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Original article

Role of Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography / Computed Tomography in Evaluation of Newly Diagnosed Breast Cancer Patients

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ABSTRACT

Background: People of various races, ages, financial backgrounds, and geographic areas are typically affected by breast cancer, which is the most common malignant disease in women. After a diagnosis of breast cancer, a precise assessment of tumor staging is necessary to establish the course of treatment and prognosis.

Aim: To investigate the role of Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography **(**18F-FDG PET/CT) in staging, pre-therapeutic metastatic workup or preoperative evaluation of newly diagnosed patients with breast cancer which subsequently affects their management.

Patients and methods: This prospective study included 30 female patients who were recently diagnosed as breast cancer and were referred for initial 18F-FDG PET/CT scans for preoperative or pre-therapeutic staging. All patients underwent both CT and PET examinations for initial staging of breast cancer. The reference standard was histopathology and 6-12 months follow-up.

Results: PET/CT revealed higher sensitivity (92%) and specificity (80%) in diagnosis of nodal metastasis compared to conventional CT with lower sensitivity (64%) and specificity (60%). Also, PET/CT had higher sensitivity (94.4%) and specificity (75%) in diagnosis of distant metastasis compared to conventional CT with lower sensitivity (88.9%) and specificity (66.7%).

Conclusions:
The quick, accurate, and noninvasive metastasis detection provided by (18F-FDG PET/CT) is valuable as it allows for the modification of the initial staging, which in turn affects the treatment regimens for newly diagnosed breast cancer patients.

Keywords: PET/CT, 18F-FDG, breast cancer.

INTRODUCTION

The second-leading cause of cancer-related death in women is breast cancer, which affects women most frequently of all malignancies. The prognosis and direction of treatment are determined by the breast cancer tumor stage at initial diagnosis. For local staging, the most recent staging recommendations call for a clinical evaluation as well as multimodal imaging, which consists of traditional mammography, breast ultrasound, and axillary fossa ultrasound. Patients with intermediate or high risk breast cancer should undergo CT scanning, bone scan, chest X-ray and a liver ultrasound to check for distant metastases **[1, 2].**

Computed tomography and Fluorine-18 fluorodeoxyglucose positron emission tomography (18F–FDG-PET/CT) has been demonstrated to identify previously undetected distant metastases and patients with recently diagnosed breast cancer and extra-axillary regional nodal metastases, which has an impact on staging, therapy, and prognosis **[3].**

18F-FDG-PET/CT may avoid needless toxicities from intense, curative neoadjuvant or adjuvant chemotherapy as well as unneeded breast surgery. Surgery may not have been necessary if 18F-FDG-PET/CT had been conducted at the first workup **[4].** Additionally, the Positron emission tomography's specificity is limited by some benign tumors' increased metabolic activity and inflammatory tissue (PET), which is somewhat mitigated by combined PET/CT. The 18F-FDG PET/CT being more advantageous for whole body pre-therapeutic staging in a single examination **[5].**

In this study, we sought to evaluate the use of 18F-FDG PET/CT for staging, pre-therapeutic metastatic assessment, and preoperative examination of individuals whose breast cancer was only recently detected.

PATIENTS AND METHODS

This prospective study comprised 30 female patients who had pathologically proven breast cancer (diagnosed within 3 months) and were referred from general surgery and clinical oncology departments to radiodiagnosis department in our institution, then referred for preliminary 18-FDG-PET / CT scans (GE DISCOVERY MI DR PET/CT scanner, USA) in a private radiology center for preoperative or pre-therapeutic staging. The study was established in from May 2022 to August 2023.Thirty women patients with histologically confirmed breast carcinoma within 3 months of diagnosis with no age predilection and did not receive any therapy were included in the study. Patients who had any treatments or surgery before PET/CT; patients with no adequate clinical follow-up of at least 6 months; pregnant; individuals who have blood glucose levels higher than 200mg/dl, patients with high serum creatinine >1.3mg/dl, all participants who were in poor general health at the time of the trial or had a contrast allergy were our exclusion criteria.

