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ORIGINAL SCIENTIFIC REPORT

Staging PET–CT Scanning Provides Superior Detection of Lymph Nodes and Distant Metastases than Traditional Imaging in Locally Advanced Breast Cancer

Pankaj Kumar Garg[1,2] · Suryanarayana V. S. Deo[1] · Rakesh Kumar[3] · Nootan Kumar Shukla[1] · Sanjay Thulkar[4] · Ajay Gogia[5] · Daya Nand Sharma[6] · Sandeep R. Mathur[7]

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Abstract

Background This study was designed to evaluate the role of a single 18-FDG positron emission tomography and computed tomography (PET–CT) scan in comparison to multiple organ-directed conventional investigations (CI) as a staging tool in locally advanced breast cancer (LABC) to detect regional and distant metastasis.

Methods All eligible patients were subjected to CI (chest X-ray, abdominal sonography, and bone scintigraphy) followed by a single 18-FDG PET–CT scan. Standard imaging criteria were used for diagnosis of metastasis. Histopathological confirmation was undertaken for suspicious lesions. An exploratory analysis was done to assess the impact of PET–CT on the staging of LABC and how it resulted in a change in management.

Result The study included 79 patients of LABC. PET–CT detected distant metastasis in 36 (45.5 %) patients while CI could identify distant metastasis in 20 (25.3 %) patients. Two of the 36 patients in whom PET–CT detected distant metastasis were false positive. Overall PET–CT upstaged the disease in 38 (48.1 %) patients as compared to CI: stage III to stage IV migration in 14 (17.7 %) patients due to identification of additional sites of distant metastasis, and within stage III upstaging in 24 (30.3 %) patients due to identification of additional regional lymphadenopathy. PET–CT led to a change in management plan in 14 (17.7 %) patients.

Conclusion PET–CT has a role in identifying additional sites of regional lymphadenopathy and distant metastasis to upstage the disease in a significant number of LABC patients in comparison to CI; this would help in accurate staging, selecting optimal treatment, and better prognostication of disease.

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✉ Suryanarayana V. S. Deo
svsdeo@yahoo.co.in

[1] Department of Surgical Oncology, Dr BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

[2] Department of Surgery, University College of Medical Sciences and Guru Teg Bahadur Hospital, University of Delhi, Delhi 110095, India

[3] Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi 110029, India

[4] Department of Radiodiagnosis, Dr BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

[5] Department of Medical Oncology, Dr BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

[6] Department of Radiation Oncology, Dr BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

[7] Department of Pathology, All India Institute of Medical Sciences, New Delhi 110029, India

Introduction

As per GLOBOCAN 2012 data (project of International Agency for Research on Cancer), breast cancer is the most frequent cancer in women with an estimated 1.67 million new cases diagnosed in 2012 (25 % of all cases) [1]. Breast cancer is the commonest type of cancer affecting Indian women constituting 27 % of all cancers excluding non-melanoma skin cancers. Majority of patients present with locally advanced disease (stage III) in developing countries including India [2]. Accurate cancer staging helps the oncologists in multiple ways: to select the right treatment plan for a particular patient, to prognosticate the disease course to the patient, to help the patient have realistic expectations, and to compare the results of various trials [3, 4]. The incidence of metastases in stage I and II (early breast cancer) is extremely low (<5 %), whereas a higher incidence of metastatic burden is reported (15–30 %) in locally advanced breast cancer (LABC). Multiple organ-based imaging has been the conventional way of assessing distant metastasis in LABC. This includes chest roentgenography (chest X-ray)/Computed tomography (CT) for lung metastasis, abdominal ultrasonography (USG) for liver metastasis, and bone scintigraphy to look for bone metastasis. Any other investigation may need to be undertaken depending upon the patient's symptoms pertaining to a particular organ. The desire to have a single accurate investigation, which can image multiple organs simultaneously, cannot be overstressed. This will greatly add to the convenience of the patients and will help avoid multiple appointments that they need to fix up for various investigations.

