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Original Article

Role of Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET)-Computed Tomography (CT) in Evaluation of Post-Treatment Response of Breast Cancer

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ABSTRACT

Background: Breast cancer (BC) is the most prevalent critical malignancy in women and the main etiology of cancer death in women. Once recognized, the tumor stage must be correctly identified to select suitable treatment and determine the prognosis. The present investigation aims to find out the crucial role of 18F-FDG PET/CT in evaluating breast cancer therapy and predicting postoperative recurrence or systemic therapy.

Methods: This follow-up prospective cohort investigation was performed on 24 admitted cases of breast cancer in the Radiodiagnosis Department at Zagazig University Hospital. All participants were subjected to the following: Informed consent from all patients participating in the study, complete history taking, imaging including CT and Gamma Camera, histopathology if applicable, and follow-up by PET CT after palliative therapy.

Results: There was a substantial association between the prevalence of local recurrence after treatment and pathology results before treatment ($P<0.001$) and type of treatment ($P=0.014$). There was a notable relationship between the incidence of local recurrence after treatment and metastasis to LN ($P<0.001$) and lung ($P=0.001$) detected by PET/CT before treatment, as all patients with LN and lung metastasis experienced local recurrence after treatment.

Conclusions: 18F-FDG PET/CT is essential in evaluating BC therapy and determining recurrence following surgical or systemic therapy.

Keywords: Positron emission tomography; Computed tomography; Treatment response; Breast cancer.

INTRODUCTION

Breast cancer (BC) is the most prevalent type of neoplasia in women. Over 90% of women in developed countries have been identified with operable BC, while 5-10% have metastatic or advanced BC at diagnosis. The prognosis is generally favorable, with 10-year survival rates of approximately 80% [1].

After preliminary diagnosis and therapy, appropriate staging of distant, regional, and even local recurrences is crucial for treatment strategy. Generally, systemic therapy is employed at practically all phases of disease; however, surgical intervention and radiotherapy can be utilized to treat isolated local-regional disease or a single site of metastatic recurrence. Following therapy, follow-up exams are necessary for the early discovery and proper staging of recurrences [2].

Positron emission tomography/computed tomography (PET/CT) using 18F-fluorodeoxyglucose (FDG) is an imaging procedure involving functional and morphologic imaging.

FDG PET/CT assessments of glucose metabolism have a great reliability and less variance among observers than tumor size assessments [3,4].

PET/CT can distinguish between active tumors and post-therapeutic alterations [5]. PET/CT tumor response has also showed potential for measuring therapy response in the palliative setting for metastatic breast cancer (MBC) [6].

Alterations in the bone metastases sizes are especially challenging to assess with traditional imaging since sclerotic lesions do not vanish and lytic lesions can exhibit sclerotic alterations as therapeutic response indicator. Two investigations found that 18F-FDG PET/CT had a high sensitivity for identifying osseous metastases in cases with newly diagnosed MBC, and osseous metastases metabolic activity gave predictive data [7,8].

The goal of the present investigation is to find out the crucial role of 18F-FDG PET/CT in evaluating breast cancer therapy and predicting postoperative recurrence or systemic therapy.

METHODS

This follow-up prospective cohort investigation was performed on 24 admitted cases of breast cancer in the Radiodiagnosis Department at Zagazig University Hospital. All patients that meet the criteria for inclusion and exclusion will be included. Throughout the 6-month study period, 4 monthly patients will be enrolled as a comprehensive sample of 24 participants. Verbal and written informed consent was collected from all cases after explaining the procedure and medical research. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research. This investigation was performed after the approval of the Institutional Review Board (IRB#9549).

Cases with the following characteristics were included: All patients of any age and female cases with metastatic breast cancer.

Cases with the following characteristics were excluded: patients with contraindications to PET /CT, pregnancy, patients with another known malignancy, obesity, patients with glucose levels above 140 mg/dl, patient refusal despite informed discussion, and uncooperative patients who may refuse to give the consent of sharing in the study.

All participants were subjected to the following: Informed consent from all patients participating in the study, complete history taking, imaging including CT and Gamma Camera, histopathology if applicable, and follow-up by PET CT after palliative therapy.

Process:

This is a sub-analysis of a prospective trial of PET/CT in breast cancer management. At our center, eligible cases with a histopathologically confirmed diagnosis of BC had 2 FDG-PET/CT scans of pre-treatment and were candidates for radical RT after the 1st scan (PET1). According to our unit procedure, if PET1 was obtained <4 weeks prior and/or without accurate RT immobilization, a 2nd scan (PET2) was systematically advised. If new clinical information from PET2 was obtained, clinical management was changed.

