td>+</td>
<td>35</td>
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<tr>
<td></td>
<td>-</td>
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(P < 0.0001, Contingency coefficient: 0.51)

Figure 1. Numerous small axillary lymph nodes and hypermetabolic left retro-pectorals with PET (arrows), some of which are negative with the CT. Avid medullary metastasis in left humerus (circle) without translation in CT. Normal uptake of FDG in heart and liver.
**Table II.** Distribution frequency of metastases detected with PET/CT in breast cancer patients and its FDG uptake index (SUVmax).

<table>
<thead>
<tr>
<th>Staging</th>
<th>Patients</th>
<th>Mtt</th>
<th>SUVmax (SD)</th>
<th>Av (SD)</th>
<th>range</th>
<th>Patients</th>
<th>Mtt</th>
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<td>19</td>
<td>54,3</td>
<td>148</td>
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<td>3,1–14,1</td>
<td>34</td>
<td>65,4</td>
<td>223</td>
<td>7,7 (5,1)</td>
<td>2,2–27,6</td>
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<td>Skeleton</td>
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<td>29,4</td>
<td>76</td>
<td>6,8 (2,6)</td>
<td>4,2–10,3</td>
<td>22</td>
<td>62,9</td>
<td>535</td>
<td>9,2 (4,9)</td>
<td>2,4–19,9</td>
<td>27</td>
<td>51,9</td>
<td>611</td>
<td>8,7 (4,6)</td>
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<td>Lung</td>
<td>3</td>
<td>17,6</td>
<td>44</td>
<td>6,5 (8,2)</td>
<td>1,7–15,9</td>
<td>11</td>
<td>31,4</td>
<td>187</td>
<td>3,7 (3,3)</td>
<td>1,2–12,4</td>
<td>14</td>
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<tr>
<td>Liver</td>
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<td>81</td>
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<td>137</td>
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<td>3,3–20,9</td>
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<td>218</td>
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<td>0</td>
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<td>--</td>
<td>3</td>
<td>8,6</td>
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<td>0</td>
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<td>--</td>
<td>3</td>
<td>8,6</td>
<td>Dif</td>
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<td>3,8</td>
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<td>3**</td>
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<td>9,6</td>
<td>11</td>
<td>3,5 (1,6)</td>
<td>2,4–5,3</td>
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SSGG - adrenal glands; Mtt: Metastasis, SUVmax: Standardized Uptake Value maximum; Dif: involvement not precise
Others: * metastases in staging patient; thyroid in one and spleen in the other.
** metastases in re-staging patient: gastric not precise, subcutaneous cellular, retroperitoneum, uterus
detect 6 in two patients. This latter group of false negatives from CT corresponded to hypercaptation of nodular lesions located within an atelectasia or condensation, in dense bands described as residual or more so pleural based or fissural nodules simulating lymph nodes.

Metastases in other sites were of frankly less frequency, predominantly adrenal glands in 8% and peritoneum in 8% of the restaging group. PET detected secondary lesions in the uterus and thyroid, unsuspected with CT (both histologically confirmed) (Figure 4).

**Figure 2.** Two hypercaptations of medullary bone lesions with PET (arrows), without representation on the CT (upper photos). The lower photos show a sclerotic lesion on CT without evident hypercaptation on PET.

**Figure 3.** Hypermetabolic liver lesion on PET, not visible to the CT and difficult visualization on the MRI.

**Figure 4.** Hypercaptation of thyroid metastases (long arrows). The presence of perithyroid lymphadenopathies (short arrows) made a second primary thyroid suspect, but the pathological anatomy showed multiple thyroid implants of ductal cancer undifferentiated from breast cancer. The patient also showed metastases in bones and in the right lung.
Characterization of metastatic lesions

In the staging patients the lymph node involvement was mainly ipsilateral axillary (66% of the cases), followed by lower cervical (14%) and internal mammary (10%). A minority had spreading to supraclavicular nodes (5%) or contralateral axillary (5%). The average number of nodes per patient was five (range 0-13 nodes). The SUVmax average in involved nodes was 8.0 (SD: 6.7, range: 2.8-27.6).

The re-staging group had multiple nodal sites, mainly in mediastinum (22%), pulmonary hilia (15%), supraclavicular (13%) and ipsilateral axillary (13%). The average lesions per patient were 4.3 (range 0-30 nodes). The SUVmax average was 7.5 (SD: 3.5, range 3.1-15.6).

The bone metastases were mainly sclerotic (380) and medulla (110), with a lower proportion of lytic lesions (69) and mixed (52). Localization was predominantly in the axial skeleton, with special involvement of the sternum and spine. Of the patients with bone metastases, the 20% in staging (1/5) and the 40% in restaging (9/22) had multiple lesions (40 or more lesions). The uptake was not significantly different between the staging group (SUVmax average: 6.8, SD: 2.6) and re-staging group (SUVmax average: 9.2, SD: 4.8).

The liver lesions were multiple in four patients, two of them in staging, and singular in four individuals, three of them in re-staging. The uptake was not significantly different between the staging group (SUVmax average: 9.2, SD: 5.2) and re-staging group (SUVmax average: 9.8, SD: 5.6).

The lung metastases were multiple in only two patients, both in restaging. The greater majority corresponded to solid nodules, showing hypercapitation on PET with sizes ranging from 6 mm. Average uptake of these lesions in the entire group of patients was SUVmax: 9.6 (SD: 5.4, range 1.1-20.9).