National Comprehensive Cancer Network (NCCN) guidelines recommend, "FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious." It is, however, stated that "FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in LABC when used in addition to standard staging studies" [5]. The impact of PET–CT may be profound in developing countries where majority of the LABC patients present in stage IIIB (clinical T4 lesions) as they seem to be just short of reflecting distant metastasis clinically. Although the evidence is emerging in favor of PET/CT for the detection of distant metastasis of LABC, more data generated through further prospective studies will be able to clear the air, and will inspire confidence in oncologists to accept it as a single staging investigation [4]. This study was designed to evaluate the role of a single PET–CT scan in comparison to multiple organ-directed conventional investigations (CI) as a staging tool in LABC.

Methods

A comparative prospective observational study was conducted at a multidisciplinary Breast Cancer Clinic of a tertiary teaching hospital in North India from May 2014 to April 2015. Institutional Ethical Clearance Committee (Human-Research) approval was obtained prior to initiation of study. A total of 79 female patients (aged 18–80 years) of LABC (stage III, AJCC 7th edition) were included in the study. All the patients were confirmed pathologically to have invasive breast cancer; all of them had good performance status (KARNOFSKY scale >60). Patients who had contraindication to PET–CT scan—pregnant and lactating mothers, uncontrolled diabetes, or reported to have present or past history of any other malignancy were not included in the study. All the patients who did not give informed consent for participation in the study were also excluded.

All eligible patients were subjected to conventional imaging investigations followed by a single whole-body 18-FDG PET–CT scan. CI included chest X-ray (PA view), USG abdomen, and bone scintigraphy. Whole body PET–CT imaging was performed using a biograph PET/CT scanner (Siemens).

The radiologist was blinded to PET–CT data while the nuclear medicine specialist was blinded to conventional imaging results. All image-detected metastatic lesions were considered positive if they were multiple with typical appearance of metastasis (multiple lung nodules or lytic/marrow lesions in the skeleton). In the remaining patients with solitary or doubtful metastasis, histopathological confirmation was done; MRI was undertaken in suspicious skeletal lesions [6].

All patients were treated as per the multimodality protocol using a combination of surgery, chemotherapy, hormonal therapy, radiotherapy, and targeted therapy. Those patients who were detected to have distant metastasis after complete staging were advised systemic chemotherapy; other patients were assessed for operability—operable LABC patients underwent modified radical mastectomy followed by adjuvant therapy while inoperable LABC patients were advised neoadjuvant chemotherapy followed by surgery and radiotherapy. Hormonal and targeted therapies were advised in appropriate patients.

A central computerized-database was maintained—all the clinical, staging, operative, histopathological, and treatment details were entered prospectively. An exploratory analysis was done for each of the variables under the study. An assessment was made of the extent of disease burden (site and number of lesions) detected by CI and PET–CT scan. The number of patients in whom treatment

strategy was changed because of the PET–CT findings was calculated.

Results

There were 79 patients with newly diagnosed LABC. The median age of the patients was 50.0 years (IQR, 40–58). All 79 patients presented with complaint of a breast lump. Eight patients had pain and seven of them had ulcers. None of the patients had nipple discharge or arm edema. Median duration of symptoms was 12 weeks (IQR 4–32).

Clinical staging

Majority of the patients ($n = 75$) had single lump while four patients had multiple lumps. Median tumor size was 6.0 cm (IQR 5–8). T4b lesions (skin ulceration, peau d'orange or satellite nodules) were present in 52 (65.8 %) patients while T4c lesion (skin and chest wall involvement) was present in 1 (1.2 %) patient. The rest 26 (32.9 %) patients had T3 lesion. Axillary lymphnodes were clinically palpable in 70 (88.6 %) patients. Ipsilateral mobile axillary lymphnodes (N1) were present in 22 (27.8 %) patients while ipsilateral fixed or matted axillary lymphnodes (N2) were present in 48 (60.7 %) patients. Ipsilateral supraclavicular lymphnodes (N3) were palpable in 7 (8.8 %) patients. Histopathological diagnosis was infiltrating ductal carcinoma in 77 (97.7 %) patients, mucinous and metaplastic carcinoma in 1 (1.1 %) patient each.

