Original Paper, Oncology.

The Diagnostic Value of PET/CT in Breast Cancer Recurrence and Metastases

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ABSTRACT:

After initial treatment of breast cancer; localization of metastases or recurrences remains a serious challenge that requiring an extensive diagnostic workup. Current literature states that FDG PET/CT should be the first whole-body imaging modality used for restaging in breast cancer patients who are suspected of having disease recurrence. **Aim of the work:** We aim in our study to highlight the value of PET/CT in diagnosis of local recurrence and/or metastasis in breast cancer. **Patients and Methods:** We performed whole body 18F FDG-PET/CT on 37 breast carcinoma patients, regardless the pathological subtypes, presenting with clinical, laboratory and/or radiological suspicion of loco-regional or distant metastatic recurrence.

Recurrence is defined as evidence of recurrent lesions within 6 months of the FDG-PET/CT based on conventional imaging techniques, pathology, or clinical follow-up.

Results: A total of thirty seven patients eliciting eighty eight suspicious lesions were evaluated. The overall sensitivity, specificity and accuracy of FDG-PET/CT in our study are 98.65%, 85.71% and 96.59%; the results provide supportive evidence for a role of 18F-FDG PET/CT in determining the stage of disease for high- and intermediate-risk patients. **Conclusion:** Our results indicated that PET/CT is the most sensitive and accurate tool for follow-up of breast cancer patients presenting with clinical, laboratory and/or radiologic suspicion of loco-regional or

distant metastatic recurrence, hence; FDG-PET/CT should be used as a first priority in patients with steadily rising serum CA 15-3 levels, or with clinical/ radiologic suspicion of recurrence.

Key words: Breast Ca. recurrence, breast cancer metastases, 18F FDG-PET/CT.

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INTRODUCTION:

Breast cancer is recognized as the most leading cause of death in women worldwide, with progressively increased incidence over the last few decades. Depending on the extent of the disease, up to 35% of patients who receive their management; including surgery and chemotherapy may develop local recurrence or secondary tumor dissemination to distant organs [1].

After initial treatment of breast cancer, follow-up based on clinical examination and conventional imaging techniques is common practice. However, localization of metastases or recurrences remains a serious challenge, requiring an extensive diagnostic workup. Mammography is of high value in the follow-up of breast cancer and is recommended to diagnose or exclude local recurrence, but it encounters obvious challenge to detect the remote metastases. The use and efficacy of other modalities such as, computed tomography, magnetic resonance imaging, ultrasound, or bone scan remain controversial [2].

Currently, integrated 18F-FDG positron emission tomography with computed tomography (18F-FDG PET/CT) has emerged as a promising imaging modality to be applied in follow up of cancer patient. In breast cancer patients, FDG-PET/CT has been reported to be useful in evaluating the initial tumor (including loco-regional or distant staging), in evaluating treatment response, and in assessing recurrent disease and clarifying equivocation with other imaging modalities [3].

The aim of this study is to evaluate the efficacy of using PET/CT in monitoring the recurrence and metastasis of breast cancer in order to optimize its utility in clinical practice.

PATIENTS AND METHODS:

We performed whole body 18F FDG-PET/CT on 37 patients with breast cancer with clinical, laboratory and/or radiologic suspicion of loco-regional or distant metastatic recurrence. Recurrence is defined as evidence of recurrent lesions within 6 months of the FDG-PET/CT scan based on conventional imaging techniques, pathology, or clinical follow-up.

PET/CT Scanner which combined a 64-slice spiral CT scanner with a dedicated, full-ring PET scanner.

Patients selected in our study had the following criteria: breast carcinoma of any pathological subtype with initial complete responses to treatment and presenting with clinical, laboratory and/or radiologic suspicion of loco-regional or distant metastatic recurrence.

Patients with a known history of other known primary tumor have been excluded from present study.

