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The Clinical Utility of PET CT in Breast Cancer Management and Follow Up

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Abstract

Aim of the work: Whole-body 18F-FDG PET/CT plays an important role in the assessment of breast cancer patients particularly as it helps detection of the extent of the disease in the body, improves staging of breast cancer patients which significantly changes the therapeutic management of these patients.

It also has proved its effectiveness that outweighs the other methods in the staging of the disease (Berney., *et al*. 2015)

Methods: This is study carried out in Cairo scan radiology center from March 2018 to September 2018 for patients who have been recently diagnosed with cancer breast and were coming to perform PET/CT scans for staging, pre-operative or pre-therapeutic assessment and also Patients underwent lumpectomy or mastectomy and coming for follow up.

A total number of 34 female patients were included in the study and they were biopsy proved to have cancer breast. The age of the patients ranged from 37 to 79 years, and the average was 56.

All exams were done on the PET/CT scanner GE multi slice 16.

Inclusion criteria: Patients with recently diagnosed breast cancers and post resection were included in this study.

Exclusion criteria: Patients with blood glucose level >300 mg/dl at the time of the study.

Imaging: All data were acquired with a combined PET/CT in-line system (Phillips Gemini 64 and Siemens 20time of flight machines). This dedicated system integrates a PET scanner with a multi-section helical CT scanner and permits the acquisition of co-registered CT and PET images in one session.

Results: A total number of 34 female patients with recently diagnosed cancer breast were included in our study. The age of the patients ranged from 32 to 79 years, and the average was 56.

Assessment of all patients will include the following items:

1. Patients characteristics.
2. Primary cancer characteristics.
3. Axillary lymph nodes involvement.
4. Contra-lateral axillary lymph nodes involvement.
5. Internal mammary lymph nodes involvement.
6. Other lymph nodes involvement.
7. Pulmonary metastasis.
8. Visceral metastasis.
9. Bony deposits.
10. Overall comparison between CET and PET/CT.

Conclusion: Breast cancer is the most common non-skin cancer and the second leading cause of cancer related death in women. Breast cancer strikes women of all ages, races, ethnicities, socioeconomic strata, and geographic locales. Once breast cancer is diagnosed, the tumor stage has to be accurately determined before therapy chosen and the prognosis known.

Conventional imaging cannot precisely detect axillary lymph node involvement and/or the presence of distant metastases, which significantly change therapeutic management of these patients. Whole-body 18F-FDG PET/CT has proven to be an effective imaging modality for staging of malignant tumors.

Combined 18-FDG PET/CT provides the ability to combine functional and morphologic information in a single study, thus becoming a powerful imaging modality for diagnosis and staging of breast cancer.

Our data and in agreement with the previous studies has demonstrated that PET/CT has shown to be useful at different stages of breast cancer, diagnosis, treatment and recurrence.

Combined PET/CT in patients with breast cancer improves the sensitivity, specificity and accuracy of local extent of the disease, axillary and extra-axillary lymph nodes involvement as well as detection of the distant metastasis compared to CT alone.

The use of diagnostic contrast enhanced CT with PET/CT helps in better anatomical localization and in addition it constitute a base line exam for staging and follow up if PET/CT is not affordable and only CT will be used.

Although whole-body FDG PET imaging does not have sufficient utility in the detection of primary disease, and is not optimized to take the place of the sentinel lymph node procedure for initial axillary staging, FDG PET scanning has efficacy superior to that of conventional imaging for the detection of locoregional and metastatic spread in the appropriate patient population, and has better diagnostic performance for detection of skeletal metastasis compared with routine bone scanning. Thus, FDG PET can serve as a one-stop shopping imaging technique for patients who would benefit from whole-body staging, such as in clinical stage 2b-or-above disease, or for patients with clinical suspicion of distant disease. FDG PET imaging can also provide prognostic information and monitor response to therapy. Although minimal residual tumor cannot be reliably excluded, FDG PET does have high PPV for predicting the presence of residual tumor. Finally, FDG PET is effective at detecting and restaging recurrent tumor, surpassing the diagnostic performance of conventional imaging. However, PET scanning should not be used for routine surveillance in asymptomatic patients who have achieved a complete response.

