

PET-CT upstaging of unilateral operable breast cancer and its correlation with molecular subtypes

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Abstract

Context: Prognosis and survival rates for breast cancer vary greatly depending on the cancer stage of the patient. Instead of a step-by-step approach using multiple investigations, we can get all the information about the metastatic load of the disease in PET-CT imaging by one single investigation. There is also a correlation between prognosis, FDG uptake, and molecular subtype of breast cancer (Luminal A, Luminal B, Human epidermal growth factor receptor 2 (HER2) positive and Triple-negative). Pre-treatment baseline PET-CT scan was done in 156 unilateral early and operable breast cancer patients from November 2017 to April 2019 in our prospective observational study.

Aims:

- To evaluate the utility of PET-CT in staging and upstaging of early and operable breast cancer by detection of unsuspected lymph nodes and distant organ metastases.
- To determine the prognostic association between SUVmax of the primary breast lesion in the upstaged cases and the molecular subtypes.

Results:

- Thus, PET-CT can serve as one-stop imaging in unilateral operable early breast cancer patients for upstaging and prognostication based on the correlation of SUVmax with molecular subtypes of breast lesions in patients who will surely benefit from whole-body imaging.
- Out of 156 patients, approximately 27 patients were upstaged after pre-treatment PET CT.
- Six patients were upstaged to stage IIIC and 21 patients were upstaged to IV.
- Regional nodes like internal mammary and supraclavicular nodes were detected in 7 patients and 5 patients, respectively, out of 156 patients.
- Non-regional distant nodes and organ metastases were detected in 11 and 18 patients out of 156 patients.
- Most common molecular subtype detected in the upstaged cases in our study was Luminal A (13 patients) followed by Triple negative (6), Luminal B (3) and HER2-neu-positive subtypes (1).

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Conclusions:

- FDG PET-CT is a substantial modality to provide information on regional, non regional lymph nodes and distant metastases in early operable breast cancer.
- It helps in evaluating the whole body metastatic burden in a single sitting, therefore, reducing the need for multiple investigations.
- SUVmax association of the index lesion with molecular subtype in the FDG PET scanning can serve as a prognostication factor in operable early breast cancer patients.

Key words: Breast cancer; metastases; molecular subtypes; operable; PET-CT

Introduction

Breast cancer may manifest as locally advanced, metastatic or in an early stage at the time of diagnosis.^[1,2] Early operable breast cancer patients undergo breast conservative surgery or total mastectomy. The presence of N3 nodes that is either ipsilateral infraclavicular node (N3a) or ipsilateral internal mammary and axillary nodes (N3b) or ipsilateral supraclavicular lymph nodes (N3c) upstages the disease to IIIC changing the course of treatment to essential pre-surgical induction chemotherapy.^[3] Detection of distant non-regional nodal or organ metastases will imply a more aggressive approach focusing more towards a palliative treatment.^[4] Therefore, it is necessary to correctly stage the patient's disease^[3] for optimization of therapy and this includes the assessment of primary tumor, regional lymph nodes and spread to distant sites.^[5]

For local staging of primary breast cancer, mammography is still the most widely utilized modality usually complemented with ultrasound (US), imaging-guided biopsy plus MRI mammography if indicated. Additional investigations for metastatic workup include Chest X-ray ± CT chest if indicated, ultrasound abdomen ± CT abdomen if indicated and bone scan if indicated. The National Comprehensive Cancer Network (NCCN) guidelines in oncology recommend 18F-FDG PET/CT as category 2B option for the workup of a breast cancer patient.^[6] PET-CT is usually not recommended for early and operable breast cancer.^[6] However, this current and routine algorithm of Diagnostic Imaging to stage early and operable breast cancer can miss the micrometastases in different regional, non-regional lymph nodes and distant organs as they might appear normal as per size and morphology criteria.^[7]

18F-2-deoxy-D-glucose (FDG) PET-CT provides important tumor-related qualitative and quantitative metabolic information that may be critical for the diagnosis and follow-up.^[7,8] It is the significant FDG uptake with a significant SUV value that exceeds the blood pool level, even in the normal-looking nodes and organs that helps to pick up the metastases.^[8] The combination of PET and computed tomography (PET/CT) allows the functional PET and anatomical CT images to be acquired under identical

conditions. Further, the combination of metabolic FDG PET data with morphologic CT data through the application of integrated FDG PET/CT has been shown to further increase diagnostic accuracy.^[8] In PET-CT, the whole body assessment is done in one single sitting, therefore, the information about the complete metastatic load of the disease can be acquired by one single investigation instead of a step-by-step approach using multiple investigations.^[9,10] Additionally, the patient can avoid the inconvenience and added expenses of multiple investigations to reach the final and total diagnosis.