Whole-body 18F-FDG PET/CT imaging protocol: Patients are asked to fast for a minimum of 4 h, but are allowed to drink water. Before administration of FDG, the weight and plasma glucose level of the patient are recorded. FDG is given only when the plasma glucose level is below 160 mg per deciliter. All patients are administered 270–370 MBq (7.3–10 mCi) of FDG intravenously, while resting comfortably on a bed. Imaging is performed after a resting period of 45-60 minutes. All patients are asked to void immediately before image acquisition. Patients are imaged on a PET/CT Scanner. The CT transmission scan for the purposes of attenuation correction and anatomical correlation and PET emission scans are obtained from the base of brain to proximal thigh. The PET emission scan is acquired at 2 to 3 min per bed position, with a whole-body scan typically requiring five to six bed positions. Unless contraindicated, patients were injected IV contrast material following PET data acquisition and a diagnostic whole body contrast enhanced CT scans were acquired. Orthogonal CT, PET & fused PET/CT images are displayed simultaneously on a workstation.

Image analysis: All the whole-body FDG PET/CT scans are evaluated by nuclear medicine physician and radiologists to generate a clinical report after reviewing previous imaging results and clinical information. The PET images are inspected visually for regions of focally increased glucose uptake and quantitatively by detecting the maximum standardized uptake value. In equivocal findings, a standardized uptake value (SUV) of greater than 2.5 is considered as positive, except the liver, Where SUV higher than 2 in the difference of the focus and the surrounding normal tissue is considered as malignant. Focally increased uptake located in the lung is considered as positive in all cases.

Data statistical analysis: To be classified as confirmed positive, a recurrence confirmation is required, based on conventional imaging techniques, pathology or clinical follow-up. To be classified as negative or false positive, a minimum of 6 months of follow-up is required, with negative conventional imaging techniques and/or repeated PET/CT imaging and clinical examination.

Accuracy, sensitivity and specificity of FDG PET/CT scan were calculated.

RESULTS:

We performed FDG-PET/CT on thirty seven patients, thirty five females and two males, with prior history of breast carcinoma,

Regard less the pathological subtype.

All patients had complete responses to initial treatment (i.e. primary surgery and/or chemotherapy), and presenting with clinical, laboratory and/or radiologic suspicion of loco-regional or distant metastatic recurrence. A total of eighty eight suspicious lesions involvements were evaluated. *(table1)*.

Table (1): The distribution of recurrence and metastases in 37 patients detected by PET/CT.

Site	Number Suspected	True +ve	True -ve	False +ve	False -ve
Local	11	10	1		
Nodal	25	21	3	1	
Pulmonary	13	11	1		1
Pleural	2	2			
Effusion	4	3	1		
Osseous	22	19	2	1	
Hepatic	7	5	2		
Adrenal	3	1	2		
Peritoneal	1	1			
Total	88	73	12	2	1

Eleven patients were referred with suspicious local breast recurrence; ten of them were correctly assigned by PET/CT as local recurrences. One case was correctly excluded by PET/CT *(Figure 1)*.

Twenty five patients were presenting with suspicious nodal metastatic recurrence, twenty one of them were correctly assigned by PET/CT as nodal recurrences. Three cases were correctly excluded by PET/CT.

One patient had false positive result by PET/CT as nodal recurrence. *(Table 1) and (Figure 2)*.

Twenty two patients were presenting with suspicious osseous metastatic lesions. Nineteen patients were correctly assigned by PET/CT as osseous metastases.

Two patients were correctly excluded to have bone metastasis by PET/CT. The last patient was identified by PET/CT as metastatic *(Figure 3 & 4)*.