Keywords: Pulmonary; Breast Cancer; PET/CT

Introduction

Breast cancer is the most common non-skin cancer and the second leading cause of cancer related death in women. Breast cancer strikes women of all ages, races, ethnicities, socioeconomic strata, and geographic locales (Dose Schwarz., *et al*. 2005).

Cancer staging is essential in determining the choice of therapy, as well as a patient's prognosis and chances for survival (Yang SA., *et al*, 2007).

Mammography has been shown to be accurate for breast cancer screening except in some specific situations, such as in patients with dense breast, significant architectural distortions, or presence of extensive scarring from prior biopsies (Fuster D., *et al*. 2008)

Contrast magnetic resonance imaging (MRI) can provide detailed information about the size and extent of the breast cancer and has an additional value for evaluating multifocal and/or multi centric tumors (Fuster D., *et al*. 2008)

However, conventional imaging cannot precisely detect axillary lymph node involvement and/or the presence of distant metastases, which significantly change therapeutic management of these patients. Whole-body 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography–computed tomography (PET/CT) has proven to be an effective imaging modality for staging of malignant tumors (Piccardo A., *et al*. 2012)

Moreover, the limited specificity of positron emission tomography (PET) that's due to the increased glucose metabolic activities of benign tumors and inflammatory tissues (such as those of tuberculosis) can be partially overcome by PET/CT. Therefore, the 18F-FDG PET/CT would be more informative for pre-therapeutic staging of the entire body in a single examination (Tatsumi M., *et al*, 2006).

18F-FDG PET/CT provides the ability to combine functional and morphologic information in a single study, thus becoming

a powerful imaging modality for diagnosis, staging of various malignancies, including breast cancer [1].

Patients and Methods

This is study carried out in Cairo scan radiology center from March 2018 to September 2018 for patients who have been recently diagnosed with cancer breast and were coming to perform PET/CT scans for staging, pre-operative or pre-therapeutic assessment and also Patients underwent lumpectomy or mastectomy and coming for follow up.

A total number of 34 female patients were included in the study and they were biopsy proved to have cancer breast. The age of the patients ranged from 37 to 79 years, and the average was 56.

All exams were done on the PET/CT scanner Phillips Gemini and Siemens time of flight 64 and 20 machines respectively.

Inclusion criteria

Patients with recently diagnosed breast cancers and post resection were included in this study.

Exclusion criteria

Patients with blood glucose level >300 mg/dl at the time of the study.

Imaging

All data were acquired with a combined PET/CT in-line system (Phillips Gemini 64 and Siemens 20time of flight machines). This dedicated system integrates a PET scanner with a multi-section helical CT scanner and permits the acquisition of co-registered CT and PET images in one session.

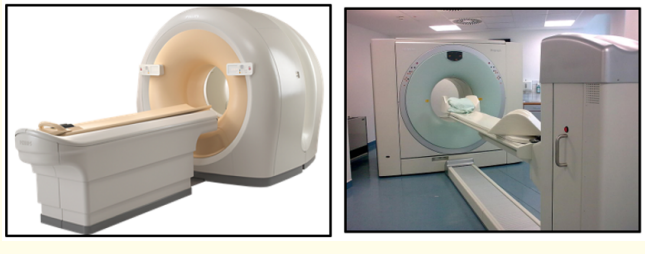

Figure 1: Showing Phillips Gemini Time of flight 64 (A)Siemens Biograph (B) PET-CT machines.

Imaging protocol

Patient preparation

All patients were asked to fast for six hours prior to scan. All metallic items were removed from the patient, including, pants with zipper, bra, belts, bracelets, etc. and the patient were given gown to wear. An intravenous (I.V) cannula was inserted in the patient's arm for administration of 18F-FDG. The patients were instructed to avoid any kind of strenuous activity prior to the examination and following injection of the radioisotope to avoid physiologic muscle uptake of FDG and the patient was asked to void prior to scanning.

In case of diabetic patients serum glucose was routinely measured prior to 18F-FDG injection, and fasting levels were 70–180 ng/dl. Diabetic patients should not have regular insulin administered subcutaneously within four hours of having FDG administered. We did not inject insulin usually to reduce blood glucose level.

Our strategies for decreasing brown fat were; providing a controlled-temperature (warm) environment for patients before 18F-FDG injection and high-fat, low-carbohydrate, protein-permitted diet before the examination.