FDG uptake is independently associated with immunohistochemically defined subtypes of breast cancer. There is also a correlation between prognosis, FDG uptake and molecular subtypes of breast cancer.^[11] Immunohistochemical classification is done by the expressional status of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) neu receptors. Different molecular subtypes are as follows:

- Luminal A (ER positive and/or PR positive and HER2 negative, low Ki-67 proliferation index).
- Luminal B (ER positive and/or PR positive and HER2 positive, high Ki-67 proliferation index).
- HER-2-neu positive (ER negative, PR negative and HER2 positive).
- Triple negative (ER negative, PR negative and HER2 negative).

However, very few studies have investigated the correlation of 18F-FDG uptake with breast cancer subtype. The purpose of this study is to assess the utility of PET-CT in early and operable breast cancer for staging and subsequent upstaging and determine whether a correlation exists between SUVmax of the breast lesion in the cases upstaged and the molecular subtypes of breast cancer.

Subjects and Methods

This is a prospective observational study including all unilateral, early and operable breast cancer patients who were referred for PET-CT, to the Department of Radiology at Apollo Speciality Hospital, Teynampet, Chennai- 600018; from 1 November 2017 to 30 April 2019.

Inclusion criteria

- Women above 18 years of age.
- Stage I and II breast cancer disease which includes lesion less than or equal to 5 cm with or without mobile axillary lymph node.
- Patients who are biopsied and clinically proven to be unilateral operable breast cancer disease (stages I and II) without any suspicion of metastases.

Exclusion criteria

- Nipple areolar complex, skin or chest infiltration.
- Palpable supraclavicular lymph nodes.
- Clinically detected distant metastases.
- Recurrent breast cancer patients.
- Post-treatment or under-treatment patients (like those who have had surgical intervention, chemotherapy or radiotherapy, etc.).
- Bilateral breast cancer patients.
- The patient not willing to take part in the study.

Imaging technique

Pre-treatment baseline 18F-FDG PET/CT was performed for each of these patients using a combined PET-CT scanner (Philips Gemini 64 Slice Tof and Siemens Biograph MCT). With the patients' arms raised above the head in supine position Spiral CT was acquired first in a craniocaudal direction, with 200-360 mAs, 90-120 kVp. Then, a PET scan was performed in a reverse longitudinal direction. The field of scan is from the vertex of skull to mid-thigh except in patients suspected to have lower limb disease, where the scan will include the whole-body field of view (head to toe).

CT image is used for attenuation correction and lesion localization. Displayed data for Diagnostic Study will include maximum intensity projection (MIP), transverse, coronal, sagittal PET and CT visualizations, as well as PET-CT fusion image.

Image analysis

The images were reviewed by the principal investigator to identify possible spread to regional, non-regional distant lymph node and any of the distant organs shown as FDG

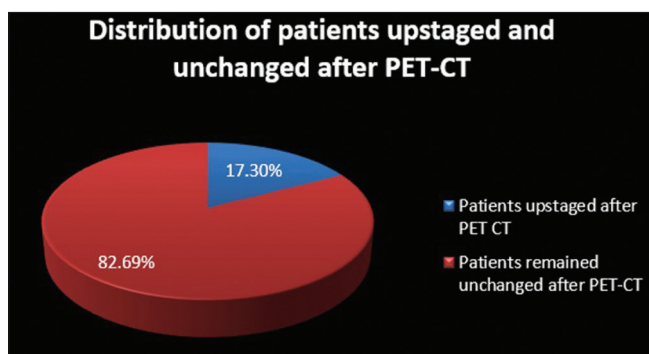


Figure 1: Percentage of the cases upstaged after PET-CT imaging

uptakes with a significant SUV value that exceeded the blood pool level and documented as uptake present or not. N stage was then upgraded if local lymph node and unknown regional lymph node involvement beyond the axillary region (infra or supraclavicular or internal mammary lymph nodes) was found. The M stage was upgraded in case if distant non-regional nodes and organ metastases were newly diagnosed on PET-CT. Following this, TNM staging was determined and final staging was assigned to each patient. The utility of PET-CT was then analyzed depending on the presence or absence of upgradation. Histopathological analysis and immunohistochemistry studies of the upgraded cases were done and classified into the molecular subtypes by the Pathology Department of our hospital. The SUVmax values of the index breast lesion in each patient upstaged was then correlated with a molecular subtype of the lesion to assess if any association existed between the two.

