Original Paper, Oncology

Role of ^{18}F- FDG-PET/CT in Restaging of Breast Cancer Patients with High Tumour Markers and Equivocal Radiological Imaging.

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ABSTRACT:

Objective: We aimed to assess the role of FDG PET/CT in detection of tumor recurrence in breast cancer patients with raised serum tumor markers and/or negative or equivocal abnormalities detected in other diagnostic imaging modalities. **Patients and Methods:** This prospective study was done on 100 previously diagnosed and treated breast cancer patients, All of patients referred for FDG-PET/CT scans in view of increased their serum tumour markers and/or equivocal abnormalities in other diagnostic imaging modalities. Clinical follow-up, tumour markers, conventional imaging modalities and FDG-PET/CT whole body scan was performed for each patient. **Results:** PET/CT detected recurrence and/or metastases in 63 out of 100 patients, including 23 loco-regional recurrence, 11 solitary organ involvement, 29 multiple organ involvement, whereas, other radiological modalities detected lesions in only 51 patients, those were 12 loco-regional recurrence, 24 solitary organ involvement, 15 multiple organ involvement. Fifty patients out of 59 with true positive PET/CT had raised tumor markers,either carcino-embryonic antigen (CEA) or CA 15-3 , while 2 patients with raised tumor markers showed negative PET/CT study(FN). Forty eight patients had normal serum level of tumor markers, nine of them showed positive PET/CT study. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of PET/CT were 96.7, 89.7, 93.7,94.2 and 94% respectively. These parameters were 72.1, 82, 86.3, 65.3 and 76% for conventional imaging modalities. **Conclusion**: PET-CT is a powerful diagnostic method in the restaging of breast cancer and detection of metastases in patients with raised serum tumor markers and/or negative or equivocal radiologic imaging modalities, however conventional imaging modalities with multiphase CT or MRI are more sensitive in detection of early small lesions in liver and lung.

Key words: conventional imaging modalities**,** ^{18}F- FDG-PET/CT**,** tumor markers

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INTRODUCTION

Breast cancer is the most common type of cancer and the second leading cause of cancer mortality in women. Although its incidence continues to rise, mortality has declined over the past several years attributed to both early diagnosis and more effective treatment[1]. Whole-body PET/CT is highly accurate method compared with conventional imaging for restaging patients with breast cancer and to evaluate sites of metastatic disease that can be extensive and separated by large anatomic distances. Several investigations have shown the added benefit of FDG-PET to conventional imaging in asymptomatic patients who had elevated tumor marker serum levels and negative or equivocal conventional imaging[2]. Also, in patients with suspected recurrence, specially in patients with prosthesis, conventional imaging modalities may be false negative (FN) because of hidden lesions or because of post-radiation changes in previously treated patients [3].

FDG PET/CT imaging has been advocated by many investigators in patients with increasing tumor markers as an optimal method in detection of early loco-regional and metastatic tumour recurrence with subsequent influence on treatment outcome [4].

FDG PET/CT is more sensitive than conventional imaging for detecting metastatic breast cancer and has improved anatomic correlations, resulting in more accurate measurement in metastatic breast cancer[5]. FDG PET/CT has been shown to be valuable for loco-regional and distant staging in both primary and recurrent breast cancer[6]. The aim of this study was to assess the role of FDG PET/CT in detection of tumor recurrence or metastatic lesions in patients with Raised serum tumor markers or with equivocal abnormalities detected in other diagnostic imaging modalities during follow up of patients with breast cancer.

PATIENTS AND METHODS

Patient population

This prospective study included 100 female patients with previously diagnosed and treated breast cancer referred to PET/CT department of the international medical centre (IMC) during the period between March 2009 and February 2012 for follow up in view of increased serum tumour markers and/or equivocal radiological imaging. The protocol of the study was approved by the ethical committee. Their main ages were 51.98 + 7.56 years. The inclusion criteria included recently increasing level of serum tumor markers during routine follow up, negative or equivocal finding in conventional imaging modalities [contrast enhanced CT, magnetic resonance (MRI) mammography, ultrasound and bone scan] and suspicious clinical local recurrence or axillary lesions.

