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The added value of hybrid ^{18}F-FDG PET/CT over CT in the detection of breast cancer metastatic deposits

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Abstract

Background: Breast cancer is a major health problem resulting in high morbidity and mortality. Early diagnosis of primary and secondary lesions is crucial to optimize treatment options. Our study aimed to investigate the role of PET-CT and CT alone in detecting metastatic lesions in breast cancer patients.

Result: This retrospective study showed better PET diagnostic performance in the detection of lymph nodal and lytic bony metastatic deposits with more accurate detection of the malignant nature of hepatic focal lesions and detection of activity in sclerotic bony lesions, compared with CT alone, while CT had a higher value in the localization of lesions. Hybrid PET/CT showed optimal diagnostic performance than each modality separately.

Conclusion: The combination of CT and PET was a powerful diagnostic tool that is more accurate than CT alone in the detection of distant metastases.

Keywords: PET, Hybrid PET/CT, Recurrent breast cancer, Staging of breast cancer

Background

Breast cancer is the most common cancer among females. It is the primary cause of cancer-related death among females globally, with an estimated 627,000 deaths in 2018 [1]. Early spread to axillary lymph nodes or distant metastasis may be encountered in patients recently diagnosed with breast cancer [2]. The distant metastatic breast cancer represents the most severe form of the disease [3]. Thus, early and accurate detection of secondary lesions is crucial to optimize treatment approaches helping in improving long-term survival rates and quality of life [4].

In case of suspected tumor metastasis, as raised tumor markers, suspicion on conventional imaging modalities, and/or suggestive clinical symptoms or physical signs, it is advised to do metastatic workup including chest X-ray, computed tomography (CT), magnetic resonance imaging (MRI), and/or PET scan [5]. The main advantage of PET over the other diagnostic modalities is that it can reveal the metabolic activity of the detected lesion more than just anatomical localization [6]. Therefore, the present study aimed to compare the diagnostic performance of FDG-PET, CT, and PET/CT in the detection of metastatic lesions in breast cancer patients

Methods

Study participants

Between April 2015 and March 2019, this retrospective study included 77 women, who had pathologically proven breast cancer, underwent whole-body PET/CT examination using PET/CT scanner

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(Gemini, Philips Medical Systems). Patients' clinical records, charts, follow-up surveys, and aftercare files were retrieved, and relevant data were taken. Six patients were lost to follow-up; thus, the final number was 71 patients.

Inclusion criteria

Patients with pathologically proved breast cancer referred for PET/CT examination.

Exclusion criteria

The exclusion criteria are as follows: co-existence of another malignancy, recent biopsy or surgery, or local radiotherapy within 1 month before PET/CT scan.

Patient preparation

All patients were instructed to fast for 6 h before the PET scan. PET image acquisition was done 45 min after the intravenous administration of 18-FDG. The dose of the tracer was 0.09–0.17 mCi/kg. Control of blood glucose below 150 mg/dl was achieved.

Study instruments and technique

A whole-body PET/CT examination from the brain to the mid-thigh was done after 45 min of 18-FDG administration with both CT and PET covering identical areas. The acquisition time was 2.5 min per bed position with eight-bed positions. CT data were used for the attenuation-correction of PET images, and then the CT attenuation correction (CTAC) series were reconstructed. After PET scan, a contrast-enhanced CT study was conducted using nonionic contrast material (Iopamiron 370; Schering, Osaka, Japan).

Data management and analysis

Two radiologists experienced in nuclear medicine reviewed, interpreted, and analyzed PET images. Any foci of higher FDG than the back-ground, located away from areas of physiologically increased uptake, were considered to be positive on PET images. Lesions were analyzed semiquantitatively using SUVmax, defined as the ratio of maximum tissue FDG concentration per milliliter of tissue to the activity injected per gram of the patient's body weight. Also, CT images were then analyzed blinded from the PET findings. Then, hybrid PET/CT images were then analyzed by both interpreters. All detected lesions, including all doubtful or contradictory findings between both modalities, were further investigated by clinical and radiological follow-up serves as a standard of reference. The following imaging modalities were used for follow-up: bone scintigraphy in 9 patients, whole spine MRI in 2 patients, and abdominal ultrasound in 3 patients.