Both scans were performed on an integrated PET/CT scanner at our facilities. Cases fasted before the FDG injection, set in a supine position, and scanned beginning with the lower neck until the pelvis, as reported previously [9]. PET/CT specialist (RH) reported the scans, which were evaluated at a meeting of all specialties involved. For each case, both PET/CT and oncology (NP) specialists worked together to detect all areas of gross illness. The main tumor was identified only by its gross tumor volume (GTV). GTV1 and GTV2 identified the primary tumor's closest and second-closest regional lymph node stations, respectively. A margin of 15 mm was applied to all GTVs to construct a PTV for each scan.

A dosimetrist (SE) created distinct procedures for the PET1 and PET2 planning target volume (PTV) for cases who remained radical candidates. Dosimetry was carried out in accordance with ICRU guidelines [10]. All cases received concomitant chemotherapy (etoposide (50 mg/m2 IV) daily days 1-5 and 29-33, and weekly carboplatin (AUC, 2 IV) and cisplatin (50 mg/m2 IV) or paclitaxel (45 mg/m2 IV) on days 1, 8, 29, and 36) based on the plan produced for PET2 to 60 Gy in 30 fractions over 6 weeks). The PET2 plan was implemented to the PET1 PTV for this investigation. PTV variations were accounted for by adjusting beam apertures. Beam angles and weightings were kept as consistent as feasible to precisely evaluate any alterations in OAR doses caused by tumor development rather than planning parameters itself. Maximum spinal canal dosage of 646 Gy, normal lungs (mean lung dose (MLD) 620 Gy and lung volume receiving 20 Gy (LV20) 635%, LV30 630%), heart (HV40 and MHD), and esophagus (OV50 and MOD), were all studied.

Overall survival (OS) was calculated from the date of PET1 until death (any cause). PFS was calculated from treatment until death (any cause) or documented disease development. Regarding cases

with PET2 progression, illness progression is defined as the following step beyond what was seen on PET2.

STATISTICAL ANALYSIS

Data was analyzed using SPSS version 28 (IBM Co., Armonk, NY, USA). Quantitative data were presented as mean and standard deviation (SD), analyzed by unpaired students' t-tests. Categorical data were presented as frequency and percentage, analyzed between groups using the Chi-square test or Fisher's exact test when appropriate, while analyzed between the two-time points in the same group using McNemar's test. A two-tailed P value < 0.05 was considered statistically significant.

RESULTS

A total of 24 MBC female cases enrolled in this study with a mean age of 51.25 ± 8.95 years (range between 36 and 65 years). More than half of the cases (58.3%) had a positive family history. The most frequently detected carcinoma by pathology was DCIS in half of cases, followed by infiltrating ductal carcinoma in one-third of cases, then infiltrating lobular and medullary carcinomas, each in 8.3%. Half of the studied breast cancer cases had palliative therapy, and the other half were subjected to combined surgical, chemo and radiotherapy. 25% of cases had local recurrence of BC after treatment (Table 1).

PET/CT was able to detect breast cancer metastasis to the liver in 33.3% of the studied cases pre-treatment, and that percentage was significantly elevated at the follow-up to 58.3% (P=0.031). Breast cancer metastasis to each of the lymph nodes and MSK was elicited in 25% of the studied cases before treatment, and that percentage didn't significantly differ after treatment (33.3%). As for lung metastasis, it was detected in 16.7% of cases before treatment and 25% at follow-up, with no remarkable variance. Also, adrenal metastasis was detected in 8.3% before treatment and 25% at follow-up, with no notable variation (Table 2).

There was a substantial relationship between the incidence of local recurrence after treatment and pathology results before treatment (P<0.001) and type of treatment (P=0.014), as the incidence rate of local recurrence was significantly higher among cases with infiltrating lobular and medullary carcinomas than those with DCIS. Moreover, patients who underwent combined surgical, chemo and radiotherapy had a lower incidence rate of local recurrence than those who had palliative treatment (Table 3).

There was a substantial association between the prevalence of local recurrence after treatment and metastasis to LN (P<0.001) and lung (P=0.001) detected by PET/CT before treatment, as all patients with LN and lung metastasis experienced local recurrence after treatment (Table 4).

A 47-year-old female participant with a history of left breast cancer underwent a left mastectomy, subsequently received chemotherapy, and was referred for further evaluation with a PET/CT scan (Case 1).