Conventional imaging

CI detected distant metastasis in 20 (25.3 %) patients: Chest X-ray showed evidence of lung metastasis in 6 patients, USG of the abdomen detected liver metastasis in 7 patients while bone scintigraphy showed skeletal metastasis in 12 patients (Table 1).

Positron emission tomography: computerized tomography

Axillary lymphadenopathy

PET–CT detected axillary lymphadenopathy in 78 (98.7 %) patients while clinical examination detected axillary lymphadenopathy in 70 (88.6 %) patients. One patient who had clinically N1 disease was found to have no FDG avid axillary nodes on PET–CT. So, overall additional axillary lymphadenopathy was detected in 9 (11.3 %) patients.

Extra-axillary regional lymphadenopathy

PET–CT detected ipsilateral supraclavicular lymphadenopathy in 18 (22.7 %) patients which was detectable clinically in only 7 (8.8 %) patients. PET–CT detected ipsilateral internal-mammary lymphadenopathy in 26 (32.9 %) patients. Overall, N3 disease was identified in additional 23 (29.1 %) patients and was not recognized by either clinical examination or CI.

Distant metastasis

PET–CT detected distant metastasis in 36 (45.5 %) patients: skeletal, lung, and liver metastasis in 22 (27.8 %), 13 (16.4 %), and 14 (17.7 %) patients, respectively, and isolated contralateral axillary and supraclavicular lymphadenopathy in 1 (1.2 %) patient each (Table 1). Four patients were shown to have isolated liver metastasis following CI and PET–CT; image-guided biopsy was done in these patients to ascertain histopathological confirmation. Three patients had suspected solitary vertebral metastasis following bone scintigraphy and PET–CT; they underwent magnetic resonance imaging for confirmation of skeletal metastasis.

Table 1 Comparison of PET–CT and conventional imaging for identification of distant metastasis

Distant sites	Conventional imaging (Chest X-ray, Bone scintigraphy, Ultrasonography abdomen)				Whole body PET–CT			
	Presence of metastasis	Number of metastasis*			Presence of metastasis	Number of metastasis*		
		1	2–5	>5		1	2–5	>5
Lungs	5	0	2	3	13	0	0	13
Liver	7	4	0	3	14	5	1	8
Skeletal system	12	3	3	6	22	7	2	13

* 1 = one metastatic lesion, 2–5 = two to five metastatic lesion, >5 = more than five metastatic lesions

Table 2 Distribution of additional FDG avid extra-regional lymphadenopathy found in fourteen patients

Site of non-regional lymphadenopathy	Number (%)*
Mediastinal lymph nodes	6 (7.5 %)
Contralateral axillary lymph nodes**	4 (5.0 %)
Contralateral supraclavicular lymph nodes***	4 (5.0 %)
Para-aortic lymphnodes	1 (1.2 %)
Posterior cervical lymphnodes	1 (1.2 %)

* Total number is more than 14 as many patients had more than one extra-regional lymphadenopathy

** One was false positive: Reactive lymphadenitis after excision biopsy

*** One was false positive: Tubercular lymphadenitis after excision biopsy

Fourteen patients had evidence of FDG avid non-regional lymphadenopathy (Table 2). Ten of these patients had associated distant organ metastasis, and so the presence of FDG avid non-regional lymphadenopathy did not alter the management. Out of the remaining four patients, one contralateral axillary lymph node was shown to be tuberculous and another contralateral supraclavicular lymph node was shown to be reactive lymphadenitis following excision biopsy; these two cases constituted false-positive findings on PET–CT. Rest two patients had mediastinal lymphadenopathy which could not be confirmed and were considered non-metastatic as patient did not have any other metastatic lesions. Only 1 patient showed atypical metastasis: multiple subcutaneous nodules along the arm and over the scapula.