Ethical consent:

The study has been approved by Academic and Ethical Committee of Zagazig University (IRB #10408). Each patient consented to participate in the study by signing a written informed consent form. The Declaration of Helsinki, the World Medical Association's code of ethics for research involving human subjects, guided the conduct of this study.

All patients were instructed to go without food or liquids for at least six hours. Prior to 18F-FDG injection, serum glucose levels were regularly monitored and needed to be lower than 200mg/dl. All patients were told to refrain from eating or drinking for at least six hours. All metallic items—including zipped pants, bears, belts, bracelets, and more were taken off, and the patient's clothing was changed. The patient's arm was implanted with a cannula for the delivery of 18F-FDG. Before the assessment, the patients were told to settle down and refrain from engaging in any strenuous activity to prevent physiological muscle uptake of FDG (for at least 24h) and following radiotracer administration. Before receiving the 18F-FDG injection, to decrease the uptake of brown fat, patients should be kept in a warm, temperature-controlled environment. Patients were instructed to have a diet rich in protein, fat, and low in carbohydrates before the examination.

A dose of 10-20mCi F18-FDG was injected 60-90min before the evaluation, the patients were told to unwind in a quiet setting without engaging in strenuous activity and with as little conversation as possible. Every patient was in a comfortable, raised-arm position ***CT.***

Technique:

We began using a low dosage of unenhanced CT scan (GE DISCOVERY MI DR PET/CT scanner,USA) and then performed whole–body The scanning of the (neck, chest, belly, and pelvis) started at the base of the cranium and went all the way down to the upper thighs. The patient was observed to be breathing lightly during the study. For low dose attenuation correction CT, the scanning parameters were 120Kv,100MA ,64X0.625 mm collimator width , 0.5 s gantry rotation time, 0.8 pitch, and 50cm field of view . 120kV, 300MA, 64X0.625mm collimator width, 0.8 pitch, 0.5 s gantry rotation time and 50 cm field of view were the scanning parameters for high –dose diagnostic CT. Retrospective reconstruction of the helical data was done at 1 mm intervals. Using a dual-syringe medical device, the patient received an injection of 100 milliliters of non-ionic iodinated contrast material (stellant) automated injector at a rate of 2.5ml /sec, followed by the CT scan 40 s later.

PET Technique:

18-FDG-PET was performed using (GE DISCOVERY MI DR PET/CT scanner, USA) while keeping the patient still during the CT scan. Trans-axial CT and PET image were transmitted to a dedicated workstation, for reconstruction and reformation into sagittal and coronal views to facilitate their interpretation. Additionally, the integration of the two types of data was done by fusing the CT and PET images.

Interpretation of images:

A nuclear medicine radiologist with skills (at least 10 years of experience) in PET/CT analysis has assessed each PET/CT study. Both CT and fused PET/CT images were used to evaluate the breast cancers as in addition to the distant and

nodal metastases. Lesions with enhanced glucose uptake that is higher as compared to the background activity in the rest of the body (qualitative study), the surrounding tissue, the chest mediastinal blood, or a standard glucose uptake result (SUV) of more than 2.5 (qualitative analysis) was seen as pathological. AutoCAD was used to manually determine the SUV a 5-10 mm region of interest (ROI) over the region of the lesion where it is most active. The nodal tumor infiltration was classified as negative or positive for the ipsilateral axillary, contralateral axillary, internal mammary, hilar, mediastinal, and pelviabdominal lymph node groups. Regardless of size, any lymph node with a preserved fatty hilum was classified as benign, whereas any lymph node with a short axis diameter of more than ten millimeter or any necrotic lymph node, all sizes together, was categorized as malignant. Metastatic spread was assumed even for lymph nodes with a short-axis diameter of less than one cm and elevated glucose content on PET images. Even lymph nodes with a short-axis diameter greater than one cm on PET scans were considered benign (negative for metastatic dissemination). The brain, lung, liver, bone, spleen, and adrenal glands were checked for distant metastases. Each of these organs was graded as negative or positive for tumor infiltration. If FDG uptake exceeds the mediastinal blood pool in patients with 5-mm lung nodules, they should be considered positive. Metastatic lung deposit cannot be ruled out if the nodule is larger than 5mm. Positive hepatic or splenic lesions are those in which FDG uptake is greater than the liver or spleen. Adrenal gland lesions were classed as benign if the density of the lesion was less than 10 HU and malignant if it was larger than 10 HU. If the density of the lesion was greater than 10 HU, the SUV max of the lesion should be examined. If a patient has focal bone marrow lesions with elevated FDG uptake, they were taken into consideration as positive for osseous deposits.