A 30-year-old female case presented with a history of modified right radical mastectomy with right axillary clearance and received CTH and RTH. She was referred for PET/CT follow-up (Case 2).

A 65-year-old female case with a history of right BC had a right mastectomy, followed by chemoradiotherapy, and was referred for additional evaluation by PET/CT scan (Case 3).

Table 1: Demographic and clinical data of the studied patients

		Total patients (n=24)
Age (years)	**Mean ± SD**	51.25 ± 8.95
	Range	36 – 65
Family history	**Negative**	10 (41.7%)
	Positive	14 (58.3%)
Pathology		
DCIS	12	50
Infiltrating ductal carcinoma	8	33.3
Infiltrating lobular carcinoma	2	8.3

		Total patients (n=24)
Infiltrating medullary carcinoma	2	8.3
Treatment		
Palliative	12	50
Combined surgical, chemo and radiotherapy	12	50
Local recurrence		
No	18	75
Yes	6	25

DCIS: Ductal carcinoma in situ. Data are presented as frequency (%) unless otherwise mentioned.

Table 2: Metastasis site in breast cancer patients according to PET/CT pre and post treatment (n=24)

	Pre-treatment	**Follow-up**	**P value**
Metastasis site			
Liver	8 (33.3%)	14 (58.3%)	**0.031***
LN	6 (25%)	8 (33.3%)	0.5
MSK	6 (25%)	8 (33.3%)	0.687
Lung	4 (16.7%)	6 (25%)	0.5
Adrenal	2 (8.3%)	6 (25%)	0.125

*Data are presented as frequency (%), *: Statistically significant as P value<0.05, LN: Lymph node, MSK: Musculoskeletal*

Table 3: Association between the incidence of local recurrence after treatment and baseline characteristics of the studied patients

	Local recurrence		**P value**
	No (n=18)	**Yes (n=6)**	
Age (years)	51 ± 8.26	52 ± 11.63	0.819
Family history	12 (85.7%)	2 (14.3%)	0.192
Pathology			
DCIS	12 (100%)	0 (0%)	**<0.001***
Infiltrating lobular carcinoma	0 (0%)	2 (100%)	
Infiltrating ductal carcinoma	6 (75%)	2 (25%)	
Infiltrating medullary carcinoma	0 (0%)	2 (100%)	
Treatment			
Palliative	6 (50%)	6 (50%)	**0.014***
Combined surgical, chemo and radiotherapy	12 (100%)	0 (0%)	

*Data are presented as frequency (%) or mean ± SD as appropriate, *: Statistically significant as P value<0.05*

Table 4: Association between the incidence of local recurrence after treatment and metastasis site by PET/CT before treatment

	Local recurrence		P value
	No (n=18)	Yes (n=6)	
Metastasis site			
Liver	4 (50%)	4 (50%)	0.129
LN	0 (0%)	6 (100%)	**<0.001***
MSK	4 (66.7%)	2 (33.3%)	0.618
Lung	0 (0%)	4 (100%)	**0.001***
Adrenal	2 (100%)	0 (0%)	>0.999
Data are presented as frequency (%), *: Statistically significant as P value<0.05			