Twelve patients were presenting with suspicious pulmonary metastatic recurrence. Ten patients were correctly assigned by PET/CT as pulmonary metastases. One patient was correctly excluded by PET/CT. The last patients had pulmonary nodules which were truly identified by PET/CT as metastases, as well as pulmonary patch of consolidation that was identified by PET/CT as inflammatory consolidation however; follow up revealed that it was also disease involved. Two patients were presenting with suspicious nodular pleural metastatic recurrence and were correctly assigned by PET/CT as pleural recurrences. Four patients were presenting with suspicious pleural effusion. Three of them were correctly assigned by PET/CT as malignant effusion. The last patient was correctly excluded by PET/CT. Six patients were presenting with suspicious hepatic metastatic lesions in four patients lesions were correctly assigned by PET/CT as hepatic metastases. One patient was correctly excluded by PET/CT. The last patient had two hepatic lesions; one was truly identified by PET/CT as metastasis and the other lesion was identified by PET/CT as being of benign nature. Three patients were presenting with suspicious adrenal metastatic lesions in one patient, the lesion was correctly assigned by PET/CT as adrenal metastases. The other two adrenal lesions were correctly assigned by PET/CT as adrenal benign adenoma *(table1).*Only one patient was presenting with suspicious peritoneal metastatic lesions and was correctly assigned by PET/CT of being so. In our study, FDG-PET/CT truly identified seventy three lesions. Involvements and truly excluded twelve lesions. FDG-PET/CT missed only one false negative lesion and showed false positive results in two lesions.
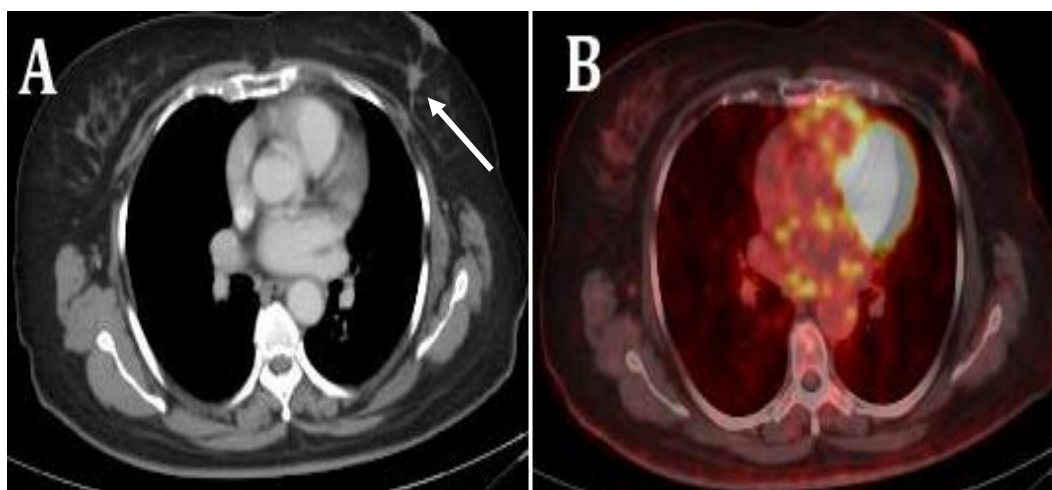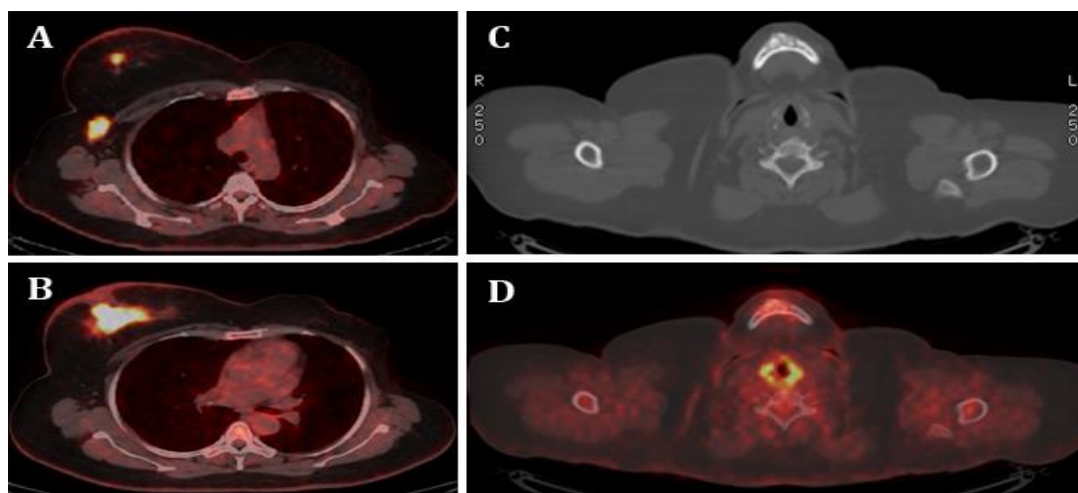
Figure 1: (A) The CT component of a PET/CT showing the left breast speculated soft tissue density (arrowed). (B) The PET/CT fused image shows that the mass has no concordant glucose avidity and this was proved by follow up.
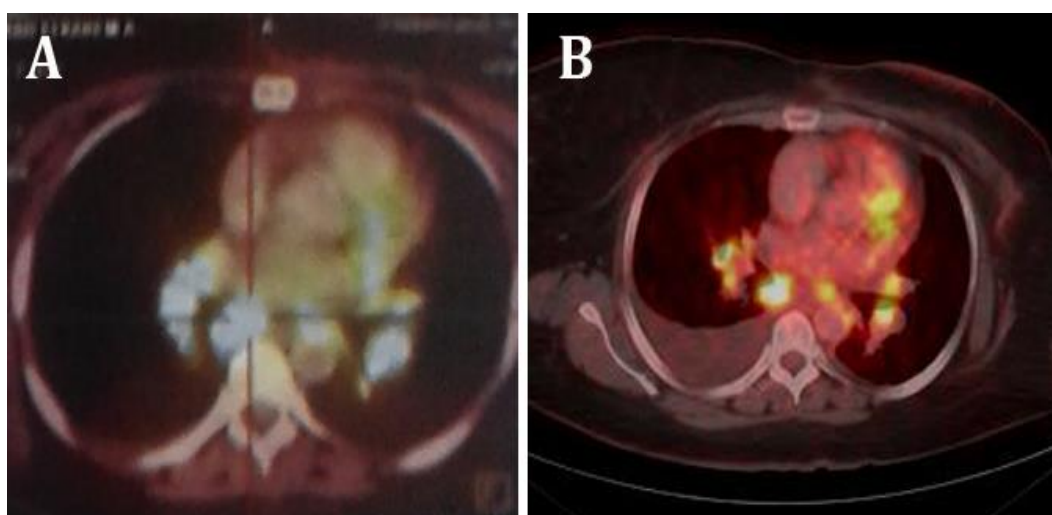
Figure 2: (A) Initial PET/CT image showing bilateral hilar and right para-tracheal lymph nodes. (B) Follow up PET/CT image showing persistence of the previously reported lymph nodes with no de novo glucose avid lesions. The patient responded well to steroid therapy and sarcoidosis was the final diagnosis.
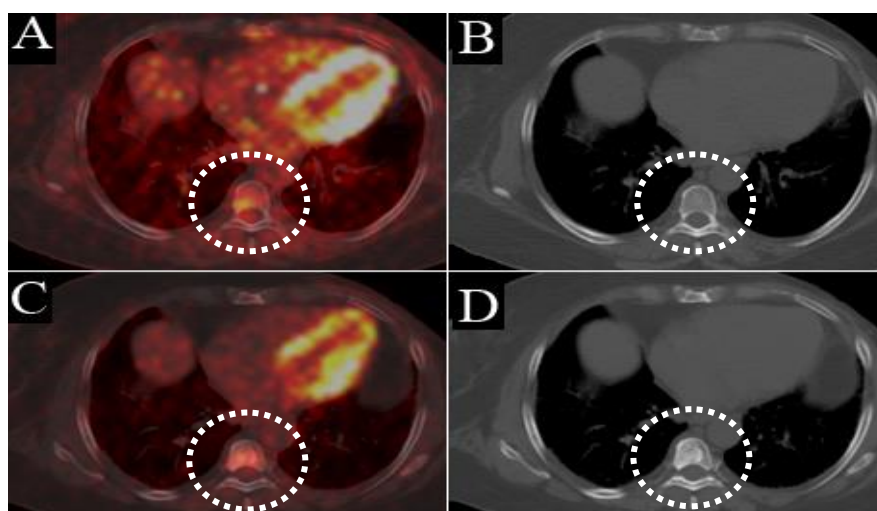
Figure 3: From our cases: PET/CT examination of a patient with Lt. MRM presented with suspicious bone scan hot foci. (A) Initial PET/CT axial fused image shows focal glucose avidity at D4 vertebral body (marrow based). (B) CT component is showing no corresponding CT abnormality. (C) Follow up PET/CT axial fused image one year later shows maintained focal glucose avidity at the previously seen D4 vertebral lesion. (D) CT component showed that the lesion became visible with some sclerotic features.