Standard of reference

When available, percutaneous biopsy and the final pathological analysis were used as the gold standard. For instances lacking pathology findings, a follow-up of 6-12 months served as the benchmark for comparison. Follow-up was employed for six to twelve months on all patients with loco-regional lesions that were later shown to be metastatic or loco-regional based on histology. The study eliminated patients whose standard of reference was unavailable.

Statistical analysis

All data were gathered, totaled, and subjected to statistical analysis using SPSS 20 .0 for windows (SPSS Inc., Chicago, IL ,USA 2011). Chi-square test, fisher exact test, pearson correlation coefficient were used.

RESULTS

About two thirds of studied patients (66.7%) were from 50 to 70 years with mean of 56.20±13.42 years. The primary breast mass mean size was 40.16± 10.80 mm and SUV max of the mass ranged from 3.7 to 23.4 with mean 6. 2± 3.1. Invasive ductal carcinoma was the predominant breast cancer lesion (46.7%), followed by invasive lobular carcinoma (36.7%), then invasive mucinous carcinoma (13.3%) and finally invasive medullary carcinoma (3.3%). Nodal metastasis was found in 80% of studied patients. While, 66.7% of them did not have distant metastasis. Patient and tumor characteristics are shown in **Table 1**.

^{18}F-PET/CT showed 11 FDG avid ipsilateral axillary LNs but only 9 of them were detected by conventional CT. ^{18}F-PET/CT showed 5 FDG avid contralateral axillary LNs but only 4 of them were detected by conventional CT. ^{18}F-PET/CT showed 4 FDG avid supraclavicular LNs but only 3 of them were detected by conventional CT. ^{18}F-PET/CT showed 2 FDG avid cervical LNs but only one of them was detected by conventional CT. The PET/CT showed one case of hyperactive intraparotid LN that was missed in conventional CT images. A paraortic metastatic LN was detected in both CT and PET/CT **(Table 2).**

The ^{18}F-PET/CT showed 3 FDG avid lung deposits but only 2 of them were detected by conventional CT. The ^{18}F-PET/CT showed 5 FDG avid osseous metastasis but only 3 of them were detected by conventional CT. The ^{18}F-PET/CT detected one case of hyperactive hepatic metastasis that was missed in conventional CT images. One adrenal metastatic deposit was seen in both CT and PET/CT **(Table 2).**

One patient was upstaged from IIB by conventional CT into IIIA by ^{18}F-PET CT. One patient of stage IIIA by conventional CT was upstaged to stage IIIC **(Fig. 1)** and one patient of stage IIIA by conventional CT was upstaged to stage VI **(Fig. 2)**. One patient of stage IIIB by conventional CT was upstaged to stage IV **(Fig. 3**). Two patient of stage IIIC by conventional CT was upstaged to stage IV . There was 10% of upstaging by PET CT in stage I and II (1/10) and 50% upstaging of stage III into higher stages (5/10) **(Table 3).**

There was a highly significant difference between PET/CT and Conventional CT regarding diagnostic performance of nodal and distant metastasis. Where, PET/CT had high sensitivity

(92%) and specificity (80%) in diagnosis of nodal metastasis compared to conventional CT with lower sensitivity (64%) and specificity (60%). Also, PET/CT had higher sensitivity (94.4%) and specificity (75%) in diagnosis of distant metastasis compared to conventional CT with lower sensitivity (88.9%) and specificity (66.7%) **(Table 4).**

Table 1 : Frequency and percentage distribution of personal and clinical data, histopathology, nodal and distant metastasis of studied patients (n=30).