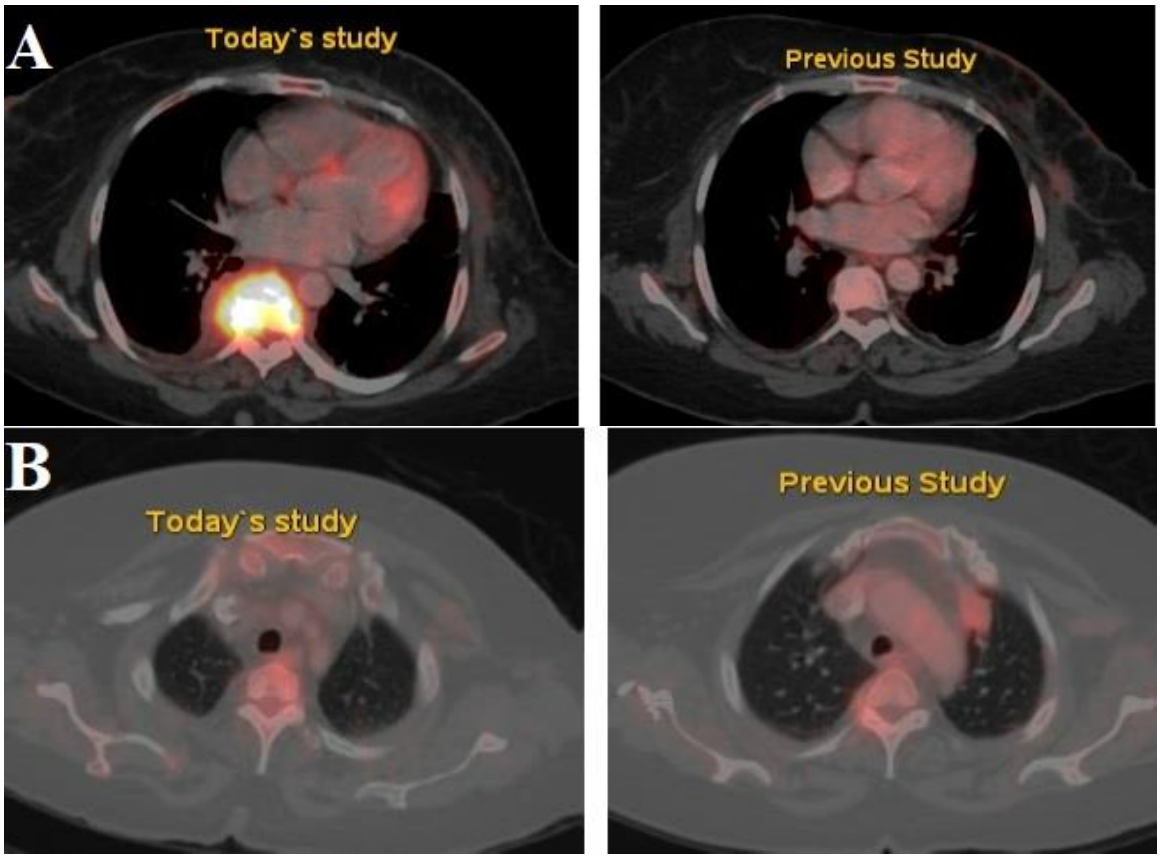

Figure 1:(A) Metabolic regressive course of the focal increased FDG uptake at the right LV4 facet joint currently achieving 7.56 SUV max (compared to 10 SUV max previously). (B) Metabolic clearance with morphologic regression of such left upper lung lobe anterior segmental pulmonary nodule currently measuring 9 x 9 mm (compared to 16 x 12 mm and being currently devoid of any metabolic activity) at the corresponding PET images.

