The role of ^{18}F-FDG PET/CT in initial staging of patients with locally advanced breast carcinoma with an emphasis on M staging

Abstract

Locally advanced breast cancer (LABC) is a distinct entity in breast carcinoma with high incidence of distant metastases (M). However, there is scarce data in the literature addressing the role of fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in LABC. *This study was performed* to assess the sensitivity of ^{18}F-FDG PET/CT in confirming known lymph nodal and M and in identifying new ones in LABC. *We performed a retrospective analysis of data* of 16 patients with LABC who underwent histopathology, for the diagnosis of LABC and clinical examination, chest X-rays, ultrasound of the abdomen and whole body bone scans. Findings for M obtained by all the above examinations were compared to the ^{18}F-FDG PET/CT findings that followed. *Lymph nodal and distant metastases detected* by all other examinations were detected by ^{18}F-FDG PET/CT in all patients, except subcentimetric metastases in 2 patients in the axilla that were detected in another examination later. Additionally, ^{18}F-FDG PET/CT identified unknown ipsilateral, supraclavicular, internal mammary metastases and upstaged disease in 3 patients and additional distant metastases were noted in 3/16 patients. *In conclusion*, our study suggests that more extra axillary lymph nodal and distant metastases can be identified by ^{18}F-FDG PET/CT as compared to a group of clinical, X-rays, ultrasound and bone scan examinations together.

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Introduction

Breast cancer (BC) is the most common non-skin cancer, and the second leading cause of cancer death in women [1]. About 20% of newly diagnosed breast cancers are locally advanced [2]. Locally advanced BC encompasses advanced primary tumors (T3 and T4); advanced lymph node disease which includes fixed axillary lymph nodes and/or involvement of the ipsilateral supraclavicular, infraclavicular, or internal mammary lymph nodes (N2 and N3); and the uncommon inflammatory breast carcinoma (IBC) variant [2, 3]. Differentiation of stage IIB and III from stage IV disease is important to determine treatment [4, 5]. Although ^{18}F-FDG PET/CT has often been used in restaging BC and to examine in response to chemotherapy [6-16], scarce literature exists for LABC [3, 17-19]. Thus, we have studied the role of ^{18}F-FDG PET-CT in staging LABC with emphasis to identifying extra-axillary lymph nodal and distant metastases (M) as compared to clinical X-rays, ultrasound and bone scan examinations together.

Subjects and methods

Retrospective analysis of medical records of the patients with LABC diagnosed histologically, with known stage IIB (T3N0) -5, IIIA (T3N1) -2, IIIB (T4N1) -3, IIIC (T4N3) -1 and stage IV -5 who underwent ^{18}F-FDG PET-CT for reaffirming known lymph nodes metastases and possibly describing new metastases. Patients who had undergone prior neoadjuvant chemotherapy or surgery were excluded. Prior to ^{18}F-FDG-PET/CT, the patients underwent clinical diagnosis by palpation, chest X-rays, USG of the abdomen and whole body bone scans. The PET/CT scans were acquired almost 60min after intravenous injection of 370-444MBq of ^{18}F-FDG via an already secured peripheral venous catheter. Images from the base of the skull to the mid thigh were acquired in 3-D mode at 2min per bed position in supine position using a PET/CT scanner (Discovery STE 16, GE Healthcare, Milwaukee, USA) having16-slice light speed CT component. All patients fasted for at least 6h before the injection and fasting blood glucose levels were ensured to be less than 150mg/dL. Non contrast-enhanced CT images (120kVp, 300mAs) were acquired in helical mode at a speed of 13.5mm/rotation with

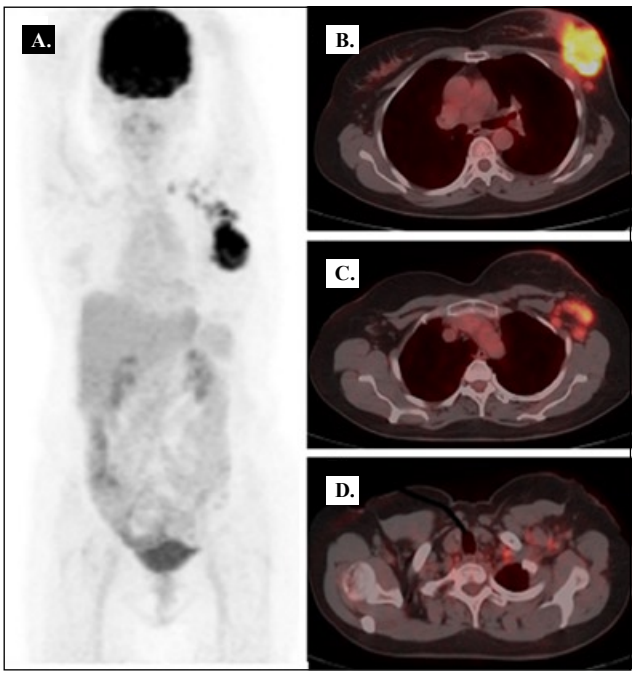

Figure 1. ^{18}F-FDG PET/CT scan in a 62 years old female patient with left breast carcinoma of size 5cm and palpable enlarged axillary lymph nodes. MIP image (**A**) showing intense ^{18}F-FDG uptake in mass in left breast and ipsilateral axillary and supraclavicular lymph nodes. Transaxial images (**B-D**) showing intense uptake in breast mass (SUVmax-13.2) along with a small satellite nodule (**B**), intense ^{18}F-FDG uptake in axillary lymph nodes (**C**) and moderate ^{18}F-FDG uptake in ipsilateral supraclavicular lymph node of 7mm size (**D**) which would have been assumed to be benign on CT.