	no	%
Age (years)		
30-<50	8	26.7
50-<70	20	66.7
≥70	2	6.7
Mean± SD	56.20±13.42	
Site of lesion		
Right breast	13	43.3
Left breast	16	53.3
Bilateral	1	3.3
Size & SUV max of lesion (mm)		
Mean± SD	40.16± 10.80	
SUV max	6. 2± 3.1.	
Histopathology		
Invasive ductal carcinoma	14	46.7
Invasive lobular carcinoma	11	36.7
Invasive medullary carcinoma	1	3.3
Invasive mucinous carcinoma	4	13.3
Nodal metastasis		
Absent	6	20.0
Present	24	80.0
Distant metastasis		
Absent	20	66.7
Present	10	33.3

Table 2: Site of nodal and distant metastasis detected by conventional and PET/CT (n=30).

	Conventional CT	**PET /CT**
Site of nodal metastasis	No.	No.
Ipsilateral axillary	9	11
Contralteral axillary	4	5
supraclavicular	3	4
Cervical	1	2
Intra-parotid	0	1
Paraortic LN	1	1
Site of distant metastasis	No.	No.
lung nodule	2	3
Suprarenal gland	1	1
Osseous metastasis	3	5
Hepatic focal lesion	0	1

Table 3: Upstaging of patients by PET/CT imaging categorized by conventional CT (n=30).

		PET /CT staging						
		Stage I	Stage IIA	Stage IIB	Stage IIIA	Stage IIIB	Stage IIIC	Stage IV (%)
Conventional CT staging	**total**							
Stage I	6	6	0	0	0	0	0	0
Stage IIA	2	0	2	0	0	0	0	0
Stage IIB	3	0	0	2	1	0	0	0
Stage IIIA	6	0	0	0	4	0	1	1
Stage IIIB	3	0	0	0	0	2	0	1
Stage IIIC	4	0	0	0	0	0	2	2
Stage IV	6	0	0	0	0	0	0	6
total	30	6	2	2	5	2	3	10

Table 4 : Diagnostic performance of PET/CT and conventional CT in diagnosis of nodal and distant metastasis.

Parameters	Nodal metastasis			Distant metastasis		
	PET/CT	Conventional CT	p-value	PET/CT	Conventional CT	p-value
True negative	4	3	0.001**	17	16	0.001**
True positive	23	16		9	8	
False negative	2	9		3	4	
False positive	1	2		1	2	
Sensitivity	92%	64.0%		94.4%	88.9%	
Specificity	80%	60.0%		75.0%	66.7%	
Negative predictive value	66.7%	25.0%		85.0%	80%	
positive predictive value	95.8%	88.9%		90.0%	80%	