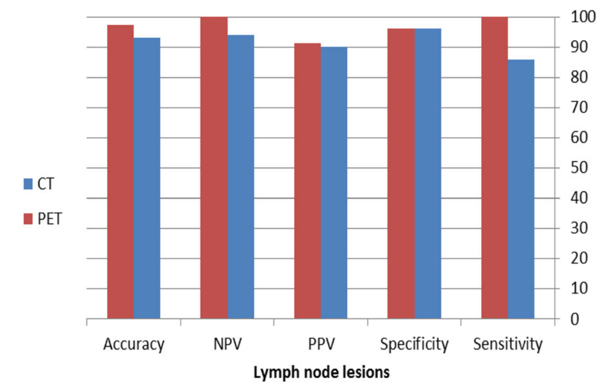

Fig. 1 Bar chart showing comparison between diagnostic results of PET and CT in lymph node metastasis

Statistical analysis

To evaluate the diagnostic performance of PET and CT, the sensitivity, specificity, accuracy, positive, and negative predictive values were calculated for all lesions; also, agreement between both methods was tested by Cohen kappa (κ). The p value was considered significant if less than 0.05. Quantitative data were summarized and expressed as mean ± SD, median (range), whereas qualitative data were expressed as frequencies and percentages. To measure the agreement between CT and PET in detecting breast lesions, the analyses were carried out using SPSS (Version 23. SPSS Inc., Chicago, IL, USA).

Results

This comparative study included 71 female patients with breast cancer, mean age 54.7 years (range 30–79 years). The results of PET, CT, and hybrid PET/CT were interpreted and analyzed for the

Table 1 Comparison between diagnostic results of CT, PET, and PET/CT in lymph node metastasis

	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%	TP	TN	FP	FN
CT	85.7	96	90	94,1	93	18	48	2	3
PET	100	96	91.3	100	97.2	21	48	2	0
PET/CT	100	96	91.3	100	97.2	21	48	2	0

Table 2 Comparison between diagnostic results of CT, PET, and PET/CT in lytic bone metastasis

	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%	TP	TN	FP	FN
CT	89	100	100	98.4	98.6	8	62	0	1
PET	100	100	100	100	100	9	62	0	0
PET/CT	100	100	100	100	100	9	62	0	0

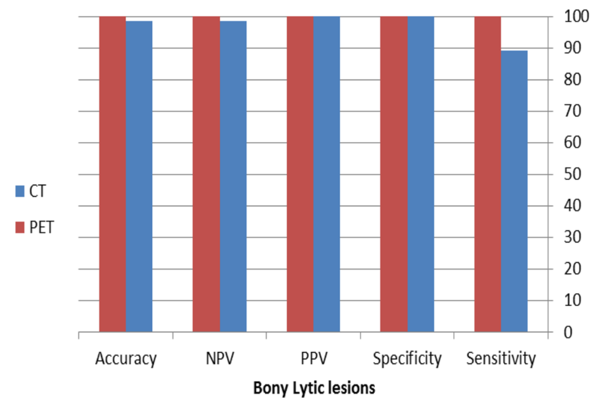

Fig. 2 Bar chart showing comparison between diagnostic results of PET and CT in lytic bone metastasis

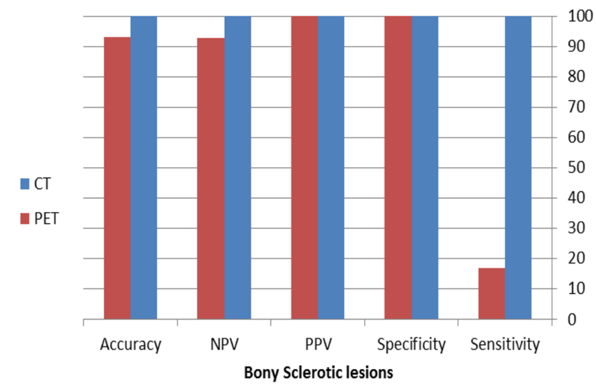

Fig. 3 Bar chart showing comparison between diagnostic results of PET and CT in sclerotic bone metastasis

lymphadenopathy, lytic, and sclerotic bony lesions and hepatic lesions. Totally, lymph nodes were the most prevalent site of metastatic disease.