Figure 4: (A) & (B) PET/CT axial fused images show glucose avid right breast mass and right axillary lymph nodes. (C) The CT component of a PET/CT showing symphesis menti expanding mixed lytic/sclerotic lesion. (D) PET/CT axial fused image showing that the mass has corresponding glucose avidity.

Pathological examination of the symphesis menti lesion reported: Fibrous dysplasia.

The overall (Table 2) sensitivity, specificity and accuracy of FDG-PET/CT in our study are 98.65%, 85.71% and 96.59%.

Table (2): Diagnostic performance of PET/CT in 37 patients with suspected breast cancer recurrence and metastases.

	No. of Organs
True Positive	73
True Negative	12
False Positive	2
False Negative	1
Sensitivity	98.65%
Specificity	85.71%
Accuracy	96.59%

DISCUSSION:

Current literature stated that FDG PET/CT should be the first whole-body imaging modality used for restaging in breast cancer patients who are suspected of having disease recurrence [4].

The aim of this study was to highlight the efficacy of using PET/CT in monitoring the recurrence and metastasis of breast cancer in order to optimize its utility in clinical practice.

A total of 88 suspicious lesions were evaluated in 37 patients with breast cancer. FDG-PET/CT truly identified seventy three lesions and truly excluded twelve lesions. FDG-PET/CT missed only one lesion (false negative) and assigned two lesions as suspicious positive for metastases however proved to be false positive (one patient of them was due to sarcoidosis and the other patient proved to be Fibrous Dysplasia).

***Groheux et al*.** analyzed 10 studies, between 2005 & 2011, to evaluate the role of PET/CT in restaging of breast cancer and reported the sensitivity of FDG PET/CT ranged between 85% and 97%; the specificity ranging 52% to 100%; and the accuracy ranging between 60% to 98% [4].

The overall sensitivity, specificity and accuracy of FDG-PET/CT in our study are 98.65%, 85.71% and 96.59%, which aligns with prior studies evaluating the role of FDG PET/CT for restaging of breast cancer.

Similar data was reported by ***Dong et al.*** comparing the efficacy of using 18F-FDG PET/CT and conventional imaging techniques in monitoring the recurrence and metastasis of breast cancer, the patient-based sensitivity and specificity of PET/CT were 95.0% and 71.43% compared to 78.95% and 57.14% for conventional imaging techniques [2].

In our study, eleven patients were presenting with suspicious local breast recurrence, ten of them were correctly assigned by PET/CT as local recurrences. One case was correctly excluded by PET/CT and proved to be post-operative scarring (***Figure 1***).

Chronic inflammation and benign focal breast masses, including fibro adenoma, granuloma, fat necrosis and postsurgical changes, may show increased FDG uptake on PET/CT.