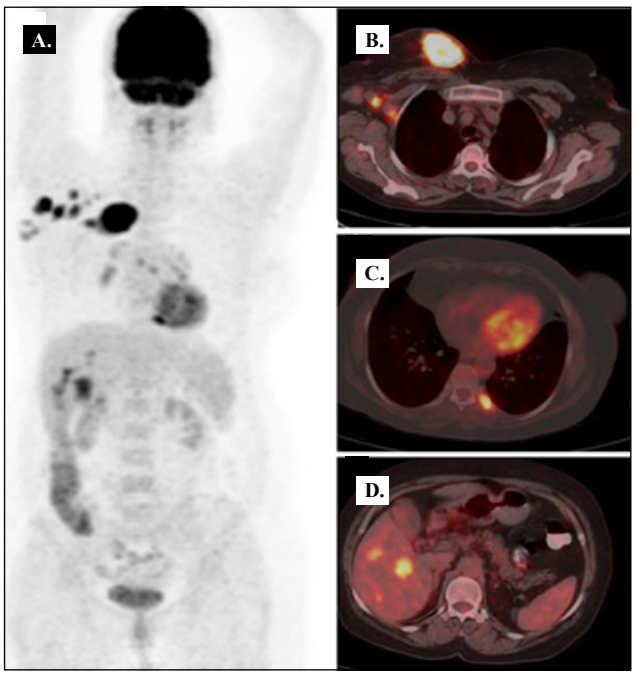

Figure 2. ^{18}F-FDG PET/CT scan in a 65 years old female with diagnosis of LABC. MIP image (**A**) showing intense ^{18}F-FDG uptake in mass in left breast. Additionally ^{18}F-FDG uptake is also noticed in bone and liver indicating presence of distant metastases. Transaxial images (**B-D**) show intense ^{18}F-FDG uptake in breast mass and axillary lymph nodes (**B**) costotransverse joint of left 9th rib (**C**) and multiple lesions in liver (**D**).

slice thickness of 5mm. The acquired data was reconstructed using standard vendor-provided OSEM (Ordered Subset Expectation Maximization) algorithm. The CT, PET, and co-registered PET/CT images were reviewed in all standard planes with maximum-intensity whole-body coronal projection images. The PET scans were analyzed visually and semiquantitatively and ^{18}F-FDG uptake was considered to be abnormal on visual analysis when uptake was visually higher than that in the background in the contra lateral breast or in the axilla. Standardized uptake value (SUVmax) for primary and all metastases was semi-quantitatively analyzed, after being corrected for radioactive decay. The CT criterion for malignant nodes included a one short-axis diameter of more than 1cm.

Results

Uptake of ^{18}F-FDG was noted in all primary lesions and in all metastatic lesions already known with a sensitivity of 100%. Mean SUVmax of the primaries was around 12.2 and mean size of lesions was around 3.84cm.

Axillary lymph nodal uptake suggesting lymph nodal metastases was noted in 12/16 (75%) of the patients. Mean SUVmax noted was around 6.6 (range 2.8-30) and mean size of lesions was around 1.3cm (range 6-40mm). The smallest lymph node to have ^{18}F-FDG uptake was around 6mm in short axis. Axillary lymph nodal metastases were missed in 2 patients. These false negative (FN) cases had lymph nodal size around 4mm. PET positive axillary lymph nodes had mean size of lymph nodes around 9mm (range 7-11mm) with mean SUV 9.4 (range 4-26). The ^{18}F-FDG-PET/CT scan identified 3 more patients with ipsilateral supraclavicular lymph nodal, internal mammary lymph nodal interpectoral lymph nodal metastases than the group of previously performed examinations

In general, distant metastases M were detected in seven patients. Four patients had multiple sites of distant metastatic involvement and 3 had isolated distant metastatic involvement. Skeleton was the most common site of involvement and was noted in 5 patients followed by liver metastases in 3, lung metastases in 2**,** mediastinal lymph nodal metastases in 2 patients. Bone metastatic lesions were purely lytic in 2 patients, purely sclerotic in one patient and mixed in 2 patients. Mean SUVmax was slightly higher in lytic lesions (SUVmax=11.2) than sclerotic lesions (8.4).

After ^{18}F-FDG PET/CT over all intrastage upstaging was noted in 3 patients and interstage upstaging was noted in another 3 patients. Furthermore**,** one patient with suspected liver metastases was accurately downstaged by ^{18}F-FDG PET/CT. Metastatic sites by ^{18}F-FDG PET/CT are summarised in Tables 1 and 2.