Patient Preparation

The patient is asked to be fasting for 6 hours prior to scan. Remove metallic items from the patient. Insert an I.V. catheter in the patient's arm for administration of 18F-FDG. They were instructed to avoid caffeinated drinks but can have water during this period. Patients are also instructed to avoid any kind of strenuous activity prior to the examination and following injection of the radioisotope to avoid physiologic muscle uptake of FDG. The patient is asked to void prior to scanning. Diabetic patients should be controlled prior to study.

Image acquisition:

PET/CT is performed at International Medical Centre (IMC) on an integrated scanner (Philips; TOF; 64 slice CT) that combines both CT and PET capabilities in two sequential gantries, avoiding the need for patient motion between the CT and PET components of the study and thereby leading to accurate co-registration of the CT and PET data. PET images will be acquired during normal breathing in the three-dimensional mode for 2 minutes per bed position 60 minutes after intravenous administration of (0.1) mCi FDG /Kg. PET images are reconstructed by using standard reconstruction algorithm (OSEM). Attenuation correction of PET images is performed by using attenuation data from the CT component of the examination; emission data are corrected for scatter, random events, and dead-time losses by using the manufacturer's software. The CT component of the study comprises a multi-detector CT examination from the base of the skull to the upper thighs (120 mAs, 140 kVp, table speed = 13.5 mm per rotation). PET/CT images are analyzed both qualitatively and semi-quantitatively. The intensity of FDG uptake within specific lesions is calculated by using a volume of interest over the lesion, according to the following formula: SUVmax = maximum measured activity in the volume of interest (milli-Curies per milli-Liter)/injected dose of FDG (milli-Curies) per gram of body weight. The standard SUVmax of 2.5 was considered a cut off point. SUV max of 2.5 and above in PET/CT studies were considered positive for disease involvement, while SUV max below 2.5 were considered to be insignificant of disease involvement.

Study interpretation:

The PET, CT, and fused PET/CT Images were separately interpreted by 2 experienced nuclear medicine physicians and were compared to PET/CT images. Qualitative assessment for presence of hyper- metabolic lesions was evaluated on corrected PET images. Semi-quantitative evaluation was performed using the Standardized Uptake Value (SUV max), of all abnormal foci (Normal < 2.5).

Comparison with other clinical and diagnostic methods including laboratory, bone scan, diagnostic CT or MRI were done. Criteria used for the evidence of recurrence were histo-pathological confirmation of suspicious lesions, further clinical follow-up (6-12 months) suggestive of disease recurrence, tumour markers and other independent imaging studies (such as CT, MRI, PET/CT, X-ray studies, bone scans, ultrasound and mammography).

The patient was considered as having recurrent cancer breast if she fulfilled one or more of these findings:

A) **Concordant positive lesions** were defined as showing true disease involvement in both PET and CT studies and confirmed with other diagnostic tools or follow up PET/CT.

B) **Discordant results** were further verified by biopsy or by follow up PET/CT or other imaging modality including CT, MRI and bone scintigraphy for 6-12 months.

Data analysis

A true-positive lesion was defined as a lesion seen on FDG PET/CT images and found to be positive for tumour tissue at

histological examination or clinical /radiological follow up. While a false positive lesion was defined as a lesion seen on FDG PET/CT images and found to be negative in tumour tissue at histological examination or clinical /radiological follow up. A true negative lesion was defined when no lesion was seen on FDG PET/CT images and the results at histological examination or clinical/radiological follow up were negative. Where as a false –negative lesion was defined as a lesion that was missed in image analysis but was found to be positive for malignancy at histological examination or clinical/radiological follow up.