Dosage administration

10-20mCi (370 MBq; approximate dose to patient, 3-5MBq/Kg) 18F-FDG 45–90 minutes before examination. This period is referred to as the uptake phase and is the necessary amount of time for the FDG to be adequately bio-distributed and transported into the patient's cells. Patients were asked to rest in a quiet room, devoid of distractions, and they were also asked to keep their movements, including talking, at an absolute minimum. This minimizes physiologic uptake of FDG into skeletal muscle, which can confound interpretation of the scan. Patients should be comfortable and relaxed.

Patient position

The patients were positioned in a Comfortable head fixation with their arms raised above their heads.

Examination time and technique

We performed low dose non enhanced CT scan first, then a whole body PET study. Diagnostic enhanced whole body CT scan was then performed. The whole study took approximately 20-30 minutes.

For a typical whole body PET/CT study (brain, neck, chest, abdomen, and pelvis), scanning began from the skull base and extended caudally to the level of the upper thighs. The total length of CT cov¬erage was an integral number of bed positions scanned during acquisition of PET data. The study was performed with the

patient breathing qui¬etly. Typical scanning parameters would be a col¬limator width of 5.0 mm, pitch of 1.5, gantry ro¬tation time of 0.8 second, and field of view of 50cm. The helical data are retrospectively recon¬structed at 1 mm intervals.

The contrast enhanced helical CT was performed following the PET study performance, using 125 mL of a low-osmolarity iodinated contrast medium using a power injector.

PET technique

Approximately six to seven bed positions are planned in the three-dimensional acquisition mode for scanning the entire patient with 3-5 minute acquisition at each bed position.

PET/CT fusion

Hundreds of trans axial PET and CT images were first reconstructed. These are then reformatted into coronal and sagittal images to facilitate image interpretation. For each of these sets of PET and CT images, corresponding "fusion" images, combining the two types of data, also were generated.

The whole acquisition time for an integrated PET/CT scan was approximately 25 min. PET image data sets were reconstructed using CT data for attenuation correction and co-registered images were displayed using special software.

Images interpretation

All CT examinations were analyzed by experienced radiologists and all PET/CT examinations were analyzed separately by a consensus of at least two experienced observers of nuclear medicine physicians and radiologists.

A region of interest (ROI) of 5 to 10mmwas placed manually over the area of maximal activity on slices with the clearest definition of the tumor mass and in the adjacent slices and the SUV was calculated.

The CT and fused PET/CT images were evaluated regarding the primary tumor and the presence of lymph nodes and distant metastases.

An increase in glucose uptake to a level greater than that in the surrounding tissue (more than the mediastinal blood pool in the chest and more than the background activity in the rest of the body) at qualitative analysis or a standard glucose uptake value of more than 2.5 were considered to characterize pathological process.

The possibility of nodal or distant metastatic disease spread was considered when lesions were clearly present on PET/CT images according to the combined morphologic CT and 18F-FDG uptake criteria. Abnormal 18F-FDG uptake was defined as radiotracer accumulation outside the normal anatomic structures and of greater intensity than background activity, excluding the known sites of physiologic FDG uptake.

For the analysis, the lymph node chains were grouped into axillary, contra-lateral axillary, internal mammary, hilar and mediastinal as well as abdomino-pelvic lymph nodes. The findings for each of these sites were graded as positive or negative for tumor infiltration.

In CT, lymph node assessment was based on size: nodes with a short-axis diameter greater than 10 mm were defined as pathologic. Furthermore, the presence of necrosis within a lymph node was considered a sign of malignancy, regardless of node size. Also, the preserved fatty hilum of the lymph node was considered to be benign regardless of node size.

In PET/CT, lymph nodes with increased glucose uptake were considered positive for metastatic spread even when they were smaller than 1 cm in short-axis diameter. PET-negative lymph nodes were characterized as benign, even when they were larger than 1 cm in short-axis diameter.

Calcified lymph nodes were considered benign regarding the degree of FDG uptake.

The following sites were evaluated for distant metastases: lung, visceral organs (liver, spleen and adrenal glands), brain and bone. The findings for each of these sites were graded as positive or negative for tumor infiltration.

Lung nodules 5 mm in patients should be considered as positive if FDG uptake is greater than the mediastinal blood pool. Metastasis cannot be excluded in lung nodules >0.5 cm.