Discussion

In our study significant ^{18}F-FDG uptake was found in all primary BC lesions with a sensitivity of 100%. This is significantly higher than of previous studies which showed less sensitivity in lower stage of BC [20, 21] and comparable to 98% sensitivity detected by previous study in inflammatory

Table 1. *Depicting the lymph nodal (N), distant metastatic (M) stage and final TNM stage in 16 patients with LABC*

S.No	Pre PET/CT stage	After PET/CT stage Same or altered	More extra axillary lymph nodal metastases	More Distant metastases	Comments TD and FN
1	T3N0M0 (IIB)	T3N0M0 (IIB)	No	No	Found to have axillary lymph node metastases atfter surgery
2	»	»	»	»	Found to have axillary lymph node metastases atfter surgery
3	T4N1M1 (?IV)	T4N2M0 (IIIB)	Yes (interpectoral lymph nodes)	Yes	PET/CT excluded liver metastases
4	T4N1M0 (IIIB)	T4N1M0 (IIIB)	No	No	
5	»	T4N3cM0 (IIIC)	Yes (ISCLN)	»	PET/CT detected unknown ISCLN metastases
6	T4N1M1 (?IV)	T4N3bM1 (IV)	Yes	»	PET/CT Confirmed lung metastases
7	T3N1M0 (IIIA)	T3N3cM1 (IV)	Yes (ISCLN)	Yes	PET/CT identified lung metastases missed on chest X ray
8	T4N1M0 (IIIB)	T4N1M1 (IV)	No	»	PET/CT identified unknown opposite SCLN metastases
9	T3N3M1 (?IV)	T3N3M1 (IV)	»	No	
10	T4bN1M1 (?IV)	T4bN3cM1 (IV)	Yes (ISCLN and internal mamary lymph nodes)	»	
11	T4bN2M1 (?IV)	T4bN2M1 (IV)	No	»	
12	T4N3M0 (IIIC)	T4bN3M1 (IV)	»	Yes	PET/CT identified coccygeal metastases missed on bone scan
13	T3N1M0 (IIIA)	T3N0M0 (IIIA)	»	No	
14	T3N0M0 (IIB)	T3N0M0 (IIB)	»	»	
15	»	T4N0M0 (IIB)	»	»	
16	»	T3N0M0 (IIB)	»	»	

ISCLN – ipsilateral supraclavicular lymph nodal metastases. LABC: TD: FN:

Table 2. *Depicting location of distant metastases identified only by ^{18}F-FDG-PET/CT*

Location of distant metastases	No. of patients
Contralateral supraclavicular nodes	3
Contralateral internal mammary lymph nodes	2
Cervical lymph nodes	3
Mediastinal lymph nodes	2
Skeleton	5
Liver	3
Lung	2

breast cancer [18]. High sensitivity may be explained by the fact that the minimum size of the lesion was around 1cm which is higher than the resolution of current generation PET scanners of 5mm. Also all patients had a histological diagnosis of IDC (invasive ductal carcinoma) which is known to be better ^{18}F-FDG avid than lobular and other carcinoma variants. Therefore our present results cannot be generalised to all histology groups of patients especially those with low volume of primary disease.

About 75% of our patients had axillary lymph nodal metastases of around 12mm diameter which might explain this increased incidence. Metastases in subcentimetric (4mm) lymph nodes were FN in 2 patients who were directly subjected to surgery because of contraindications to chemotherapy. This limitation of PET had already been previously mentioned and sentinel node scintigraphy may be better for this purpose [9, 22].

Positron emission tomography was better in detecting internal mammary nodal metastases than CT [23] and was again elucidated in our study because mean size of lesions was about 8mm which as per CT criteria was deemed to be benign lesions. Advantage of PET for M staging lies in its high sensitivity and whole body imaging in one session. In our study ^{18}F-FDG PET/CT revealed all distant metastases detected on conventional imaging in 4 patients and also identified more distant metastases in 3 other patients. Suspected liver metastases were accurately excluded by ^{18}F-FDG PET/CT also in one patient which was suspected as having M on USG which was later proven to be simple cystic by fine needle aspiration cytology. Thus ^{18}F-FDG PET/CT was 100% accurate in M staging and changed the stage of the disease in 4/16 patients when compared to the conventional imaging procedures. Positron emission tomography is known to perform poorly in sclerotic lesions when compared to lytic lesions [24]. However in our study there was no significant difference in SUV of sclerotic and lytic metastases.

Major limitations of our study were that histopathological analysis was not available at all sites of metastases but only to a few of them as it is a common clinical practice to sample only one distant metastatic site for M staging and the limited number of patients. Further prospective studies with large number of patients are needed to elucidate the cost effectiveness and prognostic value of ^{18}F-FDG PET-CT in initial staging of patients with LABC as compared to diagnosing M clinically by X-rays, US and bone scan.

In conclusion, our study shows that ^{18}F-FDG PET/CT as a single diagnostic test in LABC patients is more sensitive than clinical, X-rays, USG and bone scan examinations considered together in detecting extra axillary (supraclavicular and internal mammary) lymph nodal and distant metastases of more than 4mm diameter.

The authors declare that they have no conflicts of interest

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