Comparison of conventional imaging versus PET–CT for identification of distant metastasis

Distant metastasis was detected in 20 patients with conventional imaging, while PET–CT identified distant metastasis in 36 patients (two were false positive). Overall, PET–CT upstaged the disease in 38 (48.1 %) patients as compared to conventional imaging: stage III to stage IV migration occurred in 14 (17.7 %) patients due to identification of additional sites of distant metastasis, and within stage III upstaging occurred in 24 30.3 %) due to identification of additional regional lymphadenopathy. PET–CT led to change in management plan in 14 (17.7 %) patients who were initially planned for either upfront surgery or neoadjuvant chemotherapy followed by surgery. They were subsequently planned for systemic chemotherapy due to identification of distant metastasis in these patients.

Discussion

Although PET–CT has not been reported to be informative in the primary diagnosis of breast cancer, its role in the assessment of distant metastasis cannot be denied [4]. Many recent publications from developed countries have advocated its role in the detection of distant metastasis in breast cancer citing its higher sensitivity and specificity over CI; however, there is scarcity of prospective data from developing countries to support this notion. This becomes more relevant as PET–CT is likely to have more profound effect on staging in LABC in developing countries, where more than 50 % of LABC patients seek medical care in stage III B or stage IIIC. On the contrary, majority of LABC patients actually belong to stage IIB and IIIA in western literature [4, 6]. This prospective study is an analysis of 79 LABC patients who were staged using CI and PET–CT simultaneously in a developing country.

The sensitivity for CI to detect distant metastasis in LABC varies from 40 to 60 % and suggests an alarming high number of false negatives [7-9]. In contrast, sensitivity of PET–CT has been close to 100 % in most of the western studies [7–11]. The present study also corroborates the findings of previous studies: sensitivity of CI was pessimistically low, 58.8 % as compared to PET–CT which had 100 % sensitivity for the detection of distant metastasis in LABC. Recently, NCCN has updated its recommendation to include CT chest and abdomen to increase the sensitivity of CI to detect distant metastasis [5]. However, literature suggests that even addition of CT could raise the sensitivity to 80–90 % and would still fail to match that of PET–CT [11]. The glowing metastatic lesions in a black and white background in a PET–CT examination makes them very obvious for identification even to a less experienced examiner.

There has always been a concern for low specificity (false positives) of PET–CT as FDG avidity is considered non-specific; however, most of the previous studies have reported a high specificity 87–100 % [7–11]. Our prospective study also confirms the same finding with 95.5 % specificity. Although a number of physiological and pathological conditions are described to cause false-positive lesions on PET–CT [12]; diligent assessment of clinical data and correlation of PET and CT component of PET–CT scan largely avoid false positives. It cannot be overstressed that histopathological confirmation must not be omitted in case of any diagnostic dilemma as these false-positive lesions can potentially lead to over-staging of the disease.

The most common site of metastasis in breast cancer is the skeleton; skeletal metastasis accounts for almost 90 % of all metastatic sites in breast cancer [13]. Breast cancer-

related skeletal metastasis may manifest in three different manners: osteoblastic, osteolytic, marrow involvement, and a combination of them. Although bone scintigraphy has been the standard investigation modality to diagnose skeletal metastasis, it has its own pitfalls. Bone scintigraphy identifies lesions when the reparative process in the cortex sets in, and thus, it can be false positive in fractures, degenerative disease and inflammatory conditions [14]. Similarly, bone scintigraphy causes false-negative results in metastatic lytic lesions which may not show significant reactive bone formation and escape detection. The same holds true for metastatic bone marrow involvement. The present study shows superiority of PET–CT in detecting skeletal metastasis (osteolytic and bone marrow metastasis) as it identified 10 additional cases of skeletal metastasis as compared to CI (Fig. 1). Groheux et al. [8] reported low sensitivity of bone scintigraphy (76.7 %) in comparison to PET–CT (100 %) which indicates that all the lesions detected by bone scintigraphy were also revealed by PET–CT. However, the reverse was not true in view of the presence of osteolytic and marrow lesions in some patients (7/30, 23.3 % cases of skeletal metastasis). PET–CT also has limitations—osteoblastic lesions may not be FDG avid and may escape detection; however, these osteoblastic metastasis are usually identified on the CT part of the PET–CT [15]. One must also remember that bone scintigraphy is truly a whole-body imaging in comparison to PET–CT which captures images from the mid-thigh level to the base of the skull. Most of the skull, distal upper and lower extremities are not included in the imaged field of the PET–CT; however, the presence of these atypical skeletal metastasis involving distal extremities is rare and its true clinical significance is doubtful.