Statistical analysis:

Standard statistical methods was applied including Chi-Square test and Receiver operating characteristics (ROC) curve analysis was performed to compare sensitivity, specificity and accuracy between PET/CT and other conventional radiological modalities in follow up of breast cancer, determined on a lesion-based analysis. Statistical analysis was performed using SPSS (Version 20, 2011) (SPSS Inc., Chicago,I llinois, USA) software. Results were considered statistically-significant if ***P***-value < 0.05.

RESULTS:

A hundred female patients with previously diagnosed and treated breast cancer were included in the study with mean age of 51.98+ 7.5 years. Among those 100 female patients, PET/CT detected recurrence and/or metastases in 63 patients including 23 patients had loco-regional recurrence (12 patients had local recurrence, 6 patients had lymph nodes (LNs) involvement and 5 patients had other breast involvement). Eleven patients had metastatic lesions with solitary organ involvement (6 bone lesions, 3 liver lesions and 2 patients had lung lesions), whereas 29 patients had multiple organs involvement (Fig 1, 2). Fifty one patients out of 100 patients showed significant positive lesions by other radiological tools, their distributions were as follows: 12 patients had loco-regional recurrence (4 patients had local recurrence, 2 patients had LNs involvement and 6 patients had other breast involvement) 24 patients had solitary metastatic organ involvement (10 patients had bone lesions, 9 had liver lesions and 5 had lung lesions) Also,15 patients showed multiple organs involvement .

PET/CT versus other radiological imaging:

As regards evidence of loco-regional recurrence there was a highly significant correlation between the PET/CT findings as compared to radiological imaging (***P-value*** <0.05). Also, PET/CT scan showed a better significant detection of multiple organs involvement, while other radiological imaging tools showed better evaluation of solitary small lesions in lung and liver (***P***-value < 0.01) (**table1**).

There were 4 false positive (FP) patients in our study with moderate FDG uptake in benign lesions. In one of them there was significant FDG avid uptake in the axillary LNs and biopsies revealed inflammatory reaction, the other 3 patients showed FDG avid osseous lesions attributed to post therapy effect at follow up PET/CT. Also, two false negative (FN) patients in which PET/CT was negative and bone scan revealed osteoblastic metastatic osseous lesions that were missed by PET/CT (table3). In other radiological modalities there were 7 FP, 17 FN patients attributed to either post therapy changes

or small lesions size. Diagnosis of recurrence and/or metastases were confirmed in all of the true positive (TP) 59 patients during the clinical follow up. Fifty patients out of 59 with true positive PET/CT had raised tumor markers carcino-embryonic antigen (CEA) or CA 15-3 . While, 2 patients with raised tumor markers showed negative PET/CT study (FN). Forty eight patients had normal serum level of tumor markers, nine of them showed positive PET/CT study **(table 2).**

Sensitivity and specificity were statistically calculated by comparing the results of the study between the findings of PET/CT and the findings of the other radiological imaging tools based on the criteria of disease recurrence that included the confirmed results by either histo-pathological assessment or follow up PET/CT or other imaging 6-12 months **(table 3).**

(Table 1) Comparison between PET/CT findings and other radiological modalities as regards lesions distributions