Results

A total of 156 cases of unilateral early and operable breast cancer female patients of stages I and II were included in our study. Out of 156 patients (17.30%), 27 were upstaged in our prospective study after PET-CT imaging [Figure 1]. The nodal staging was upgraded to N3 in 12 patients after the detection of new regional nodes on PET-CT [Figure 2] where the final stage was upgraded to IIIC in 6 patients (3.84%) [Figure 3]. Different distant nodal and organ metastases were seen in 21 out of 27 upstaged patients, upstaging the M stage from 0 to 1; therefore, changing the final stage to IV (13.46%) [Figure 3]. Distribution of metastatic foci was seen at different sites including regional, non-regional lymph nodes and different organs [Figure 4].

One of pre-PET-CT stage IIA patients and five of stage IIB patients were upstaged to stage IIIC after ipsilateral internal mammary and supraclavicular nodes were detected on PET-CT. IHC subtype of one such patient (pre-PET-CT stage IIA): Luminal B. SUVmax of the breast lesion: 7.0 [Figure 5].

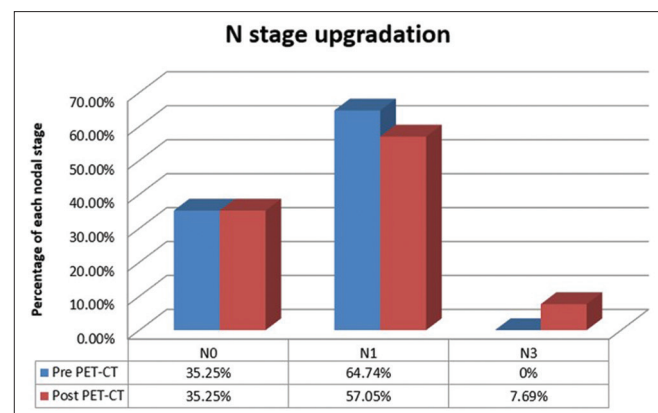


Figure 2: N stage upgradation after PET-CT

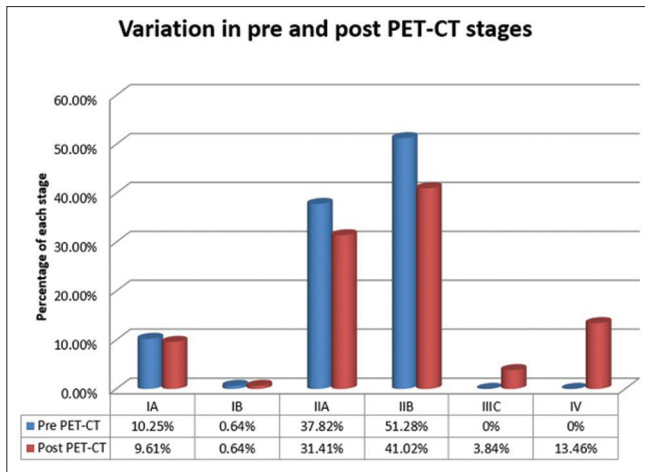


Figure 3: Distribution of Pre and Post PET-CT stages

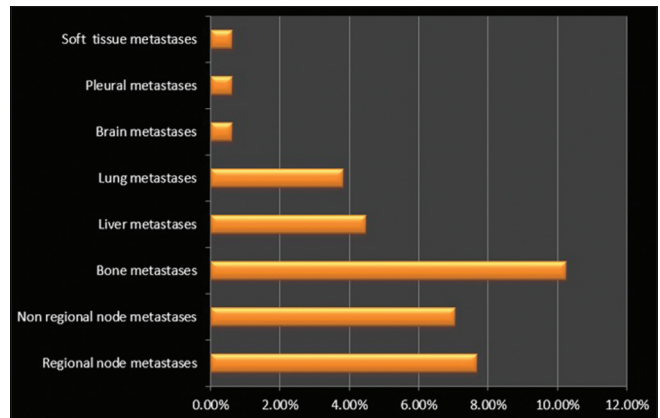


Figure 4: Distribution of metastases at different sites: regional, non-regional nodes and different organs