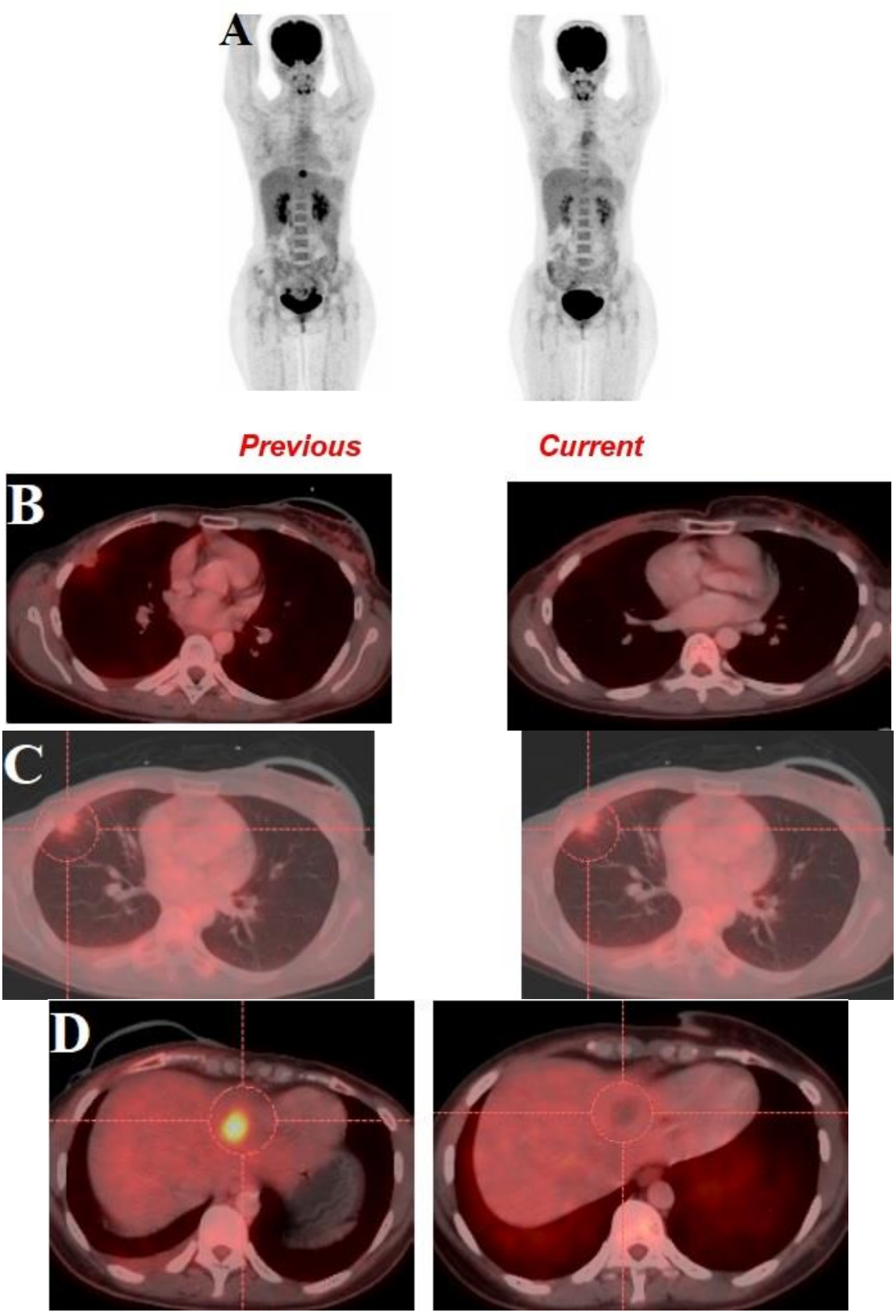

Figure 2: (A, B) Still noted clear right breast operative bed is keeping from any abnormal metabolic activity that would account for recurrent or residual breast masses. (C) Regressive course of the previously noted ill-defined patchy area noted at the right middle lung lobe consistent with sub-segmental consolidative changes as well as

the surrounding ill-defined nodular densities, currently noted as residual subpleural reticulations and parenchymal linear atelectatic bands with surrounding faint parenchymal veiling with no appreciable corresponding metabolic activity, confirming being mostly post therapeutic inflammatory changes. (D) It shows complete metabolic clearance with almost stabilize size of the previously noted hypermetabolic hypodense hepatic focal lesion seen at sub-segment II of the left hepatic lobe, currently such lesion is still seen measuring about 20x17.5 mm with no corresponding related metabolic activity at PET images (compared to SUVmax of 6.3 previously).

