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Role of FDG-PET/CT in Assessment of Response to Therapy in Breast Cancer Patients

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ABSTRACT:

Objective: We aimed to assess the role of FDG PET/CT in evaluation of early response to chemotherapy after 2-3 cycles and late response after 6 cycles of chemotherapy to define responders from non-responders to treatment in breast cancer patients. **Patients and Methods** This prospective study included 52 female patients with locally advanced breast cancer, **Group 1:** Included 27 patients referred for PET/CT for assessment of primary lesion following 2-3 cycles of chemotherapy, twenty patients underwent a baseline study before initiation of therapy. **Group 2:** Included 25 patients with recurrent breast cancer referred for PET/CT following 6 cycles of chemotherapy for assessment of disease remission. They underwent a midline study after 2-3 cycles of chemotherapy. **Results** Only 4 patients out of 27 of group 1 showed significant early metabolic response with decrease of SUV value by (65.8%) following 2-3 cycles of treatment with significant reduction of mean SUV max implicating good response to therapy ($p<0.005$), while 23 patients showed partial metabolic response, with reduction of mean SUV max (36.2%). Nineteen out of 25 patients of group 2 (76%) showed significant metabolic response on completion of 6 cycles of chemotherapy with significant reduction of mean SUV max (69.6%) impressive of good therapy response ($p<0.0001$), while the other 6 patients (24%) showed poor metabolic response with mean reduction of SUV max of 30.8% and evidences of metastatic disease signifying poor therapy response.

Conclusion: PET-CT seems to be useful for monitoring response to chemotherapy in locally advanced breast cancer differentiating responder from non-responder in therapy evaluation.

Key words: breast cancer, - 18 F -FDG-PET/CT, treatment monitoring

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INTRODUCTION:

Neoadjuvant therapy is now commonly used in patients with locally advanced breast cancer, as it improves surgical options and provides prognostic information[1]. Primary systemic chemotherapy was first introduced for managing inoperable locally advanced breast cancer [2]. The availability of various new therapies for relapsing breast cancer as well as determination of the extent of disease and its precise localization of utmost importance [3].Combined PET/CT showed superior results in staging and impact on therapy response in advancing breast cancer [4]. Imaging with PET/CT for tumor therapy monitoring has been introduced as it provides proper assessment of tumor response and improve the accuracy in the evaluation of treatment response by directly defining metabolic and morphological changes [5]. Multiple studies have evaluated serial FDG PET imaging performed at different time points after initiation of neoadjuvant therapy and have demonstrated the following: (a) A serial decrease in tumor FDG uptake measured using SUV or the metabolic rate of FDG, is an indicator of response. (b) FDG PET performed early at mid therapy is predictive of complete microscopic response and may serve as a surrogate marker for response. (c) Changes in FDG metabolism often precede morphologic changes in tumor and therefore PET can demonstrate response sooner than conventional imaging techniques. (d)

FDG PET is likely to be most helpful as an early marker for resistance to therapy. FDG PET imaging performed after completion of therapy allows confirmation of gross residual disease but does not allow exclusion of residual microscopic malignancy [6]. The mean reduction in 18F-FDG uptake after the first 2 cycles of chemotherapy was significantly higher in responding than in non-responding tumor[6]. We aimed to assess the role of FDG PET/CT in evaluation of early response to chemotherapy after 2-3 cycles and late response after 6 cycles of chemotherapy to define responders from non-responders to treatment in breast cancer patients.

PATIENTS AND METHODS:

Patient population this prospective study included 52 female patients with locally advanced breast cancer referred to PET/CT department of the International Medical Centre (IMC) between March 2009 and February 2012, their main age were 52.36 +5.76 years. Clinical and diagnostic methods including mammography, abdominal ultrasonography, bone scan, diagnostic CT and/or MRI were done for diagnostic work up. Patients were divided into two groups **Group** 1: 27 patients with locally advanced breast cancer referred for early PET/CT assessment of primary lesion before chemotherapy (20 patients) and following 2-3 cycles of chemotherapy, **Group** 2: 25 patients with recurrent breast cancer referred for PET/CT following 2-3 cycles and 6 cycles of chemotherapy for assessment of disease remission. The protocol of the study was approved by the ethical committee.