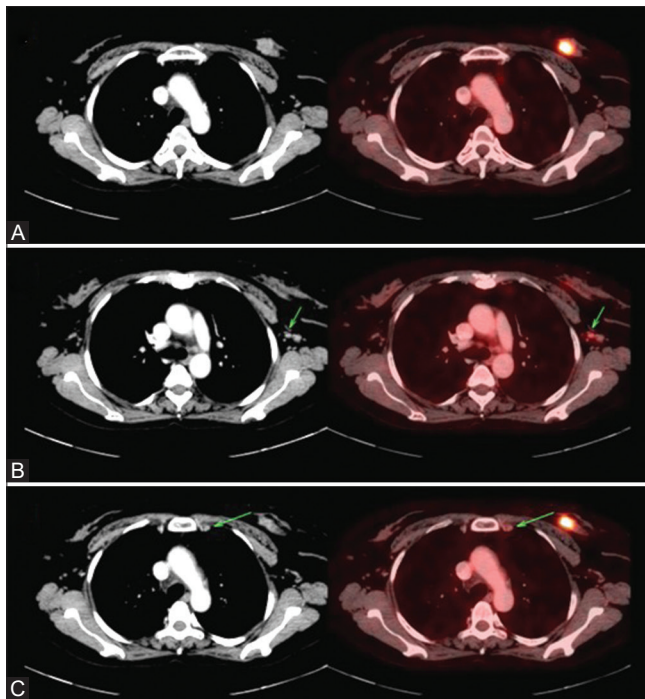


Figure 5 (A-C): A 50-year-old female of left breast carcinoma and ipsilateral axillary nodes (Pre PET-CT stage IIA: T1N1M0). (A) Axial PET-CT images show the T1 stage: Left breast lesion. (B and C) Axial PET-CT images show the N3b stage: Prominent FDG-positive left axillary nodes and ipsilateral internal mammary nodes (green arrows) (Post PET-CT stage IIIC: T1N3bM0). IHC subtype: Luminal B. SUVmax of the breast lesion: 7.0

One of stage IA patient was upstaged to stage IV after solitary skeletal metastases was detected on PET-CT. IHC subtype of the patient: Luminal A. SUVmax of the breast lesion: 6.6.

Nine of pre PET-CT stage IIA and 11 of stage IIB patients were upstaged to stage IV. One of the stage IIA patients showed soft tissue deposit in the Pectoralis Major muscle (discontinuous with the mass) [Figure 6], prominent to enlarged mediastinal nodes, multiple FDG-positive bilateral subpleural and pulmonary nodules [Figure 6], hepatic, axial

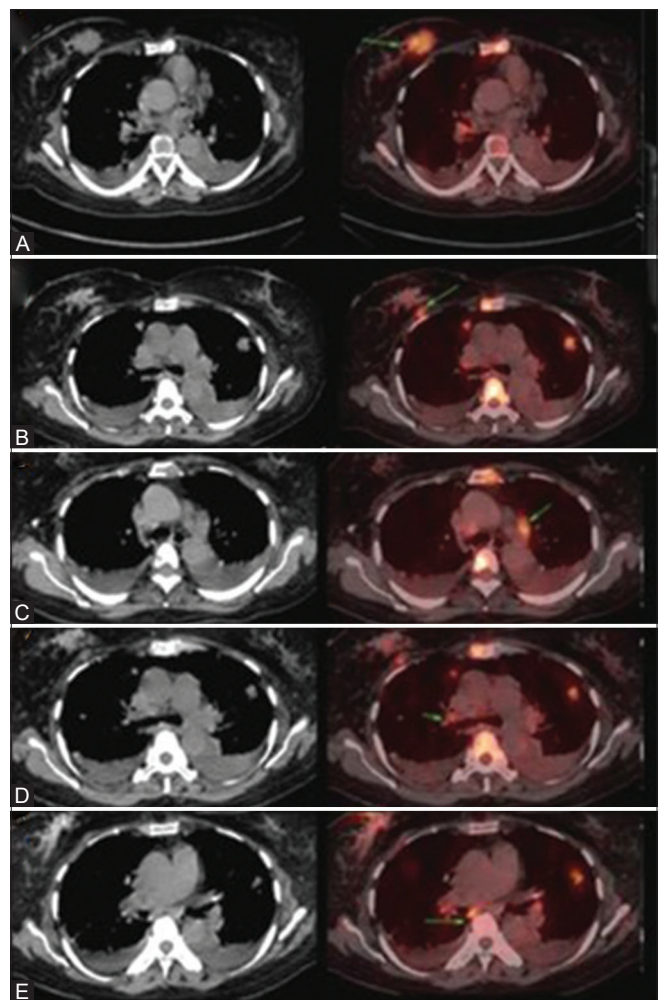


Figure 6 (A-E): A 50-year-old female of right breast carcinoma. (Pre PET-CT stage IIA: T2N0M0). (A) Axial PET-CT images show the T2 stage: Right breast lesion (green arrow). (B-E) Axial PET-CT images show the M1 stage: Soft tissue deposit in the Pectoralis Major muscle (green arrow) (B), mediastinal nodes and multiple FDG-positive pulmonary nodules (green arrows) (B-E), vertebral lesions (B-D)

and appendicular skeletal lesions on PET-CT [Figure 7]. IHC subtype of the patient: Luminal A. SUVmax of the breast lesion: 6.6.

One of stage IIB cases (upstaged to IV) showed hypermetabolic extensive mixed lytic and sclerotic skeletal metastases [Figure 8] with cord compression at D5-D8 vertebral levels. IHC subtype of the patient: HER-2 neu positive. SUVmax of the breast lesion: 7.6.