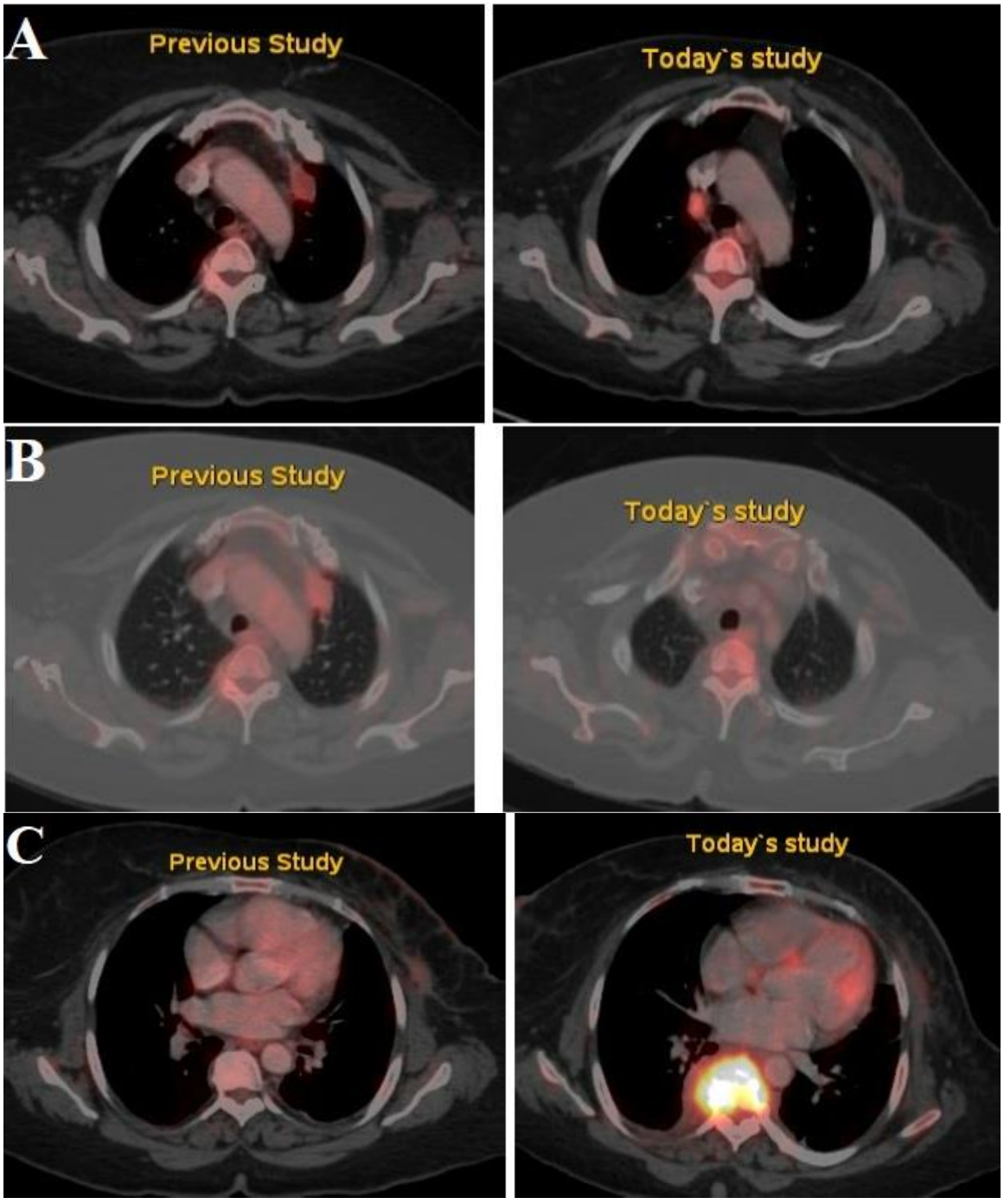

Figure 3:(A, B) The left mastectomy operative bed is still clear and devoid of any hypermetabolic soft tissue lesions that would account for recurrent neoplasia. Still noted the mildly active subcutaneous soft tissue plaques and minimal thickening of the overlying skin (likely post therapeutic changes). Newly developed hypermetabolic mediastinal retrocaval lymph node measuring 11 x 14 mm and achieving 4.89 SUV max. Metabolic clearance with morphologic regression of such left upper lung lobe anterior segmental pulmonary nodule currently measuring 9 x 9 mm (compared to 16 x 12 mm and being currently devoid of any metabolic activity) at the corresponding PET images. (C) Newly developed cortical irregularities at opposite end plates of DV6 and DV7 associated with subchondral sclerosis and erosions as well as active peri and prevertebral soft tissue thickening and phlegmon with relative focal kyphotic deformity at the same level.

DISCUSSION

In cases with equivocal anatomic imaging data, FDG PET is especially beneficial for distinguishing between live tumors and post-therapy alterations such as fibrosis or necrosis. FDG PET is also effective in cases whose only sign of recurrence is elevated tumor markers levels in serum like carcinoembryonic antigen (CA 15-3) [11].

Our study was conducted at the Radiodiagnosis Department, Zagazig University Hospital. This study was performed on 24 cases.

The goal of the current investigation is to find out the crucial role of 18F-FDG PET/CT in evaluating breast cancer therapy and predicting postoperative recurrence or systemic therapy.

Our study showed that 24 MBC female cases were enrolled with a mean age of 51.25 ± 8.95 years (between 36 and 65 years). More than half of the cases (58.3%) had a positive family history.

Our results are consistent with Sarhan et al. [12], who determined the usefulness of an 18F-FDG PET/CT scan in assessing response to cases received neoadjuvant chemotherapy that had locally advanced BC before operation. Their research comprised 29 cases with unilateral primary breast cancers and only one case with bilateral primary BC. The cases' mean age was 53.57±12.27 years. 56.7% of cases were postmenopausal, while 43.3% were premenopausal. Of the 30 individuals evaluated, 29 had nodal metastasis, but none had distant metastases.

Also, Reis et al. [13] aimed to analyze MRI diagnostic accuracy and its connection with axillary nodal histopathological evaluation in cases with locally advanced BC who were treated neoadjuvantly with endocrine treatment. In all, 33 cases with clinically node-positive locally advanced BC (mean age of 74.4 years) were enrolled with histological types of ductal (78.8%), lobular (15.2%), and other (6.1%).

Moreover, sang et al. [14] aimed to study the survival outcomes of cases managed with various surgical approaches. Among these, 87.5% were classified as mastectomy patients, while 12.5% were classified as breast conservation cases. Cases undergoing conventional mastectomy (CM) and M+IBR accounted for 82.5% and 5% of the mastectomy group, respectively. Most cases were over the age of 50.