Images causing diagnostic controversies and may be misinterpreted as local recurrence in women treated with breast cancer [5].

Investigators in many studies have showed that PET/CT is more accurate than CT or MR imaging for detecting nodal recurrences. In the study by Schmidt et al., PET/CT was more sensitive than whole-body MR imaging to detect lymph node involvement.

One of the advantages of PET is the ability to detect abnormal increase of the glucose metabolism even in normal sized lymph nodes that are not captured by conventional CT or MRI [4].

Sarcoidosis is a granulomatous disorder of no clear cause. It has been reported to associate a variety of malignancies either synchronously or after treatment with chemotherapy. Sarcoidosis or sarcoid like reaction to malignancy typically manifests increased,

Relatively symmetrical, bilateral hilar, and mediastinal nodal uptake, although it can affect lymph nodes more widely. Therefore, sarcoidosis should always be considered as a differential diagnosis when a cancer patient presents with lymphadenopathy [6].

In our study, twenty five patients were presenting with suspicious nodal metastatic recurrence, 21 of them were correctly assigned by PET/CT as nodal recurrences. Three cases were correctly excluded by PET/CT and proved to be benign in nature. One patient was diagnosed by PET/CT as nodal recurrence and proved by clinical follow up to be sarcoidosis. *(Figure 2)*.

Among the various imaging modalities currently available for imaging skeletal metastasis, hybrid techniques, PET/CT and PET/MRI, which fuse morphological and functional data enabling the radiologist to determine if focal radiotracer uptake on a nuclear medicine study corresponds to a discrete skeletal lesion [8].

Regarding bone metastases, bone scintigraphy is the most widely used technique for survey of skeletal metastases primarily due to its widespread availability and the ability to image the whole skeleton in a single exam using skeletal scintigraphy, however skeletal

scintigraphy has some limitations. It's non-specific and multiple benign osseous lesions, such as fibrous dysplasia and enchondroma can lead to a false positive result. Consequently, other imaging modalities such as CT or MRI are often required for correlation to exclude benign causes. The spatial resolution of scintigraphy is poor; measuring approximately 1cm and can result in difficulty determining the precise location of a lesion which can be of a diagnostic significance.

Also bone scintigraphy assesses osteoblastic processes rather than tumor proliferation and, consequently, false negative results can occur [7].

Morris et al. comparing the diagnostic performance of PET/CT and bone scintigraphy in women with suspected metastatic breast cancer, PET/CT was found to be more precise than scintigraphy to identify bone metastases, consequently, the authors concluded that bone scanning may potentially be avoided in patients undergoing FDG PET/CT [9].

In comparison with other imaging modalities including conventional CT and MRI,

FDG-PET/CT demonstrates better reliability in diagnosis of osseous metastases.

CT may be used for the detection of cortical and trabecular bone destruction but, in general, It has a low sensitivity because usually bone metastases start in the bone marrow.

Contrarily, MRI is sensitive for detection of bone marrow involvement but not for cortical disruption [10].

Fibrous dysplasia is a benign fibro-osseous lesion of the bone, considered to be a developmental abnormality. Abnormal fibrous tissue replaces normal cancellous bone with varying amounts of woven bone. Fibrous dysplasia may show various FDG uptakes on PET/CT and so should not be misinterpreted as bone metastasis in cases with intense FDG uptake [11].

In our study, twenty two patients were presenting with suspicious osseous metastatic recurrence. Nineteen patients were correctly assigned by PET/CT as osseous metastases *(Figure 3)*.

Two cases were correctly excluded by PET/CT and proved to be benign in nature.

The last case was mistakenly identified by PET/CT as metastatic and proved by pathologic examination to be fibrous dysplasia *(Figure 4)*.

Twelve patients were presenting with suspicious pulmonary metastatic recurrence.