Hypermetabolic thick-walled cystic metastatic lesion in superior vermis [Figure 9] was detected in one of our pre-PET-CT IIB cases. IHC subtype of the patient: Luminal A. SUVmax of the breast lesion: 3.2.

Another stage IIB case (upstaged to IV) showed hypermetabolic solitary hepatic metastasis [Figure 10]. IHC subtype of the patient: Triple negative. SUVmax of the breast lesion: 11.3.

One of our case series presented with enlarged axillary nodes and loss of fatty hilum. The clinical diagnosis was made as lymphoma. A preliminary routine ultrasound scan of breasts showed no suspicious lesion in the breasts. PET CT showed a FDG-positive subcentimeter heterogeneously enhancing nodule in the lower outer quadrant of the right breast (0.8 × 0.6 cm SUVmax 4.2) [Figure 11] which was later confirmed to be primary cancer on biopsy. Multiple axillary, supraclavicular and cervical lymph nodes and diffuse marrow metastases (with no corresponding CT abnormality) [Figure 11] were detected on PET-CT. IHC subtype of the patient: Luminal A. SUVmax of the breast lesion: 4.2.

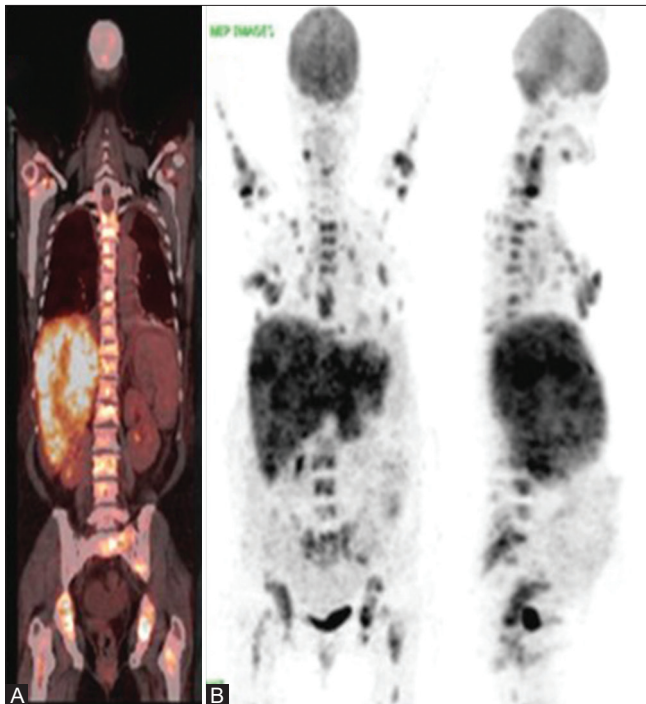


Figure 7 (A and B): Continued...(A) Coronal PET-CT and (B) Maximum intensity projection images show the N1 stage: Prominent right axillary nodes. M1 stage: hepatic, axial and appendicular skeletal metastases (Post PET-CT stage IV: T2N1M1). IHC subtype: Luminal A. SUVmax of the breast lesion: 6.6

Molecular subtypes of the upstaged tumors with mean and median SUVmax values are as follows:

1. Luminal A: 13 cases of Luminal A with a median SUVmax value of 9.3 and mean SUVmax value of 8.5 [Figure 12].
2. Luminal B: 3 cases of Luminal B with a median SUVmax value of 5.8 and mean SUVmax value of 6 [Figure 12].
3. HER2 neu positive: There was only 1 HER2 neu-positive case which was upstaged with a SUVmax value of 7.6 [Figure 12].
4. Triple negative: 6 cases of Triple negative with median SUVmax value of 8.4 and mean SUVmax value of 8.2 [Figure 12].

No immunohistochemistry report was available in four patients who were upstaged. Distribution of the various immunohistochemistry subtypes related to their SUVmax values [Figure 12].

Discussion

The total number of cases that were upstaged after the local initial staging of the primary breast lesion and before initiating any treatment was 27 out of 156 patients who participated in our study. In a study by Anshu Tiwari *et al.* in 2016, the number of patients upstaged was 9 out of 72 patients. In other studies performed by Ashley M. Grooves *et al.* and M. Bernsdorf *et al.*, the total number of patients upstaged was 9 out of 70 and 14 out of 103 patients, respectively.