**: statistically highly significant (p<0.001).

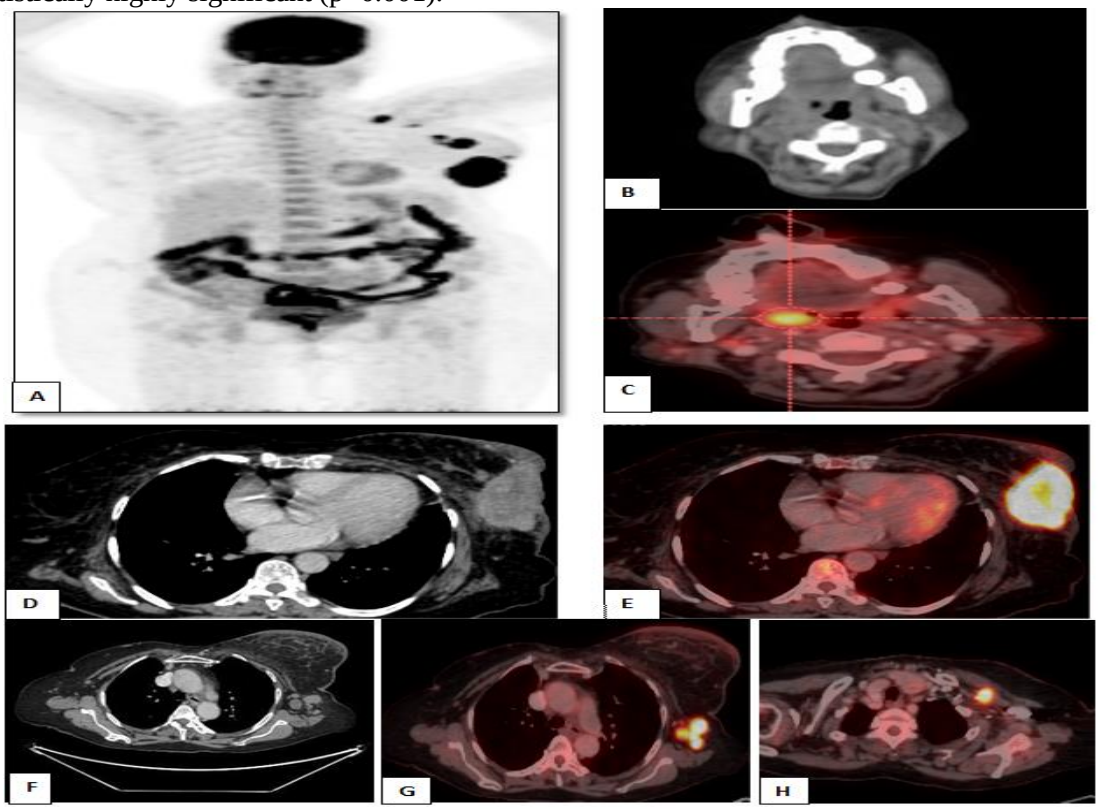

Figure1. A65 year old female patient presented with newly diagnostic left breast cancer (IDC). **A**: PET MIP picture of entire body indicated active lesions in left breast and left axilla. **B&C**: Axial CECT and Fused PET/CT scans respectively indicated few hypermetaboilic right submandibular and right lower deep cervical enlarged lymph nodes, the most active is measuring about 15×14mm and achieved up to 5.6SUVmax, not appreciated in CT image alone. **D&E:** Axial CECT and fused PET/CT scans respectively revealed ill-defined hyper dense soft tissue mass lesion lower outer quadrant of left breast. indicated active ill-defined heterogeneous soft tissue mass lesion with infiltrating the overlying skin and inseparable from underlying pictorialize muscle with related parenchyma distortion and fat planes stranding as well as internal foci of calcification it measures about 8.5x4.6x7.5cm at its maximum dimension and achieves up to 19.4SUVmax.associated thickened overlying skin and subcutaneous edematous changes. Other tiny metabolically active hyper dense subcutaneous nodule closely related to upper aspect of previously described lesion is seen measuring about 6mm and achieving up to 3.9 SUVmax. **F,G&H:** Axial CECT and fused PET/CT scans of the chest revealed multiple hyper metabolic enlarged left axillary as well as left retro-pectoral lymph nodes (not appreciated on conventional CT), the largest and most active one is measuring about. 2.2x 2cm and achieving up to 13.4 SUVmax…The patient was staged IIIA (T3 N2 M0) by conventional CT and upstaged into IIIC (T4 N3 M0) by PET CT .