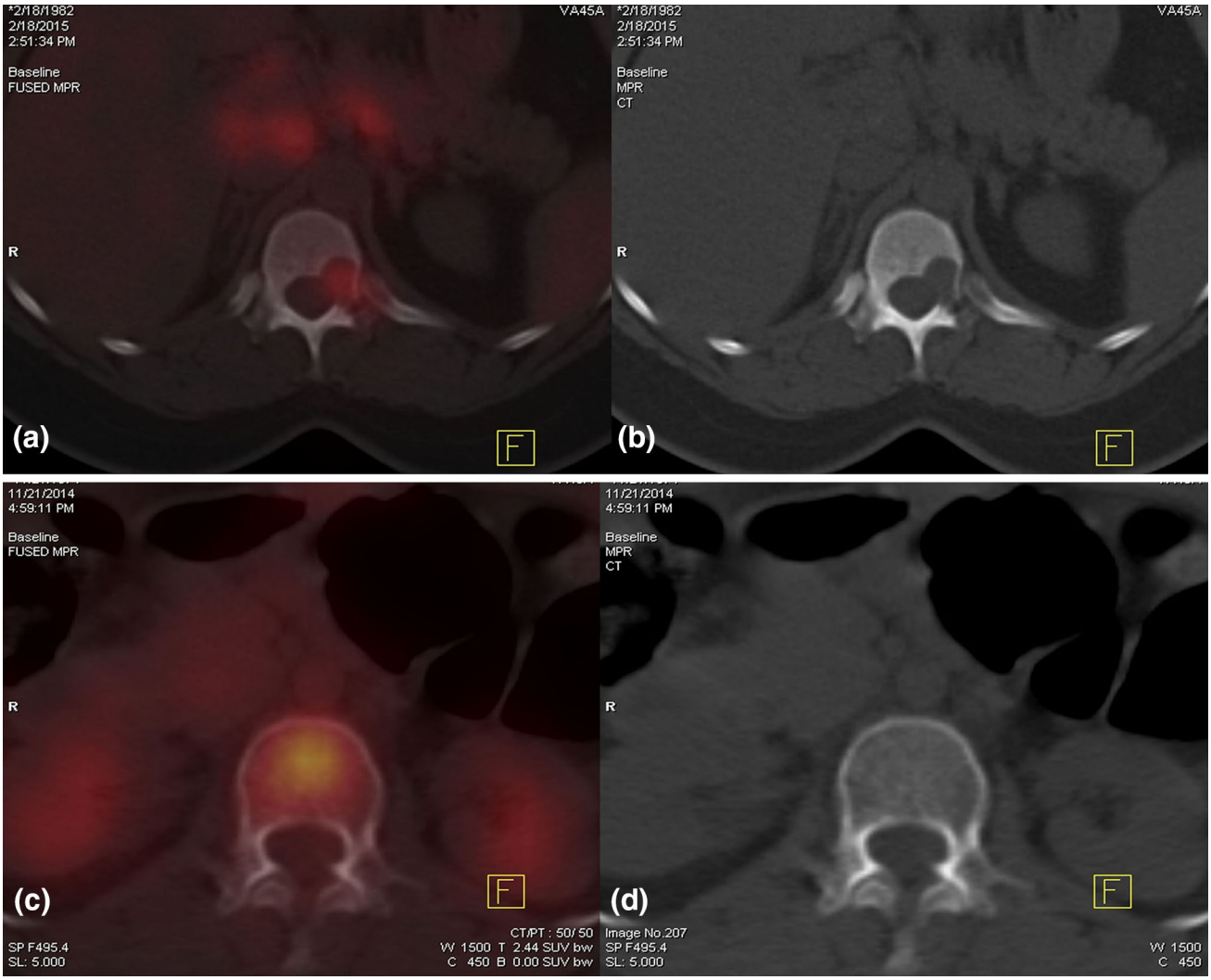

Fig. 1 **a**, **b** Reveals FDG avid lytic lesion in the vertebra, **c**, **d** reveals diffuse uptake of FDG without any concomitant bony lesion on CT suggestive of pure bone marrow involvement