Hepatic or splenic lesions should be considered as positive if their uptake is higher than or equal to that of the liver or spleen, and negative if their uptake is lower than that of the liver and spleen.

The assessment of adrenal gland lesions was done according to a certain algorithm as follows: If the density of the lesion is less than 10 HU, it is considered as benign and if more than 10 HU, we assess SUV max of the lesion. If SUV max less than 3.1, it is considered benign and if more than 3.1, it is considered malignant.

If there was a clearly multifocal increase in FDG uptake in the bone marrow, the patient was considered as PET positive.

Statistical analysis

Data were statistically described in terms of range, mean ± standard deviation (± SD), median, frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Kruskal Wallis analysis of variance (ANOVA) test. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2010 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

A total number of 34 female patients with recently diagnosed cancer breast were included in our study. The age of the patients ranged from 32 to 79 years, and the average was 56.

Assessment of all patients will include the following items

1. Patients characteristics.
2. Primary cancer characteristics.
3. Axillary lymph nodes involvement.
4. Contra-lateral axillary lymph nodes involvement.
5. Internal mammary lymph nodes involvement.
6. Other lymph nodes involvement.
7. Pulmonary metastasis.
8. Visceral metastasis.
9. Bony deposits.
10. Overall comparison between CET and PET/CT.

	Minimum	Maximum	Mean	Std. Deviation
Age	34	78	56	11.82
Weight	49	130	78.05	14.53
Height	130	178	161.05	8.254
Blood Glucose	64	138	105.17	17.43
Dose of 18F-FDG injected	222	560	348.48	68.47

Table 1: Showing the patients' characteristics.

Primary cancer characteristics

combined PET/CT sensitivity 98.11% compared to CT alone 81.7% with ρ value of combined PET/CT 0.002 compared to CT alone.

Modality	Patients	
	+ve	-ve
PET/CT	(98%)	(2%)
CT	(82.4%)	(17.6%)

Table 2: Showing the patients with detected breast cancer by PET/CT versus CT.

	Minimum	Maximum	Mean	Standard Deviation
Size	1.0	11.0	3.03	1.83
SUV max	2.1	36.3	8.01	6.79

Table 3: Showing the PET/CT characteristics of breast cancer lesions.

Size	Percentage
≤ 2 cm	28%
> 2 cm but ≤ 5 cm	64%
> 5	8%

Table 4: Showing the percentage of the different size of breast cancer lesions.

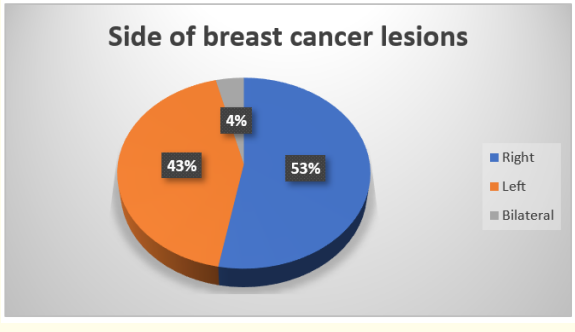

Figure 2

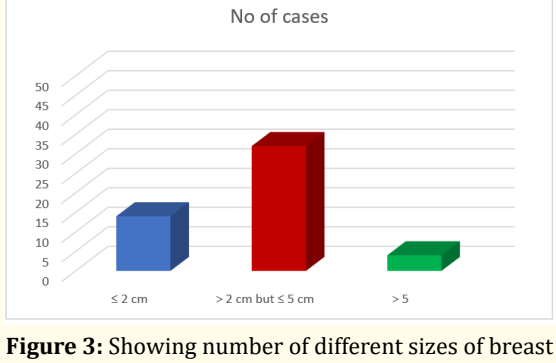

Figure 3: Showing number of different sizes of breast cancer lesions.

Axillary lymph nodes

Axillary lymph nodes involvement was detected by combined PET/CT in 33 patients, while CT alone was able to detect infiltrated axillary lymph nodes in 23 patients.

Ona lymph node count, combined PET/CT detected 115 infiltrated lymph nodes, with 87 lymph nodes detected by the CT alone.

Comparing the results of combined PET/CT with CT alone in detection of ρ value of PET/CT over CT alone 0.001.

Modality	Patients		(n) Lymph nodes
	+ve	-ve	
PET/CT	(64.7%)	(35.3%)	115
CT	(45%)	(55%)	87

Table 5: Showing the axillary lymph nodes involvement by PET/CT versus CT.