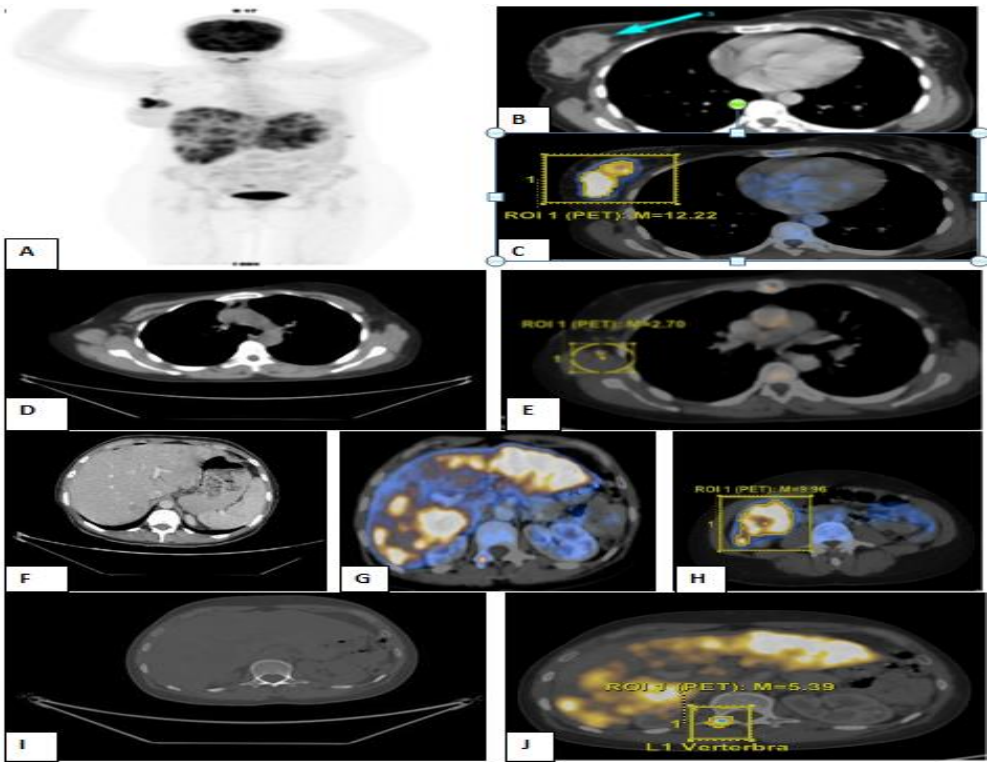

Figure 2: A 36years old female patient presented with recently diagnosed breast cancer. **A:** whole –body PET MIP picture revealed active breast cancer and hepatic lesions. **B &C:** axial CECT scan and fused PET /CT scan of the chest revealed a large lobulated mass with heterogeneous enhanced soft tissue mass lesion noted at upper outer quadrant of right breast measuring about 6.6x3.3 cm and achieving SUV max up to 12.22. **D&E:** axial CECT scan and axial fused PET/CT scan revealed multiple enlarged metabolically active right axillary and pectoral lymph nodes the largest and most active is seen measuring about 14x9mm and achieving SUV max up to 3.02. **F,G&H:** axial CECT scan and axial fused PET/CT scan of the abdomen reveled multiple hyper metabolic focal lesions seen all over the hepatic lobes largest and most active one at left lobe is noted measured about 2x1cm and achieving SUV max up to 9.97, not appreciated in CT image alone . **I&J:** axial CECT and fused PET /CT scan reveled hyper metabolic active lytic osseous lesion at right transvers process of L1 vertebra achieving SUV max 5.39….The patient was stage IIIA(T2 N2 M0)by CT and upgrade to stage IV (T2 N2 M1) by PET/CT.