Lesion-site based analysis of the diagnostic results of PET, CT, and hybrid PET/CT

Metastatic lymph node lesions

CT showed metastatic lymph node lesions in 18 cases (25.4%) while PET showed abnormal FDG uptake in 21 cases (29.6%), with higher sensitivity for PET and hybrid PET-CT over CT (Table 1, Fig. 1). There was very good agreement between the two modalities, κ = 0.9, p value = 0.000.

Lytic bony metastatic lesions

CT showed lytic bony lesions in 8 cases (11.3%) while PET showed abnormal FDG uptake in 9 cases (12.7%), with higher sensitivity for PET and hybrid PET-CT over CT (Table 2, Fig. 2). There was very good agreement between the two modalities, κ = 0.933, p value = 0.000.

Sclerotic bony metastatic lesions

CT showed sclerotic bony lesions in 6 cases (8.5%) while PET showed abnormal FDG uptake in only in 2 cases (2.8%), with higher sensitivity for CT and hybrid PET-CT over PET (Table 3, Fig. 3) with a weak agreement between the two modalities, κ = 0.268, p value = 0.001.

Other metastatic lesions

CT showed hepatic focal lesions in 6 cases (8.5%) while PET showed abnormal FDG uptake in only 3 cases (4.2%). Further abdominal ultrasound done revealed that 3 of 6 hepatic focal lesions were benign; 2 were hemangiomas, and 1 was cyst (Table 4, Fig. 4).

In our study, 6 cases had small pulmonary nodules, and only one was FDG avid. Our study detected 2 cases with cerebral metastatic deposits (4.2%); CT detected both while PET only detected one lesion. Also, metastases in the adrenal glands were seen in 3 cases, adnexal in 1 case, and muscle deposits in 1 case.

In general, hybrid PET/CT showed superior excellent diagnostic performance over both CT and PET alone (Tables 1, 2, 3, and 4; Figs. 5, 6, and 7).

Discussion

Several studies investigating different tumors have recommended the added advantage of hybrid PET/CT over anatomical and functional imaging modalities alone [7].

Our study revealed higher sensitivity for PET over CT in metastatic lymph nodes with sensitivity 100% and 85.7% for PET and CT respectively, with an equal specificity of 96%. A previous study done by Schirrmeister revealed sensitivity and specificity of

Table 3 Comparison between diagnostic results of CT, PET, and PET/CT in sclerotic bone metastasis

	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%	TP	TN	FP	FN
CT	100	100	100	100	100	6	65	0	0
PET	16.7	100	100	92.9	93	1	65	0	5
PET/CT	100	100	100	100	100	6	65	0	0

Table 4 Comparison between diagnostic results of CT, PET and PET/CT in hepatic metastasis

	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%	TP	TN	FP	FN
CT	100	95.6	50	100	95.8	3	65	3	0
PET	100	100	100	100	100	3	68	0	0
PET/CT	100	100	100	100	100	3	68	0	0

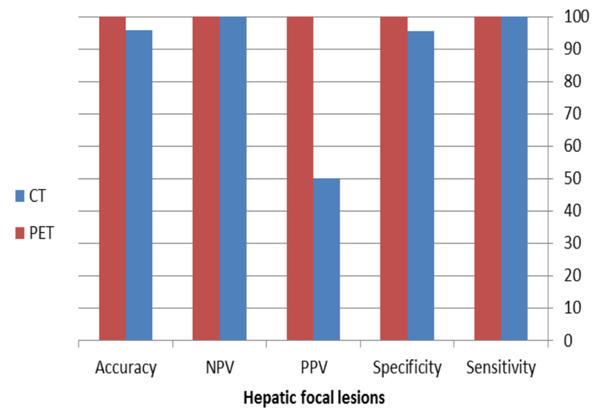

Fig. 4 Bar chart showing comparison between diagnostic results of PET and CT in hepatic metastasis