Ten patients, with sub-cm to supra-cm pulmonary nodules, were correctly assigned by PET/CT as pulmonary metastases. One patient with sub-cm pulmonary nodules was correctly excluded by PET/CT and proved to be benign in nature on follow up. The other patient had two types of pulmonary involvement; pulmonary nodules which were truly identified by PET/CT as metastases and pulmonary patch of consolidation which was mistakenly identified by PET/CT as inflammatory consolidation and proved by clinical and radiological follow up to be of a neoplastic nature.

Negative PET/CT scan findings cannot exclude the presence of a small microscopic malignant metastases and because of the limited spatial resolution of PET, may lead to false-negative results [10].

Six patients were presenting with suspicious hepatic metastatic recurrence. In four patients lesions were correctly assigned by PET/CT as hepatic metastases.

One patient was excluded by PET/CT and proved to be benign in nature on follow up. The other patient had two types of hepatic lesions; one was truly identified by PET/CT as metastasis and the other was identified as being of benign nature; likely hemangioma.

Two patients were presenting with suspicious nodular pleural metastatic recurrence, and correctly assigned by PET/CT as pleural recurrences.

Four patients were presenting with suspicious pleural effusion. Three of them were correctly assigned by PET/CT as malignant effusion. The fourth patient was excluded by PET/CT and proved to be benign in nature.

18F-FDG PET/CT is a very useful method for differentiating malignant from benign adrenal lesions in patients with proven malignancy with an overall specificity between 69 % and 100 % and sensitivity between 74 % and 100 % [12].

However A false-positive rate of 5% is reported in the characterization of adrenal masses by F-18 FDG PET/CT due to significant FDG uptake in some adrenal adenomas, adrenal endothelial cysts, infectious and inflammatory lesions [13].

Different algorithms for differentiating benign from malignant adrenal tumors with 18F-FDG PET/CT have been suggested. Recent studies have shown that the adrenal to liver (T/L) maximum standardized uptake value (SUV max) ratio is a more accurate and reliable parameter.

In a study by *Kunikowska et al*. using a T/L SUV max ratio cutoff value of >1.53, led to high diagnostic sensitivity and specificity (94% and 91%) for characterizing adrenal tumors [12].

In our study, three patients were presenting with suspicious adrenal metastases. In one patient, the lesions were correctly assigned by PET/CT as adrenal metastases with a T/L SUV max ratio of 3.6. In the other two patients identified as benign lesions as they presented T/L SUV max ratio of 1.40 and 1.32. And this was confirmed on follow up. CT images also had a complementary role beside PET. In the former case both adrenals were bulky and diffusely infiltrated by tumor with a HU >30. In one of the later two cases the adrenal mass was small in size (1cm) and presenting fat density with HU less than 10.

The last one had no corresponding visible CT abnormality and is likely presenting a microscopic adenoma. Peritoneal carcinomatosis is among the rare sites for breast cancer metastases, that is a rare event but one that has a poor clinical outcome [14]. 18F-FDG PET/CT is a useful diagnostic method when peritoneal biopsy cannot be performed. In a study by *Chang et al*. evaluating the diagnostic performances of 18F-FDG PET or PET/CT in identification of peritoneal carcinomatosis in patients with cancer, they were of high specificity that may provide the reliability of a positive FDG PET or PET/CT to detect peritoneal carcinomatosis.FDG PET or PET/CT has only weak power to exclude the presence of peritoneal carcinomatosis [3]. Only one patient had suspicious peritoneal metastatic spread and was correctly assigned by PET/CT of being so.

At the end of this study we concluded that 18F-FDG PET/CT were valuable in the management and therapy planning of our patients who presented with suspicious breast cancer recurrence and/or metastases.

Therefore, FDG-PET/CT may be used as a priority in patients with increased serum CA 15-3 levels, or with clinical/ radiologic suspicion of recurrence. However, in certain circumstances, pathological evaluation of query lesions is recommended to avoid any unnecessary treatments [17].

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