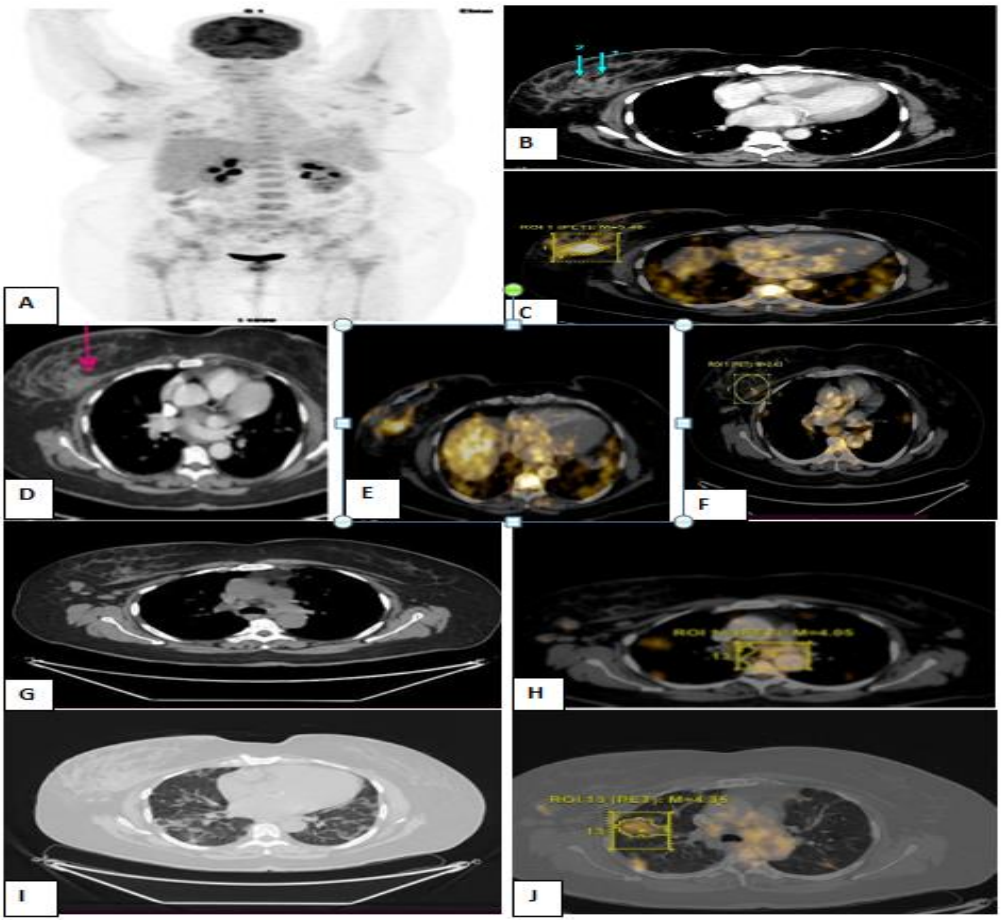

Figure 3: A 64 years old female patient present with right breast cancer (IDC). **A:** whole –body PET MIP picture active right breast cancer **.B&C**: axial CT scan a and fused PET /CT scan of the chest revealed an ill-defined hyper metabolic heterogeneous soft tissue mass is noted at lower outer quadrant of right breast with irregular border and speculated margins(green arrows) measured about 28x24mm and uptake achieving SUVmax up to 5.4. **D,E&F:** the breast mass infiltrating the most lower of right lateral chest wall muscle(pink arrow) achieving SUV max 2..43. **G&H:** axial CT scan axial fused PET /CT scan of the chest revealed multiple enlarged metabolically active mediastinal lymph nodes largest one measuring about 23x18mm and achieving SUV max up to 4.05,not appeared in CT alone**. I&J:** axial CT scan axial fused PET /CT scan of the chest show reticular bands on CT image which displayed peripheral irregular interlobular nodular septal thickening uptake achieving SUV max up to 5.02. The patient was stage IIIB (T4 N2 M0) by CT and upstaged into stage İV (T4 N2 M1) by PET CT.

DISCUSSIONS

An accurate assessment of recently diagnosed breast cancer patient is crucial for optimal treatment decision and predicting the prognosis of breast cancer. Many traditional imaging modalities, including sonomammography, pelviabdominal ultrasound, chest X ray and bone scan are all used in the early staging work-up **[6,7].**

Pelviabdominal ultrasound and plain chest radiography were the basic staging imaging methods for detection of pathologically enlarged LNs and distant metastatic deposits and has been replaced nowadays by bone scan and contrast enhanced CT **[8,9]**. Despite that, histopathological examination and sentinel LN biopsy remains the clinical gold standard for precise evaluation of metastatic deposits **[10].**

Comparing hybrid imaging modalities to traditional imaging methods has shown to be more advantageous for cancer staging **[11-13]** but even these hybrid modalities could not limit the need for biopsy **[14].** Better pre-selection of nodal-positive individuals, however, might lead to fewer operations and prevent the need for a prior lymph node biopsy. However, the National Comprehensive Cancer Network (NCCN) and European Society For Medical Oncology (ESMO) does not recommend using these hybrid imaging methods in the routine pretreatment and preoperative breast cancer staging except in high-risk patients and indeterminate standard imaging results **[11,15,16].**