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 ^{18}F-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 with maximum glucose level of 160 mg/dl.

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. 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: SUV max = maximum measured activity in the volume of interest (millicuries per milliliter)/injected dose of FDG (millicuries) per gram of body weight. The standard SUV max of 2.5 was considered a cutoff 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).

Data analysis:

True-positive lesion was defined as a lesion seen on FDG PET/CT images with high SUV max >2.5 and found to be positive for tumor tissue at histological examination or clinical /radiological follow up.

True-negative lesion was defined when no lesion was seen on FDG PET/CT images and the results on clinical /radiological follow up were negative.

Assessment of response to therapy:

(a) Good response to therapy was considered when there was significant metabolic response on PET/CT with reduction of SUV max 60% or more than the baseline study in the first group after 2-3 cycles or at end of 6 cycles of therapy in the second group.

(b) Poor therapy response was considered when there was residual metabolic uptake by PET/CT with reduction of SUV max<60% than the baseline study or appearance of new metastatic lesions.

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, llinois, USA) software. Results were considered statistically-significant if P-value <0.05.

RESULTS:

Fifty two female patients with previously diagnosed and treated breast cancer were included in the study with mean age of 52.36 ± 5.76 years.

Group1: Early Therapy Monitoring

27 patients with locally advanced breast cancer (21 patients with stage III B and 6 patient with stage III C) referred for PET/CT assessment of primary lesion before and following 2 -3 cycles of chemotherapy. Only 4 out of 27 showed significant metabolic response on PET/CT with reduction of mean SUV max from 7.9 ±1.5 to 2.7±0.3 with (65.8%) degree of response (P<0.005). These 4 patients performed surgery in view of good response to therapy. The other 23 patients had mean SUV max of 8.3±1.2 with partial response and decrease of mean SUV max to 5.3±1.0 with response rate of (36.2%). These patients did not perform surgery and suggest to change line of chemotherapy. All results were confirmed by histo-pathological assessment following surgery or biopsy **(Table1).**

(Table 1): Quantitative baseline PET/CT and following 2 -3 cycles of chemotherapy in 27 patients of locally advanced breast cancer