The final stage was upgraded to IIIC in 6 of our patients. While the detection of different distant nodal and organ metastases in different patients upstaged the M stage from 0 to 1, therefore, changing the final stage to IV in 21 patients. In the study by Anshu Tiwari *et al.* in 2016, PET/CT evaluation

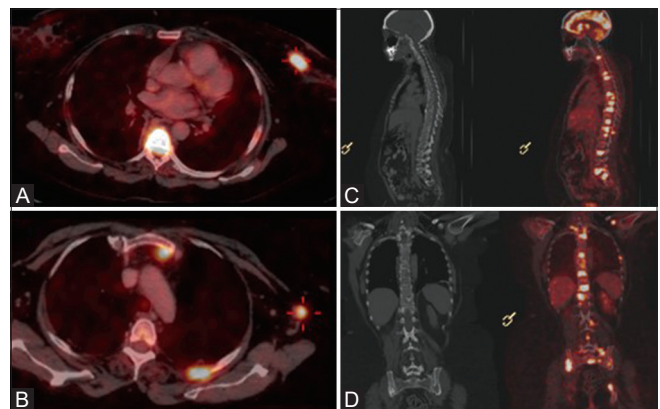


Figure 8 (A-D): A 51-year-old female of left breast carcinoma and ipsilateral axillary lymph nodes. (Pre PET-CT stage IIB: T2N1M0). (A) Axial PET-CT image shows the T2 stage: Left breast lesion. (B) Axial PET-CT image shows the N1 stage: Enlarged FDG-positive axillary nodes. (C and D) Sagittal and coronal PET-CT images show the M1 stage: Hypermetabolic extensive mixed lytic and sclerotic skeletal metastases. (Post PET-CT stage IV: T2N1M1). IHC subtype: HER-2 neu positive. SUVmax of the breast lesion: 7.6

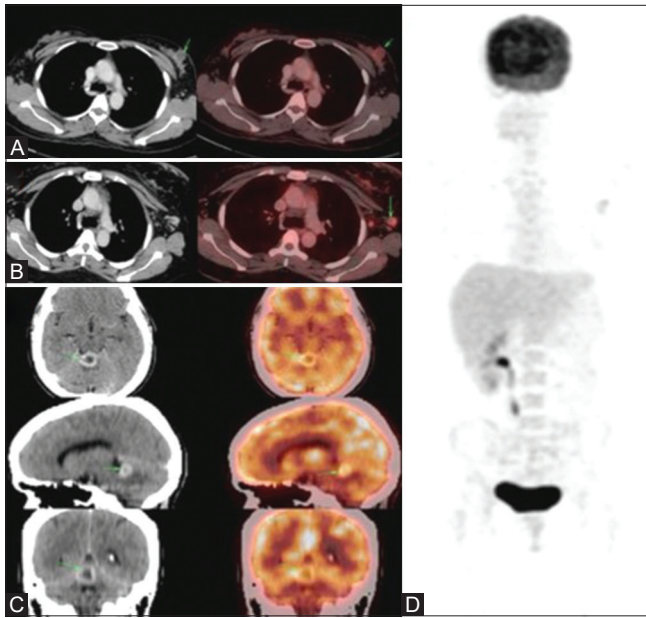


Figure 9 (A-D): A 41-year-old female of left breast carcinoma and ipsilateral axillary nodes. (Pre PET-CT stage IIB: T2N1M0). (A) Axial PET-CT images show the T2 stage: Irregular necrotic left breast lesion (green arrows). (B) Axial PET-CT images show the N1 stage: FDG-positive left axillary lymph nodes (green arrow). (C) Axial, sagittal and coronal PET-CT images show the M1 stage: FDG-positive cystic metastatic lesion in superior vermiform appendix (green arrows). (D) MIP image shows no abnormal uptake in the rest of the body (Post PET-CT stage IV: T2N1M1). IHC subtype: Luminal A. SUVmax of the breast lesion: 3.2

led 5 patients of stage II A to stage IV, 3 patients of stage II B to stage IV and 1 patient to Stage IIIB which further modified treatment plan from an adjuvant to a metastatic approach.

Presence of high FDG uptake on PET-CT in the regional nodes like internal mammary (7 patients), supraclavicular (5 patients) and non-regional distant nodes (11 patients) like mediastinal, retroperitoneal nodes etc., helped us to infer that these are malignant even though they didn't meet the size criteria on CT. In Anshu Tiwari *et al.*, 2016 study, 6 out of 72 patients showed extra axillary regional and distant metastatic nodes on PET-CT. In a study of 103 patients, M. Bernsdorf *et al.*, 2012 reported extra axillary regional and distant metastatic nodes in 12 patients.

Multiple system metastases were seen in the 18 patients in our study. Eight out of 27 upstaged patients had multiple metastases involving different organs. In all these patients, the accessible nodes and organs were biopsied and confirmed on histopathological analysis as the metastatic disease. Post chemotherapy follow-up PET-CT scan showed that the metastases responded to the treatment, thereby, confirming their metastatic nature. Anshu Tiwari *et al.* showed the presence of distant organ metastases in 9 out of 72 patients while Ashley M. Grooves *et al.* showed 2 out of 70 patients were positive for distant organ metastases. In a study of 103 patients, M. Bernsdorf *et al.* reported distant organ metastases in 6 patients.