PET in detecting axillary lymph node metastases were 79% and92% [8]. The higher values in our study may be due to larger size of lymph nodes in our sample. PET/CT appeared to produce equivocal or negative findings in be smaller lymph nodes sometimes [9]. Lymph node measures above 1 cm were easily demonstrated by enhanced CT in our study, yet overall sensitivity was lower than that for PET/CT, with 3 falsely negative patients; this is due to PET had the ability to demonstrate activity in small lymph nodes. Metastatic deposits at abdominal lymph nodes are uncommon; 4 cases are reported in our study and were concomitant with thoracic lymph node involvement.

In bony lytic lesions, it is reported that CT has lower sensitivity than PET. A study conducted by Sugihara et al. [10] revealed sensitivities of CT and PET were 77.9% and 94% respectively. Our study revealed similar sensitivities where it was for CT 89% and for PET it was 100%. Hydrid PET/CT was found to give optimum sensitivity and specificity in our study. PET/CT was able to detect metastases at an early stage, even when there is no morphologic abnormality detected on CT; this may be due to PET detected the activity within the bone marrow with an absence of sufficient bone destruction. It was close to that found by Teke et al. [11] who found a

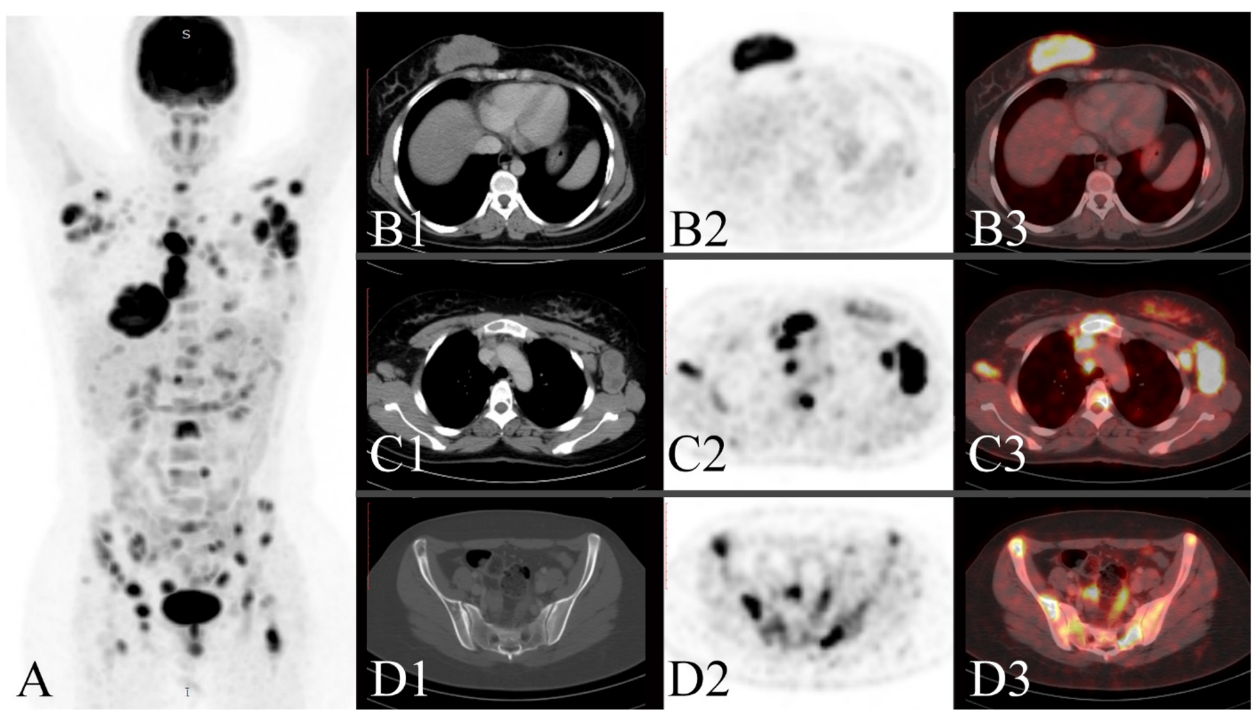

Fig. 5 Thirty years old female patient complain of bilateral breast swelling. Tru cut biopsy from right breast mass done showed invasive duct carcinoma. No operation or therapy. **A** Reconstructed whole body PET-MIP showed bilateral metabolically active breast masses, multiple variable sized metabolically active bilateral axillary lymph nodes, upper and lower paratracheal, prevascular, and bilateral hilar lymph nodes as well as multiple metabolic active bony lytic metastatic deposits at right scapula, head of the left humerus, sternum, multiple ribs, multiple vertebrae, both iliac and ischium bones right pubic, sacrum, and upper femuri. **B1** Axial CT, **B2** axial PET, and **B3** axial hybrid PET/CT showed right breast metabolically active mass and multiple metabolically active bony lytic metastatic deposits. **C1** Axial CT, **C2** axial PET, and **C3** axial hybrid PET/CT showed bilateral metabolically active lymph nodes and metabolically active sternal metastatic deposit. **D1** Axial CT, **D2** axial PET, and **D3** axial hybrid PET/CT showed multiple metabolic active bony lytic metastatic deposits at both iliac bones