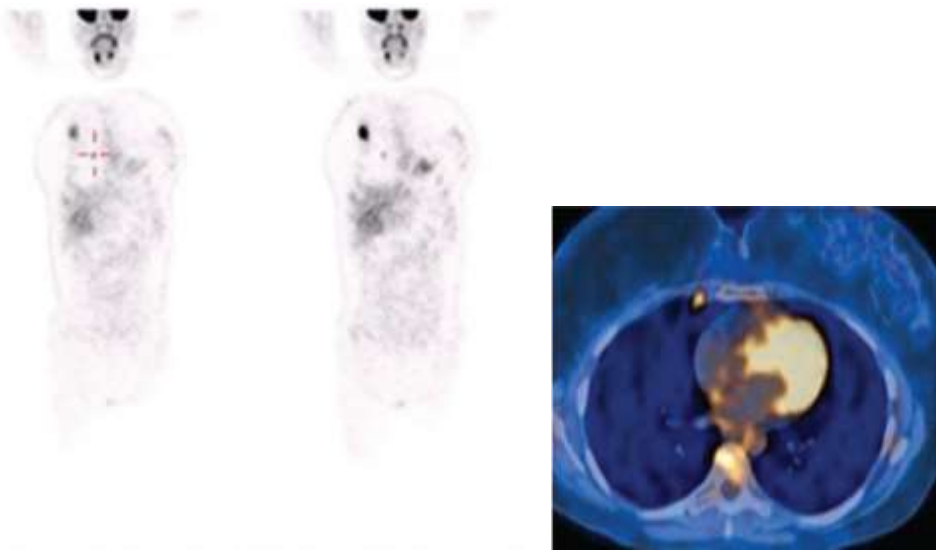
Distribution of findings	by PET/CT	by other radiological modalities	p-value
Non detectable lesions	37	49	<0.01
Detectable lesions	63	51	
Loco-regional recurrence	23	12	<0.01
Solitary organ involvement	11	24	<0.01
Multiple organ involvement	29	15	<0.01

(Table 2) Relationship between level of serum tumour markers and PET/CT findings

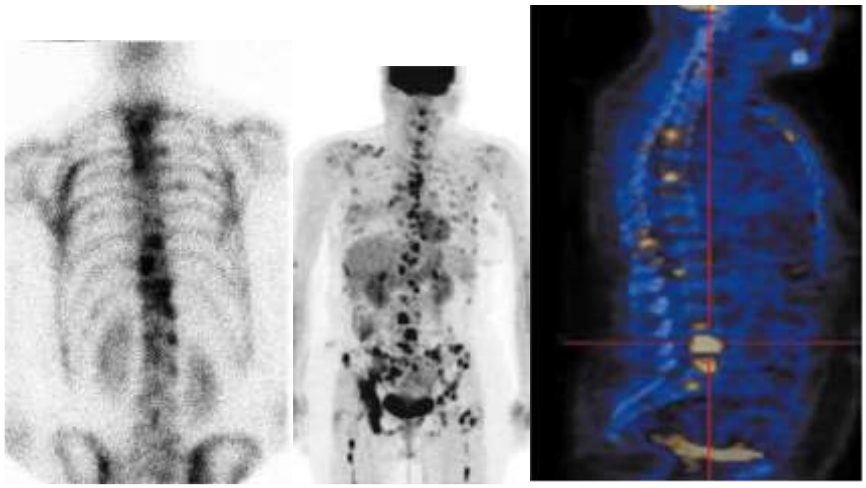
Serum Tumour Markers	PET/CT -VE	PET/CT +VE	Total number
High serum tumor markers	2	50	52
Normal serum tumor markers	39	9	48
Total number	41	59	100

(Table 3) Sensitivity and Specificity of the PET/CT findings versus the other radiological imaging findings

Characteristic	N	FN	TP	TN	FP	Total	Sensitivity	Specificity	Accuracy	PPV	NPV
PET/CT	100	2	59	35	4	100	96.7	89.7	94	93.7	94.2
Radiological tools	100	17	44	32	7	100	72.1	82	76	86.3	65.3



(Fig 1) 46-yrs old woman with Rt breast cancer, stage IIIa , she underwent mastectomy 9 yrs ago, follow up PET/CT showed focal area of intense 18F-FDG uptake in right breast, and small area of increased tracer uptake is seen in right internal mammary lymph node suggestive of loco-regional recurrence.



(Fig 2) 64 yrs-old female patient, with RT breast cancer, her follow up revealed elevated level of tumour markers, bone scan revealed multiple osseous deposits. PET/CT study showed multiple metastatic lesions at bone, liver and LNs.