Regarding the N staging of breast cancer, numerous authors has highlighted the value of using ^{18}F-FDG PET/CT for evaluation of lymph

node affection. **Bitencourt et al. [11,17]** described a significant superiority of ^{18}F-FDG PET/CT compared to conventional CT imaging in detection of LN metastatic affection especially in non-axillary and normal sized LNs**. Mahner et al. [18]** showed that PET CT sensitivity regarding mediastinal ,suraclavicular and axillary LNs involvement were 96 %,84% and 86% compared to conventional CT sensitivity of 31 %,40% and 53% . These statements were in line with our study results. ^{18}F-FDG PET/CT had showed high sensitivity (92%) and specificity (80%) in diagnosis of nodal metastasis compared to conventional CT with lower sensitivity (64%) and specificity (60%) in our study . Thus, ^{18}F-FDG PET/CT can limit the amount of unnecessary LN biopsies as well as accurate estimation of N staging with proper treatment selection and precise determination of required amount of radiation field.

Our analysis of the M staging of cancer breast revealed that ^{18}F-FDG PET/CT had high sensitivity (94.4%) and specificity (75%) in diagnosis of distant metastasis compared to conventional CT with lower sensitivity (88.9%) and specificity (66.7%). Fewer studies have examined the advantages of hybrid ^{18}F-FDG PET/CT imaging for people with recently diagnosed breast cancer. **Hildebrandt et al. [13]** compared diagnostic value of conventional CT ,^{18}F-FDG PET/CT, and bone scan in 100 breast cancer women and found a greater superiority of PET/CT than contrast enhanced CT and bone scintigraphy**.** Our results are also in line with a study of **Gajjala et al. [19]** that examined 61 locally advanced breast cancer patients and declared that ^{18}F-FDG PET/CT staging had a higher accuracy than the conventional imaging staging. In the study of **kamal et al. [20]**, 50 women with newly diagnosed breast cancer showed higher diagnostic performance of ^{18}F-FDG PET/CT with % 100 sensitivity in comparison to 96 % sensitivity of contrast-enhanced CT. ^{18}F-FD PET/CT is highly sensitive imaging technique for metastatic tumor detection and proper planning of the treatment and surgery but this imaging technique still can not eliminate the role of biopsy for histological verification

Regarding the initial staging of the breast cancer, our findings revealed 10% of upstaging by PET CT in stage I and II (1/10 patients) and 50% upstaging of stage III into higher stages (5/10 patients). It is widely known that the stage of breast cancer upon diagnosis directly correlates with the frequency of distant metastases **[21,22].** Thus,18 FDG PET/CT is highly beneficial in initial evaluation of stage III breast cancer for identifying distant metastases and extra-axillary nodes which lead to upstaging to stage IV and modifies the treatment plan from surgical removal with or without preoperative chemotherapy to palliative therapy **[23, 24].** FDG PET/CT is not advised for patients with stage I and stage IIA illness because of the very low rates of upstaging in these conditions**[25, 26].** According to recommendations made by the National Comprehensive Cancer Network 2022, individuals with stage III cancer or those whose results from routine staging investigations are non-diagnostic or suspicious should have PET/CT scanning **[26].** Additionally, according to the NCCN guidelines, performing PET/CT examination may be more effective in detecting suspected nodal and distant metastatic involvement in locally advanced breast cancer stage III, but not advised for stage I, II, or operable III (T3 N1) breast cancer because of the high probability of false-negative results of the tiny lesions. The main limitation of this study was that it was performed at a single center as well as the relatively small sample size.

CONCOLUSIONS

From our study we can conclude that 18F-FDG PET/CT is an emerging technology that efficiently, accurately, and noninvasively detects metastatic illness among individuals with recently discovered breast cancer, changing the original staging and having an effect on the patients treatment decisions.

Abbreviations

18F–FDG-PET/CT: Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography , **I.V:** Intravenous ,**IDC**: Invasive ductal carcinoma, **M** : Metastasis, **N** : Lymph nodes, , **PET**: Positron emission tomography, **ROI** :Region of interest , **SUV**: Standard glucose uptake value ,**T:** tumor.

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