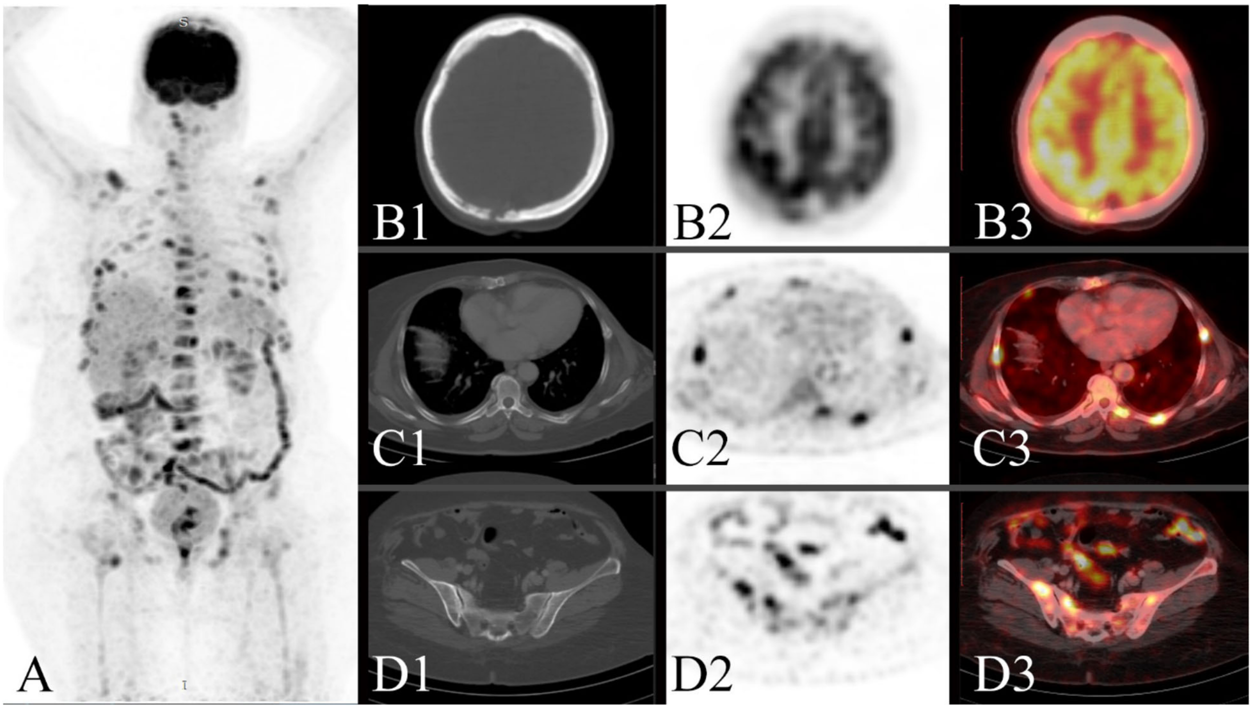

Fig. 6 Fifty-eight years old female patient presented with left breast mass underwent left radical mastectomy with histopathology revealed invasive duct carcinoma grade II. **A** Reconstructed whole body PET-MIP showed clear operative bed with no residual/recurrent lesions, multiple metabolically active lytic bony lesions involving multiple vertebrae, pelvic bones, and multiple ribs bilaterally. **B1** Axial CT, **B2** axial PET, and **B3** axial hybrid PET/CT showed multiple metabolic active lytic bony lesions at the right occipito-parietal bones. **C1** Axial CT, **C2** axial PET, and **C3** axial hybrid PET/CT showed multiple metabolic active lytic bony lesions involving multiple ribs bilaterally. **D1** Axial CT, **D2** axial PET, and **D3** axial hybrid PET/CT showed multiple metabolic active bony lesions involving pelvic bones

sensitivity of 93.4% and a specificity of 99.4% for hybrid PET/CT.

On the other hand, the osteoblastic metastases showed lower metabolic activity, thus lower sensitivity for PET compared to CT [12]. Our study revealed weak sensitivity for PET just 16.7% while CT showed 100% sensitivity. A study made by Sugihara et al. [10] found the sensitivity of PET was 69% (11/16). This difference can be explained by the smaller sample size in our study for the osteoblastic metastases. The integration of PET and CT significantly improved the specificity of CT and the accuracy of diagnosis through identifying metabolic