DISCUSSION:

Imaging techniques play an important role in the detection and staging of breast cancer. Early detection improves patients' prognosis, and accurate staging has a substantial influence on therapy management[7&8]. The more widespread availability is an important advantage of CT but, unfortunately, CT is not applicable for proper restaging[9].Currently PET/CT is used to provide reliable restaging information with high rates of sensitivity and accuracy (approximately 90%) for detecting loco-regional and metastatic tumour recurrence[10]

In our study PET/CT scan showed a significant better detection of the recurrent breast lesions (loco-regional recurrence) in 23 patients with PET/CT compared to 12 patients with other radiological modalities (***P***-value < 0.01) and also helped in changing patients management. Similar to our study, ***Aukema et al.*** conducted a study on 56 patients to assess the role of FDG PET/CT in patients with loco-regional breast cancer recurrence compared to conventional imaging techniques and revealed that in 25 patients (45%), PET/CT detected additional lesions not visible on conventional imaging. Also PET/CT had an impact on clinical management in 27 patients (48%) by detecting more extensive loco-regional disease [11].

In our study, combined PET/CT revealed 6 patients with lymph nodes versus only 2 patients by other radiological modalities.

Gerwin et al. studied 33 breast cancer patients with suspicious of recurrence and concluded that whole body MRI is highly sensitive to distant metastatic disease, while PET/CT is highly sensitive in detecting lymph nodes involvement[12].

In this study, PET/CT revealed only 6 patients with osseous lesions, whereas, other radiological modalities including bone scan, revealed 9 patients with bone metastases. The three patients missed by PET/CT had sclerotic lesions. PET/CT is more sensitive in evaluation of lytic or mixed lesions with low detection rate in sclerotic lesions, these lesions appear non avid to FDG and showed false negative results.

In general the most common reason for false-negative results on PET/CT imaging is sclerotic bone lesions[13].

In our study, detection of multiple metastatic lesions in multiple organs by PET/CT was possible in 29 patients versus 15 patients using other radiological modalities. Such findings reflect the importance of whole body PET/CT in evaluation of metastatic lesions, however, PET/CT is less sensitive in detection of small solitary lesions in liver or lungs which is better detected by CT or MRI. Only 2 patients with lung lesions was detected by PET/CT versus 5 patients by other radiological tools, also 3 patients with liver metastases detected with PET/CT versus 10 patients by other radiological tools. Also, ***David et al.*** reported that PET/CT out performed conventional imaging for bone metastases, distant lymph nodes, and liver metastases, whereas CT was more sensitive for lung metastases.

Also he declared that PET/CT had the advantage of allowing chest, abdomen and bone to be examined in a single session. Almost all distant lesions detected by conventional imaging were depicted with PET/CT, which also showed additional lesions[14].

Bast et al. stated that increasing tumour markers are non-specific and cannot indicate the true extent of the disease and the sites of recurrence and that the precise restaging requires the use of imaging modalities[15]. Increasing tumour markers may be false positive in some benign and physiologic conditions [16]. In our study, fifty patients out of 59 with true positive PET/CT had raised tumor markers, carcino-embryonic antigen (CEA) or CA 15-3 levels for diagnosis of systemic recurrence. Forty eight patients had normal serum level of tumor markers, nine of them showed positive PET/CT study. ***Duska et al.*** in a study conducted at 61 patients with breast cancer on the role of FDG PET/CT and conventional imaging for predicting outcome in previously treated breast cancer declared that the sensitivity of PET/CT reached 93% versus 79% for conventional imaging and specificity of PET/CT reached 84% versus 68% for conventional imaging and an accuracy of PET/CT 84% versus 59% for conventional imaging [17]. Similarly, our study showed that the sensitivity of the PET/CT reached up to 96.7 % versus 72.1 % of the other radiological tools and its specificity was 89.7 % versus 82 % for other radiological modalities with an accuracy reaching 94 %.versus 70% for other radiological modalities.

CONCLUSION:

PET-CT is a useful tool in assessment of loco-regional recurrence and detection of multiple metastatic lesions in patients with raised serum tumor markers and/or negative or equivocal radiological imaging modalities. However, conventional imaging modalities with multiphase CT or MRI are more sensitive in detection of early small lesions in liver and lungs.

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