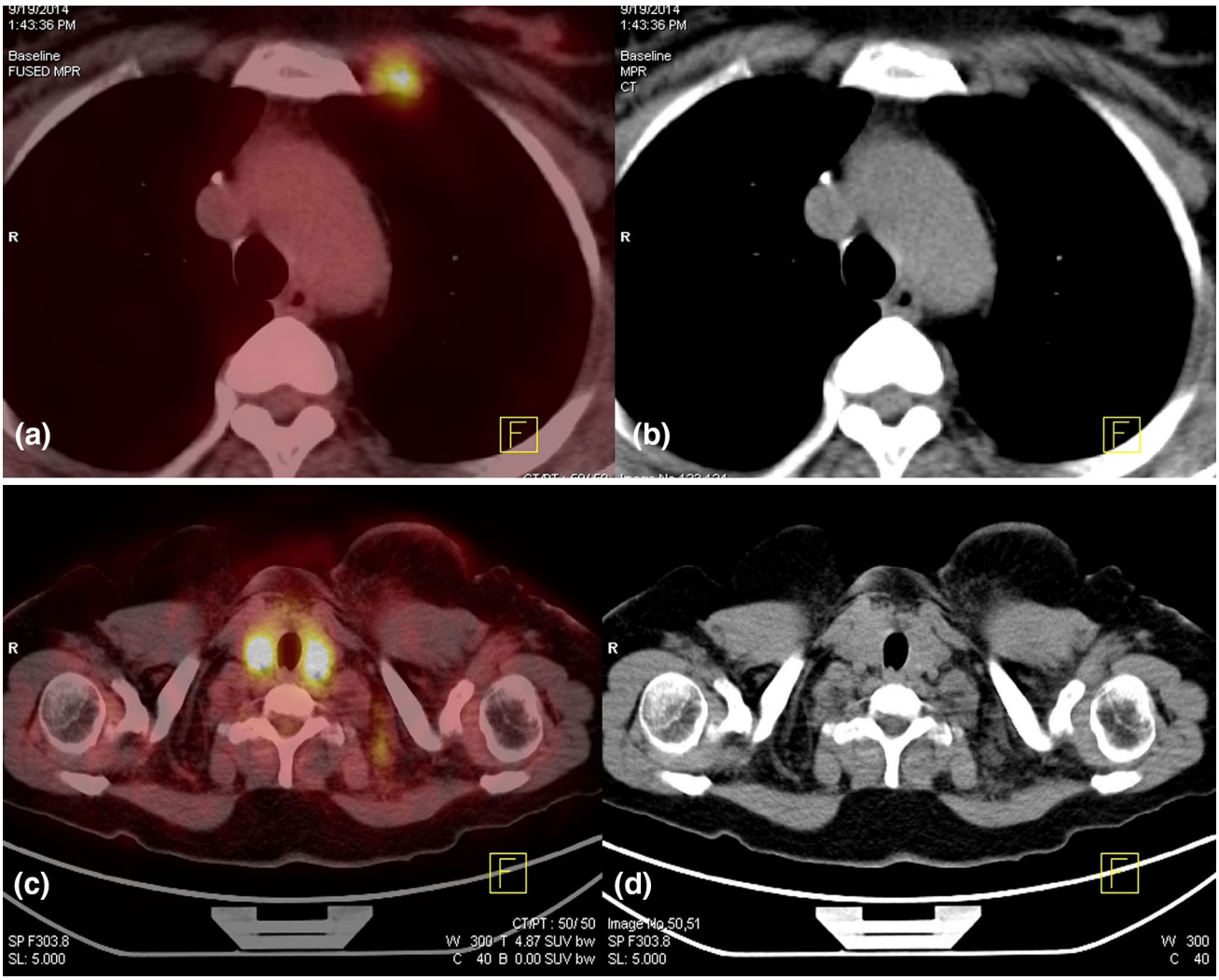

Fig. 2 **a**, **b** Reveals FDG avid left internal-mammary lymphadenopathy, **c**, **d** reveals FDG avid left supraclavicular lymphadenopathy