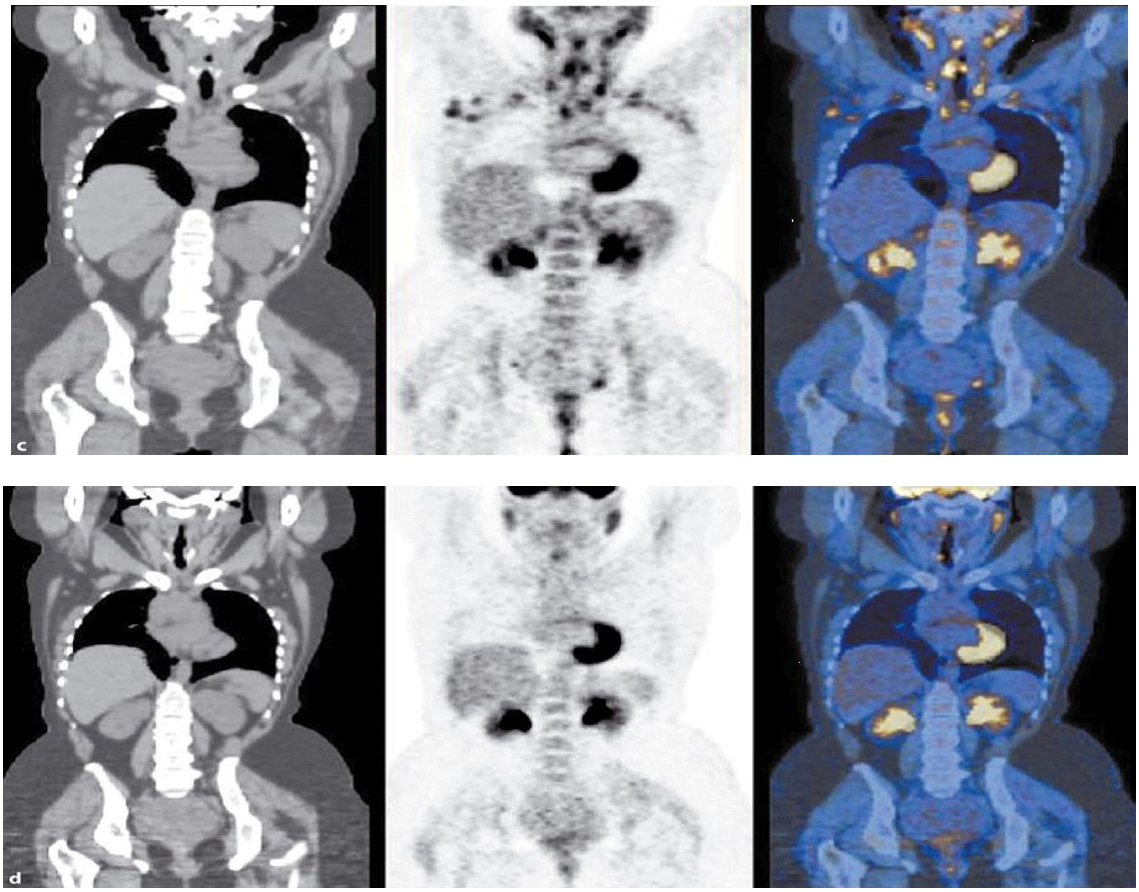
No of patients	Degree of response to therapy with % reduction on SUV value	Mean SUV max in baseline PET'CT study	Mean SUV max after2-3 cycles of chemotherapy
4	65.8%	7.9±1.5	2.7±0.3
23	36.2%	8.3±1.2	5.3±1.0

Group 2: Late Therapy Monitoring

25 patients with either recurrent or metastatic breast cancer referred for therapy monitoring after 2-3 cycles and repeated after 6 cycles of chemotherapy for assessment of disease remission. Nineteen out of 25 patients (78%) showed significant metabolic response on PET/CT with reduction of mean SUV max, from 6.5±1.1 to 2.1±0.6 (69.6%) (p<0.0001) denoting good responder **(fig 1).** While, the other 6 patients (24%) showed poor metabolic response with reduction of mean SUV max from 6.5±1.1 to 4.5±0.7 (30.8%) signifying non responders to therapy **(Table 2).** All 6 non responders showed also metastatic spread at 6-12 months follow up (bone in 2 patients, liver in one patient, lung in one patient and multiple organs in 2 patients. Metastatic spreads were confirmed by follow up PET/CT or other radiological imaging including chest and abdominal CT and bone scan.

(Table 2): Quantitative PET/CT after 2-3 and 6 cycles of chemotherapy in 25 patients with recurrent breast cancer

No of patients	Degree of response to therapy	Mean SUV max at 2-3 cycles of chemotherapy	Mean SUV max at 6 cycles of chemotherapy
19	69.6%	6.9±0.8	2.1±0.6
6	30.8%	6.5±1.1	4.5±0.7



(Fig 1): 35 year-old female patient, (A) she has got right breast cancer, initial base line study showed right axillary LNs, (B) post therapy study showed complete disappearance of the axillary nodal lesions signifying good response to the given therapy.

DISCUSSION:

Primary systemic chemotherapy was first introduced for managing advanced breast cancer [2].The availability of various new therapies for relapsing breast cancer as well as determination of the extent of disease and its precise localization of utmost importance[3].The main rationale for primary chemotherapy is to test for chemosensitivity, allowing for subsequent changes in the chemotherapy regimen, with the aim of designing a more individualized treatment plan [7, 8, 9].