The remaining sites were less frequent both in staging patients (Thyroid and spleen) and re-staging patients (adrenal glands, peritoneum, ovary, etc.), as shown in Table II.

Detection of a second primary tumor

Synchronous breast cancer was observed in 6% (1/17) of patients in staging (renal cell carcinoma). The PET/CT detected a second neoplasm in 11% (4/35) of patients in follow-up (cancer of the pancreas, thyroid, primary peritoneal and fallopian tubes). One of these cases is shown in Figure 5.

Discussion

Current consensus protocols mentioned 18F-FDG PET in the initial staging of breast cancer from stage IIIA as an alternative to the traditional study(1). Its main contribution lies in its high performance in detecting nodal disease (N) and distant metastasis (M). On the other hand, its usefulness in monitoring and restaging in treated patients has been largely demonstrated in numerous publications(3,4). Its high performance in the detection of secondary lesions has changed the paradigm in the evaluation of metastatic breast cancer disease, redefining the frequency and distribution of lesions with respect to the traditional techniques(5).

In this study we focus on describing the distribution of metastatic disease in patients performed with 18F-FDG PET/CT in our center, dealing separately with two groups of patients: recently diagnosed and those already treated with recurrence, also evaluating the relative utility of the two components of the hybrid study, PET and CT.

Our study demonstrated the complementary value of PET and CT in the detection of lesions, showing a higher relative contribution of the CT in lungs and of PET in skeletal evaluation and atypical sites such as Figure 5. Cancer of the right fallopian tube with retroperitoneal lymphadenopathy investigated in one patient monitored for breast cancer, treated 9 years ago.
as uter, thyroid and spleen. Both techniques were also complementary in liver.

The nodal involvement in the staging group involved primarily the ipsilateral axillary, and the PET/CT identified the majority of the lesions, even when there were 20 false negative nodes with PET, 16 of which corresponded to micro-metastases nodes. The existence of only one false positive indicates a high positive predictive value for PET in the axilla. In the group of treated patients who relapsed, the distribution of nodal metastasis was dispersed, having numerous locations, the most frequent in the mediastinum, pulmonary hila and supraclavicular.

The most frequently found distant metastases were bone, corresponding to 29% of the sample in staging. Although the population of our study is not representative of that with recently diagnosed cancer because the patients without metastases were excluded, the reported prevalence described approaches the 31-42% reported in large series\(^5,6\). Our lower prevalence of skeletal metastatic disease could be partly explained by the selection criteria of the patients to those who have asked for PET/CT, and the increasingly earlier diagnosis of cancer because of the stringent screening policies. In the group of monitored patients after treatment, the occurrence of bone metastases was 62%, closer to the 58% reported for this group\(^6\).

The variable characteristics of the types of secondary bone lesions found in breast cancer, which can be lytic, mixed, blastic or medullary, means that no single test exists that detects all at once. The PET was better for detecting the medullar and incipient lytic lesions, which are often not visible with CT due to the absence of or insufficient bone destruction necessary to appear as lower density than normal bone. On the other hand, CT showed superiority in detecting sclerotic or blastic lesions, which cannot pick up on noticeable glucose because it is associated with reduced tumor activity. Mixed metastases i.e. with lytic and sclerotic areas, were apparent using the two techniques, as well as the purely lytic. As already mentioned, an important complementarity of the PET and CT components was observed in skeletal evaluation.

Lung metastases were the second most frequent in our study, with 17% in the staging group, similar to the published prevalence\(^5\) and 34% in the treated/monitored group. The most common presentation is the lung nodule, most of the times of solid type. The 18F-FDG uptake was detectable in nodules from 6 mm, which coincides with the spatial resolution typical of the PET/CT equipment of today. The CT showed clear superiority in displaying pulmonary nodules compared to PET. However, it is interesting to note that PET was able to pick-up on lesions that go unnoticed with CT, such as lesions included in the thickness of atelectasis, condensations or pulmonary bands, or nodules in the pleural or cisural plane that simulate lymph nodes.

Liver metastases have a prevalence of approximately 13% in series about recently diagnosed breast cancer\(^5\) and up to 61% in autopsies\(^7\). The first figure is consistent with the 17% obtained in our study. It is worth noting that these lesions are those that show a tendency to increased uptake (SUVmax index). The detection of three liver lesions by PET were not visible on CT, and the fact that these lesions are often singular, is a point in favor for the use of the hybrid technique in liver study of these patients.

The high frequency of secondary pleural involvement described in the literature, with up to 27%\(^5\), was not reflected in our experience, where it was present in only two re-staging patients.

It should be taken into consideration that our study necessarily underestimates the frequency of brain metastases, because the brain is not considered as a habitual imaging field (images are taken from the base of skull), unless a brain lesion is previously suspected. This adds to the low sensitivity of PET in the brain due to high physiological uptake of the cerebral cortex, that often mask the lesions. In fact, the two patients in which brain metastases were detected, showed a high metabolic activity, even greater than that of the brain, which is associated to the high aggressiveness of the lesion\(^8\).

The presence of two false positive cases for PET/CT (hypercaptation of lymphadenopathies that resulted in chronic inflammation in one patient and a focus of necrosis mammary fat hypercaptation in another) reaffirms the idea that every single hypermetabolic lesion must be biopsied before being considered metastasis. The occurrence of second primary malignancies which can be confused with the spread of breast cancer endorses the aforementioned.

Bibliography