activity regardless of the suspected or malignant looking CT appearance. We suspected that sclerotic metastases on PET scan had lower FDG uptake values, and the hybrid PET/CT limits the possibility of missing such lesions with low avidity that is readily detectable by CT.

The liver is the main site of visceral breast cancer metastases. In our study, liver metastasis was detected in 3 cases (4.25%). Three cases were detected as false positive in CT without being really active metastatic lesions. It is worth mentioning that malignant lesions show a tendency to increased FDG uptake; thus, PET showed higher diagnostic performance than CT [13]. A study conducted by Cornelis [14] who study PET/CT in colorectal liver metastases showed a higher sensitivity of PET over CT.

PET/CT could detect small pulmonary parenchymal nodules. However, partial-volume effect and respiratory movements reduced PET sensitivity for small nodules [15], so accurate CT study of the lung with maximum intensity projection will improve the sensitivity of PET/CT. In our study, 6 cases had small pulmonary nodules; only 1 lesion was FDG avid.

Our study revealed better diagnostic performance in brain lesions for CT over PET. This could be explained as brain metastases can be missed in ^{18}F-FDG PET/CT examinations due to the high physiological uptake of the cerebral cortex [16]. Our study detected 2 cases with cerebral metastatic deposits (2.8%); both were detected by CT, and only one hardly detected by PET.