Groheux et al. [15] revealed that premenopausal cases had 1.3 times elevated 18F-FDG uptake values.

Our findings showed that the most frequently detected carcinoma by pathology was DCIS in half of cases, followed by infiltrating ductal carcinoma in one-third of cases, then infiltrating lobular and medullary carcinomas, each in 8.3%. We revealed that half of the studied breast cancer cases had palliative therapy, and the other half were subjected to combined surgical, chemo and radiotherapy.

Our results are like Sarhan et al. [12], who demonstrated that Based on a Tru-cut biopsy, 96.7% of individuals had IDC, while 3.3% of cases had ILC. Regarding histological grade, 60% of cases had GII tumors, while 40% had GIII tumors.

The current study reported that PET/CT was able to detect breast cancer metastasis to the liver in 33.3% of the studied cases pre-treatment. That percentage was significantly elevated to 58.3% at follow-up (P=0.031). Breast cancer metastasis to each of the lymph nodes and MSK was elicited in 25% of the studied cases before treatment, and that percentage didn’t significantly differ after treatment (33.3%). As for lung metastasis, it was detected in 16.7% of cases pre-treatment and 25% at follow-up, with no remarkable difference. Also, adrenal metastasis was detected in 8.3% of pre-treatment and 25% at follow-up, with no notable difference.

Our results are consistent with Sarhan et al. [12]; the primary tumor mean size was 3.64, while the mean SUL peak was 6.96. Among the cases

analyzed, there was a substantial positive connection (P <0.05) between SUL peak using PET and CT assessed pre-chemotherapy tumor size.

RANIA et al. [16] also revealed that 32% of cases had nodal metastasis, 24% had liver metastasis, 20% had bone metastasis, 16% had lung metastasis, and 8% had adrenal metastasis.

Furthermore, Kamal et al. [17] revealed that PET/CT scans indicated lesions in the right breast in 52% of cases, the left breast in 40%, and bilaterally in 8%. Combination PET/CT indicated that the nipple and skin were involved in 28%. The SUV of BC lesions had a mean value of 9.92. The size of 63% of the 54 breast cancer lesions was less than or equal to 2 cm, 33.3% were more than 5 cm, and 3.7% were between > 2 cm and ≤ 5 cm.

In our present study showed that 25% of cases had local recurrence of breast cancer after treatment. There was a substantial association between the incidence of local recurrence after treatment and pathology results before treatment (P<0.001) and type of treatment (P=0.014), as the incidence rate of local recurrence was substantially higher among cases with infiltrating lobular and medullary carcinomas than those with DCIS. Moreover, patients who underwent combined surgical, chemo and radiotherapy had a lower incidence rate of local recurrence than those who had palliative treatment.

Koo et al. [18] who demonstrated NAC can cause breast tumor reduction, enhancing operability and boosting the rate of breast preserving surgery. Nevertheless, determining residual neoplasia is challenging, particularly for cases that have reacted well to therapy.

The difference in tumor size pre- and post-therapy measured the response to treatment. Additionally, considerable functional and structural imaging breakthroughs over the last two decades have resulted in better therapy response assessment [19].

The current study showed that there was a substantial association between the incidence of local recurrence after treatment and metastasis to LN (P<0.001) and lung (P=0.001) detected by PET/CT before treatment, as all patients with LN and lung metastasis experienced local recurrence after treatment.

The analysis of the PET CT data in our investigation corresponded to the findings of Iagaru et al. [20]. The 18F FDG PET/CT research in BC therapy demonstrated that PET/CT has a crucial function for identifying BC distant metastasis, assisting in planning surgical and medicinal therapy, and evaluating response to therapy. Conventional imaging cannot reveal axillary lymph node involvement or the presence of distant metastases, which seriously impacts the therapy of these individuals. Total-body 18F-FDG PET/CT imaging was a potential method for malignant tumor staging. Additionally, PET/CT can compensate for PET's low specificity caused by the elevated glucose metabolism of inflammatory tissues and benign neoplasms [21].

Furthermore, Tatsumi et al. [22] found that in identifying metastatic axillary lymph nodes, PET/CT combination has a privilege on CT alone since tiny lymph nodes are negative and typically evaluated by CT. PET/CT may be beneficial in predicting case outcomes because cases with nodal metastases have a worse prognosis than those without nodal involvement.