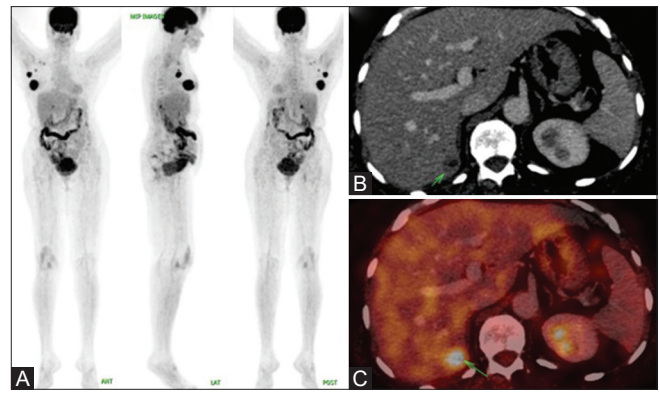


Figure 10 (A-C): A 56-year-old female of right breast carcinoma and ipsilateral axillary nodes. (Pre PET-CT stage IIB: T2N1M0). (A) Maximum intensity projection images show the T2 stage: Right breast lesion. N1 stage: Enlarged and prominent FDG-positive axillary lymph nodes. (B and C) Axial PET-CT images show the M1 stage: Hypermetabolic solitary hepatic metastasis in segment VII (green arrows) (Post PET-CT stage IV: T2N1M1). IHC subtype: Triple negative. SUVmax of the breast lesion: 11.3

Bone metastases are the most commonly seen system metastases in upstaged patients. These bone metastases can also be detected on bone scan but PET-CT combines the anatomical configuration with the metabolic status of the metastases, thereby, can be used in follow-up also. One of our patients showed diffuse marrow infiltration in vertebra without any CT abnormality which could be picked up only because of high-FDG uptake on PET-CT [Figure 11]. These metastases could be easily missed on CT imaging alone.

Though PET-CT is not a very good modality for detecting neuroparenchymal and leptomeningeal metastases due to high-FDG uptake in normal brain tissue^[12] still one patient (0.64%) in our study showed solitary brain metastases [Figure 9]. Likewise, soft tissue deposits can also be missed on conventional imaging like ultrasound and CT but whole-body PET-CT imaging will identify these types of metastases. In our study also, high-FDG uptake soft tissue deposit was seen in Pectoralis Major muscle in one of our patients (0.64%) [Figure 6]. It is very valuable in detecting occult breast carcinoma for all patients being investigated for unknown primary cancer [Figure 11]. In all these upstaged patients, PET-CT also offers a good baseline for interval follow-up of the metastases in advanced breast carcinoma.

¹⁸F-FDG uptake in breast cancer depicts increased glucose metabolism in the cancer cells and can predict its behavior. On the other hand, the ER, PR and HER2 or neu state of breast cancer is a biomarker that provides important prognostic information regarding aggressiveness of the tumor in addition to predicting response to therapy.^[11] Literature says that the degree of ¹⁸F-FDG uptake (SUVmax) of breast cancer lesions with Triple negative and HER2 neu positive is significantly higher