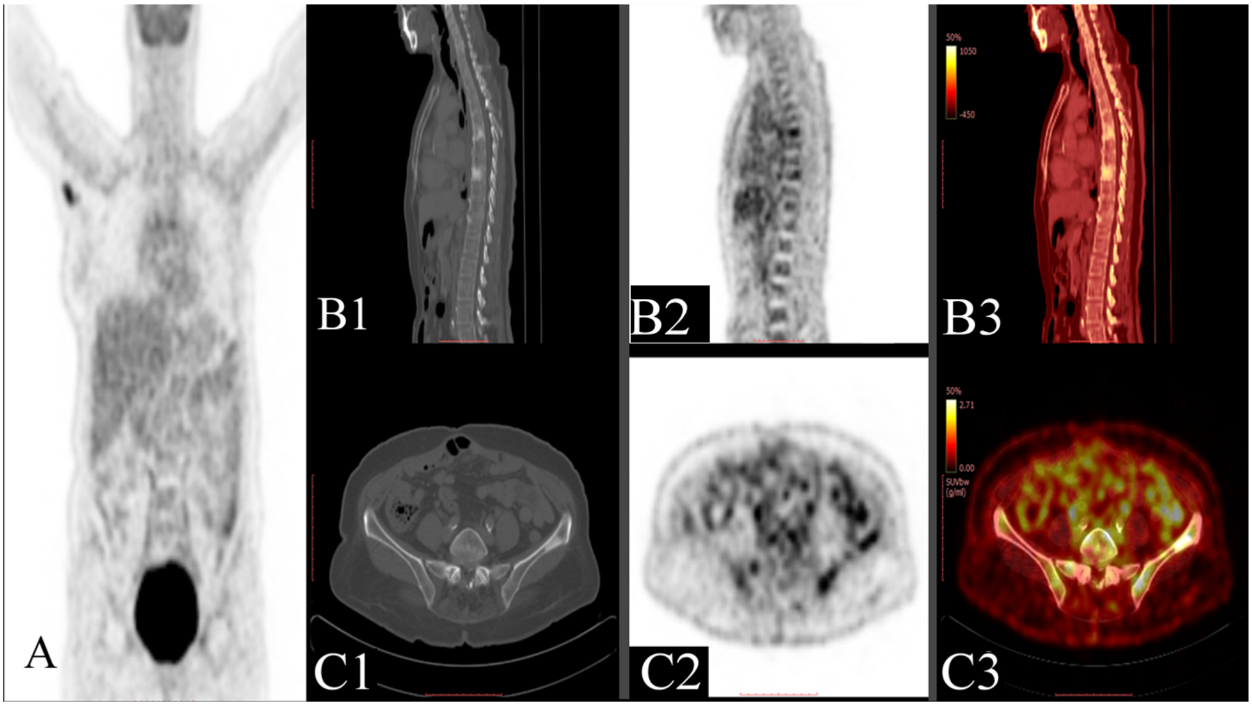

Fig. 7 Sixty-five years old female patient presented with left breast mass underwent left radical mastectomy with histopathology revealed invasive duct carcinoma grade II. **A** Reconstructed whole body PET-MIP showed clear operative bed with no residual/recurrent lesions, two metabolically active right axillary lymph nodes, and multiple mediastinal lymph nodes. **B1** Sagittal CT, **B2** sagittal PET, and **B3** sagittal hybrid PET/CT showed multiple metabolic active sclerotic bony lesions at the left iliac bone, D6, and D9 vertebral bodies. **C1** Axial CT, **C2** axial PET, and **C3** axial hybrid PET/CT showed multiple metabolic active sclerotic bony lesions involving left iliac bone

There were some limitations to our study. The first was its retrospective type. Another limitation was the histological confirmation of recurrence was not amenable for all distant lesions, and our standard of reference was the combination of clinical and radiological follow-up that had been employed in many similar studies [17, 18].

Conclusion

The fusion of high-performance CT and PET was the best modality in breast cancer patients staging, an excellent imaging technique to identify distant metastases of breast cancer and efficient to assess treatment response of distant metastases and pick up new deposits compared with CT alone.

Abbreviations

FDG: Fluorodeoxyglucose (^{18}F); PET: Positron emission tomography

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Authors' contributions

A. A. H. and N. N. M. suggest and develop the research idea, reviewing the literature. N. N. M., M. A. M., and M. A. were responsible for data collection and analysis, perform statistical analysis, write and revise the manuscript, prepare cases and perform required measurements, and prepare figures and tables. M. F. H. was responsible for reporting the cases of PET/CT and refer to us a result to compare it with our radiological results. All authors have a major contribution in preparing and editing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from Diagnostic Radiology Department–Tanta University, but there are restrictions apply to the availability of data, which used under license for this study, and so were not publicly available. Data were available from authors upon request with permission of the head of the Diagnostic Radiology Department–Tanta University.

Ethics approval and consent to participate

This study had approval from Egypt, Assiut University, Faculty of Medicine Research Ethics Committee. All patients participated in this study signed informed written consent for participation.

Consent for publication

All patients participated in this study signed informed written consent for publication.

Competing interests

Authors declare that they had no competing interests.

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