Our results were supported by Sarhan et al. [12], who reported that the primary tumor mean size was 3.64 cm on baseline PET CT images, while the mean SUL peak was 6.96. Regarding the patients analyzed, there was a substantial positive connection (P < 0.05) between CT-assessed pre-chemotherapy tumor size and SUL peak on PET. The initial tumor mean size was 2.27 on follow-up PET/CT images, while the mean SUL peak was 3.43. Among the individuals analyzed, there was a highly remarkable positive connection (P < 0.001) between CT-assessed pre-chemotherapy tumor size and SUL peak on PET. Based on RECIST 1.1, 66.7% of cases had SD, and 33.3% had PR. According to PERCIST 1.0, however, 16.7% of cases had CMR, 60% had PMR, 13.3% had SMD, and 10% had PMD. Groheux et al. [15] showed that the levels of 18F-FDG uptake in several cancers have been linked to tumor biology.

Yildirim et al. [23] examined 51 cases with locally advanced BC who got NAC and were studied retrospectively. It has been found that the PET/CT had a 75% specificity and sensitivity and may be beneficial in prognosis prediction as no cases had recurrence after full response in PET/CT. False positivity was seen in three of fifteen cases with pCR. Additionally, 60% of cases with complete PET/CT responses had real positivity, while 40% had false positivity. There was no substantial variance in the mean SUVmax pre-treatment values of cases with and without PCR. SUVmax post-treatment value and pCR had a strong association.

Our results are consistent with RANIA et al. [16], who found that FDG-PET-CT is quite effective for monitoring therapy response. This technology can detect therapy response faster than any other

imaging tool now available, considerably improving patient treatment by allowing the discontinuation of inefficient and harmful medicines. PET-CT was beneficial in evaluating anatomic regions previously treated with surgery or radiation, where distinguishing between post-treatment scars and recurring tumor can be difficult.

Unlike Rezkallah et al. [24], who demonstrated that in breast cancer cases, MRI is an excellent test for assessing residual tumor disease after NAC. However, incidents of under- and overestimation continue to occur, necessitating additional caution when deciding how to manage such patients.

Agrawal [25] and Helland et al. [26] who concluded that the clinical assessment of cancer cases is critical for therapy beginning and observation. The extra functional data provided by FDG PET might enhance CT findings, especially in the follow-up of cancer cases after surgery, radio-or chemotherapy.

Also, Cochet et al. [27] who concluded in terms of initial cancer evaluation and development, FDG PET outperforms standard CT. Weak metabolic activity in FDG PET may produce false findings that are misunderstood for normal physiological activity. Additional CT scans may aid in the identification of abnormal areas of FDG aggregation.

The PET and CT combined images allow for comprehensive functional and morphologic imaging with one scanner. FDG PET's enhanced functional data assists the assessment of confusing CT findings, especially in the follow-up of tumor cases who have had operative, radio-, or chemotherapy [28].

Choi et al. [29] assumed that PET/CT combination was more effective than contrast-enhanced CT in terms of locating extra-axillary nodal involvement. Aukema et al. [30] reported that FDG PET/CT is a useful imaging tool for detecting extra-axillary lymph node metastases, which could affect adjuvant radiotherapy.

Bernsdorf et al. [31] showed that PET/CT scans can detect involved extra-axillary nodes, distant metastases, and other concealed primary cancers. They demonstrated that FDG PET/CT preoperative scans considerably impacted staging and postoperative treatment.

This is like the results from previous investigations by Choi et al. [29] and Groheux et al. [15] that 18F-FDG PET/CT offers greater overall specificity and sensitivity than traditional imaging for identifying distant metastases and is also superior when assessing breast cancer lesions.

Li et al. [32] aimed to detect crucial factors that restrict the adoption of BCS following NAC among cases with BC in China. This investigation enrolled 916 cases. BCS was performed in 20.9% of cases, and mastectomy was performed in 79.1%. They observed that pretreatment clinical disease size is still a major predictor of surgical treatment. In contrast, NAC's response seemed to play no role in the surgical choice, implying that the prospective surgical benefits of NAC are still under-appreciated in northwest China.

The present study findings also were in accordance with Esmail et al. [33] findings who assessed the role of Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in evaluation of newly diagnosed breast cancer patients, they concluded that 8F-FDG PET/CT is a valuable technique that detects metastasis in newly diagnosed breast cancer patients in an efficient, accurate, and noninvasive manner, resulting in modification of the initial staging, which in turn reflected on the patients' therapeutic plans.

CONCLUSION

18F-FDG PET/CT effectively assesses BC therapy and determines recurrence after surgical or systemic treatment. We recommended larger scales studies for confirming our results.

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