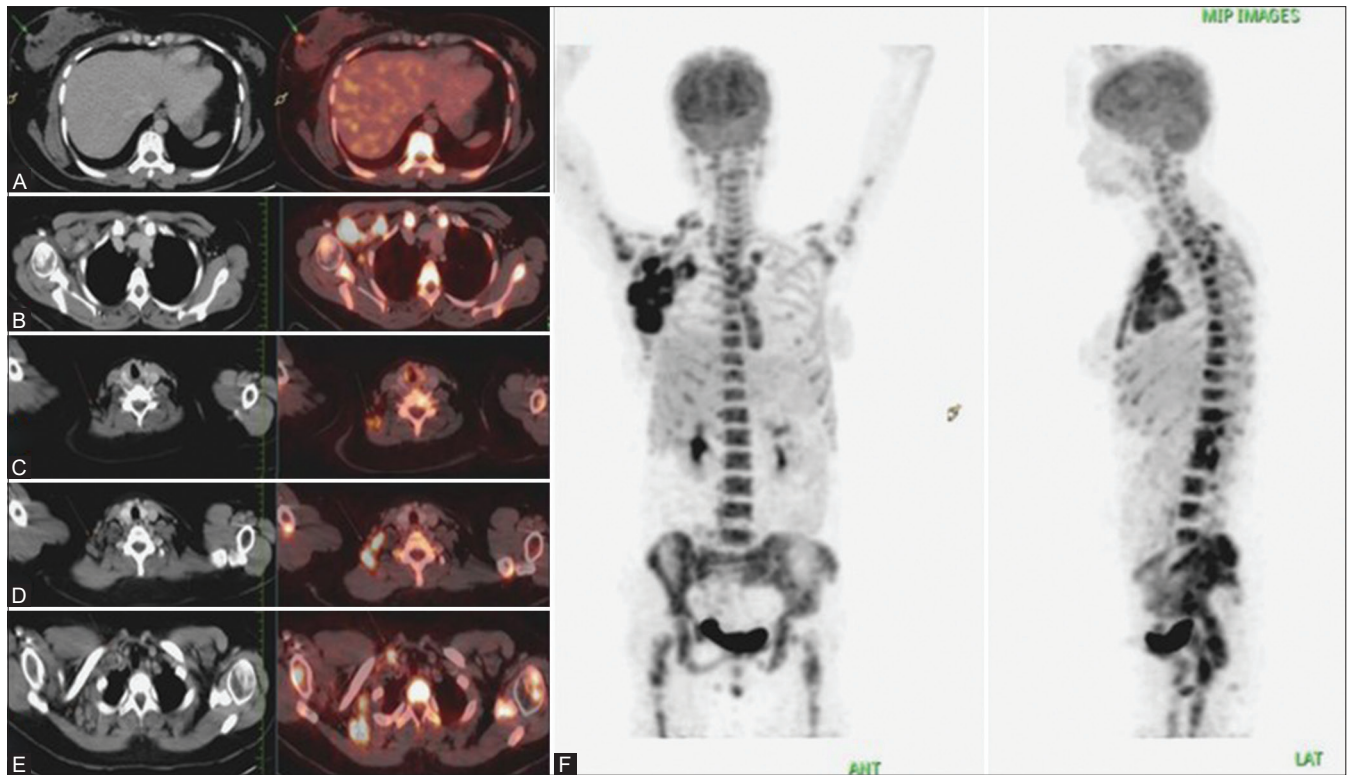


Figure 11 (A-F): A 29-year-old female presented with enlarged right axillary nodes. (Pre-PET-CT stage IIA: T0N1M0). (A) Axial PET-CT images show the T1 stage: a subcentimeter FDG-positive nodule detected in the right breast (proven to be the primary cancer on biopsy)(green arrows). (B-E) Axial PET-CT images show the N3c stage: Multiple right axillary nodes and FDG-positive right supraclavicular node. (F) MIP images show the M1 stage: Enlarged cervical nodes, diffuse marrow metastases seen with no corresponding CT abnormality (post-PET-CT stage IV: T1N3cM1). IHC subtype: Luminal A. SUVmax of the breast lesion: 4.2

than that of Luminal A and B tumors.^[13] In our study the most number of cases that were upstaged had molecular subtype Luminal A, that is, 13 cases followed by 6 cases of Triple negative, 3 cases of Luminal B and 1 case of HER-2 neu positive. The SUVmax value of Triple-negative subtype as assessed in our study is significantly higher than Luminal B [Figure 12]. But the same association could not be determined with other molecular subtypes. Therefore, further prospective studies with more sample sizes are required to derive the same expected association with other molecular subtypes as mentioned in the above literature.

Conclusions

Our study showed that PET-CT can serve as a one-stop imaging technique for upstaging of unilateral early and operable breast cancer in the patients who would benefit from whole-body staging.

SUVmax within the tumor can be a marker for predicting the aggressiveness of the tumor. In our study, the mean SUVmax and median SUVmax value of Triple-negative subtype is significantly higher than Luminal B but further studies are needed to determine the same association with other molecular subtypes.

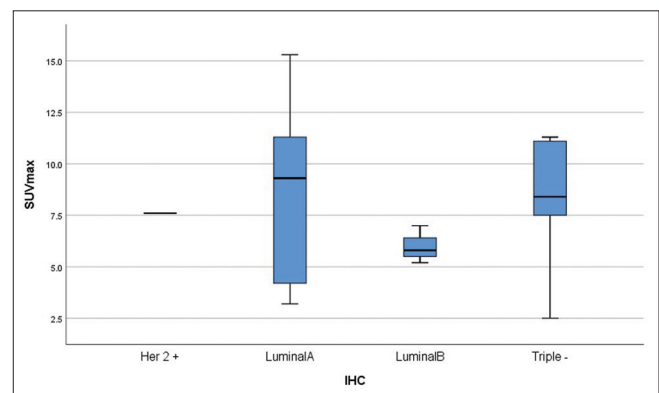


Figure 12: Box and whisker plot showing distribution of SUVmax in various IHC types of the cases upstaged.

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Conflicts of interest

There are no conflicts of interest.

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