The use of 18F-FDG PET for predicting a therapeutic response is based on early changes in tumor glucose use and changes in 18F-FDG uptake indicating effectiveness of treatment [10, 11].

The degree of change in FDG tumor uptake between baseline and after one or two courses of chemotherapy is correlated with histo-pathologic response after the completion of therapy. This approach appears to be of particular interest because it might offer an early opportunity to change therapeutic strategy in case of inadequate response [12, 13].

The present study, confirms previous reports on the predictive value of early changes in glucose metabolism after initiation of chemotherapy. Four out of 27 patients with locally advanced breast lesions assessed after 2-3 cycles of chemotherapy, showed significant metabolic response in PET/CT in view of reduction of SUV max (65.8%) as compared to baseline study. while 23 patients (85%) defined as having poor therapy response in view of reduction of SUV max (36.2 %) than baseline study **(Table 1)**.

Andrade et al. suggested that the FDG-PET/CT after the second cycle of chemotherapy can predict pathological response in breast cancer, and potentially identify a subgroup of non-responding patients for whom ineffective chemotherapy should be avoided [14]. Many studies determined a threshold value of decrease in FDG uptake to predict response to chemotherapy: This cutoff varies from 40% to 60% of baseline uptake after two courses of chemotherapy [15, 16, 17].

Wahl et al. reported on changes in tumor metabolic activity in a series of 11 women who had locally advanced primary breast cancers and who had received a combination of primary chemotherapy and hormone therapy. Tumor 18F-FDG uptake promptly decreased in 8 patients, with subsequent partial or complete pathologic responses, whereas tumors in 3 non responding patients did not show a significant decrease in 18F-FDG uptake[18].

Later studies confirmed a more pronounced decrease in 18F-FDG uptake SUV max after the first and second cycles of primary chemotherapy in patients showing a histo-pathologic response than in non-responders [19, 20].

In another study, 30 breast cancer patients received 8 cycles of primary chemotherapy and the mean reduction in 18F-FDG uptake after the first cycle was significantly higher in lesions with a partial, complete macroscopic or complete microscopic response than in non-responding lesions[16].

Furthermore, a multicenter trial in which

272 18F-FDG PET scans were performed for 104 patients, confirmed that the greater the reduction in tumor metabolic activity early in the course of therapy, the more likely that patients would achieve a histo-pathologic response[17].

Also, in another study with In patients who showed histo-pathologic response, the SUV decreased by 50.5%± 18.4% after the first cycle of primary chemotherapy; in comparison, the SUV decreased by 36.5%±6 20.9% in non-responders. Patients who did not show a histo-pathologic response were identified when the relative decrease in the SUV max of less than 45%was used as a cutoff [17].

Emmering et al suggested that the residual tumor FDG uptake after completing neoadjuvant chemotherapy predicts residual disease and is highly predictive of relapse [21].

In our study the second group of 25 patients referred for therapy monitoring after complete cessation of the therapy, 19 patients of them (76%) showed significant metabolic response in PET/CT in view of reduction of mean SUV max 69.6% as compared to mean value after 2-3 cycles suggestive of good responder **(Table 2).**

Also, in monitoring disease response for metastatic cancer, a study involving 20 patients demonstrated that 75% of patients showing a metabolic response on visual analysis responded well to therapy [21].

Dose Schwarz et al. confirmed previous observations on the predictive value of information about early changes in glucose metabolism for metastatic breast cancer, compared with the baseline PET/CT data, the18F-FDG uptake in responding metastatic lesions decreased to 54% ±16% after the second cycle of chemotherapy. In contrast, the 18F-FDG uptake in metastases not responding to chemotherapy declined only to 79% ± 6.9 % after the second cycle of chemotherapy[22] to conclude, FDG/PET can differentiate responder from non-responder to chemotherapy after 2-3 cycle and end of 6 cycle of treatment.

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