PET–CT helps in identifying non-regional distant lymphadenopathy, both supra-diaphragmatic (cervical, mediastinal, hilar, and/or contralateral axillary) and infra-diaphragmatic (para-aortic, pelvic, and/or inguinal) in LABC. Previous studies [7, 8, 11] have shown that metastatic mediastinal nodes can be identified with high sensitivity and specificity (more than 90 %); however, most of the PET–CT detected distant lymphadenopathy was not confirmed pathologically in any of these studies. The additionally identified non-regional distant lymphadenopathy assumes significance when it is not accompanied by other sites of distant metastasis and is not easily accessible for biopsy as well (mediastinal, para-aortic, and pelvic). Available literature suggests that distant metastatic lymphadenopathy is identified in a sizeable number of LABC patients; should these patients be really labeled as metastatic based on these PET–CT-detected lymphnodes in the absence of pathological confirmation is an open question.

Overall, various studies have showed that PET–CT leads to upstaging—both inter-stage, i.e., Stage III to IV due to identification of distant metastasis, and intra-stage, i.e., within stage III due to identification of additional regional lymph nodes. This upstaging can result in change in management in a significant number of patients. Manohar et al. [6] reported that PET–CT resulted in upstaging in 17/43 (39.5 %) of LABC patients when compared to CI. Fuster et al. [10]) and Groheux et al. [8] also reported similar results with upstaging of LABC in 42 and 52 % patients, respectively, with PET–CT.

Extra-axillary regional lymphadenopathy (supraclavicular and internal-mammary nodes) has also been shown to be delineated better with PET–CT in comparison to CI (Fig. 2).

Manohar et al. [6] reported that PET–CT detected additional regional lymphadenopathy in 16 of 43 (37.2 %) in a study of 43 LABC patients who had no evidence of distant metastasis. Groheux et al. [8] also reported that PET–CT revealed additional N3 nodal disease (infraclavicular, supraclavicular, or internal-mammary nodes) in 32 of 117 (27.3 %) patients. The significance of identifying N3 disease not only lies in upstaging the disease but also in optimizing the therapeutic decisions related to extent of surgery or placement of radiation portals.

Although the high number of distant metastasis (45.5 %) detected in clinically LABC (stage III) patients in the study seems unexpected, it must be emphasized that most of the patients (67 %) in the present series belonged to stage IIIB (T4 lesions). This difference in the spectrum of LABC in developing countries and developed countries is potentially accountable for high frequency of image-detected distant metastasis in these patients.

There are certain limitations of the present study. Conventional imaging protocol in the series included chest X-ray, ultrasonography abdomen, and bone scintigraphy as per the prevailing recommendations at the time of drafting the protocol proposal for this study. Recently, CT of chest and abdomen has been incorporated in the staging of LABC. Addition of CT is likely to improve sensitivity of conventional imaging and leads to more accurate staging. In the present study, histopathological confirmation was not undertaken for all areas of suspected distant metastasis especially when there were classical features of disseminated metastasis on imaging. Moreover, histopathological confirmation is not available in all the patients of N3 lymphadenopathy and distant lymphadenopathy seen on PET–CT.

We conclude that PET–CT has a role in identifying additional sites of regional lymphadenopathy and distant metastasis in locally advanced breast cancer; this results in disease upstaging in a significant number of patients both between stages (stage III to IV) due to identification of additional distant metastasis as well as within stage III due to identification of additional regional lymph-nodal metastasis. Further studies are needed to define the role of PET–CT in a large cohort of patients with the incorporation of CT chest and abdomen as a part of CI.

Compliance with ethical standards

Conflict of interest None.

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