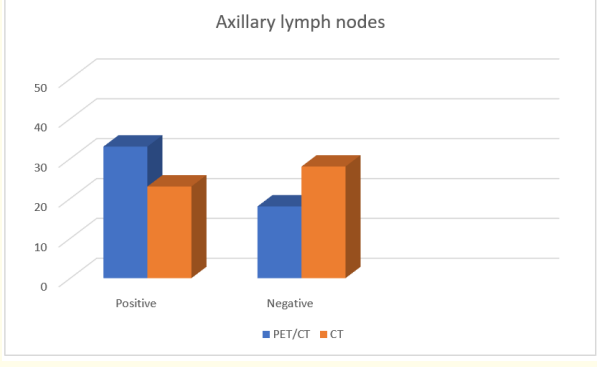

Figure 4: Showing number of patients with involved axillary lymph nodes by combined PET/CT and CT.

Contralateral axillary lymph nodes

Contra-lateral axillary lymph node metastases were detected by combined PET/CT in 8 patients (29 lymph nodes), while CT alone was able to detected in 6 patients (17 lymph nodes) with ρ value of combined PET/CT over CT alone 0.066.

Modality	Patients		(n) Lymph nodes
	+ve	-ve	
PET/CT	(16.32%)	(83.68%)	29
CT	(12.25%)	(87.75%)	17

Table 6: Showing the contralateral axillary lymph nodes involvement by PET/CT versus CT.

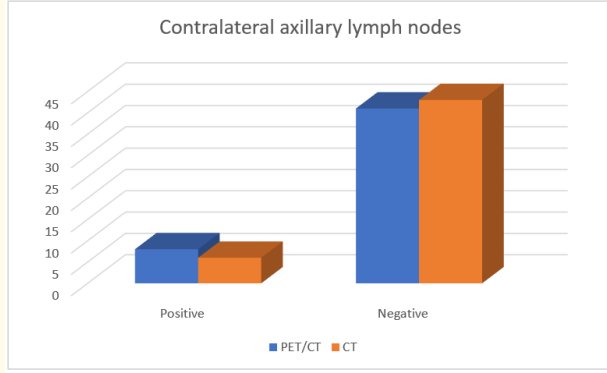

Figure 5: Showing number of patients with involved contralateral axillary lymph nodes by combined PET/CT and CT.

Internal mammary lymph nodes

Internal mammary lymph node metastaseswere detected by combined PET/CT in 9 patients (9 lymph nodes), while CT alone was able to detected in 4 patients (4 lymph nodes), with p value of combined PET/CT over CT alone 0.025.

Modality	Patients		(n) Lymph nodes
	+ve	-ve	
PET/CT	(17.65%)	(82.35%)	9
CT	(7.84%)	(92.16%)	4

Table 7: Showing the internal mammary lymph nodes involvement by PET/CT versus CT.

Other lymph nodes

Extra-axillary lymph nodes metastasis include cervical, mediastinal, hilar abdominal and pelvic lymph nodes. Combined PET/CT found distant lymph node metastasis in 18 patients (145 lymph nodes), with 15 patients (86 lymph nodes) found to have positive lymph node metastasis by CT alone, with ρ value of combined PET/CT over CT alone 0.005.

Modality	Patients		(n) Lymph nodes
	+ve	-ve	
PET/CT	(35.3%)	(64.7%)	145
CT	(29.4%)	(70.6%)	86

Table 8: Showing the other extra-axillary lymph nodes involvement by PET/CT versus CT.

These extra-axillary lymph nodes were found in the cervical group (in 8 patients), mediastinal (in 12 patients), hilar (in 9 patients) and pelvi-abdominal lymph nodes (in 5 patients).

Site	No of cases	Percentage
Cervical	8	15.7%
Mediastinal	12	25.5%
Hilar	9	17.6%
Pelvi-abdominal	5	9.8%

Table 9: Showing the site and percentage of the patients with extra-axillary lymph nodes involvement.

Pulmonary metastasis

Out of 34 patients, combined PET/CT detected pulmonary metastasis in 7 patients. On the other side, CT alone detected 6 patients with pulmonary metastasis (ρ value of combined PET/CT over CT alone was 0.317). The patient with mismatch findings proved to have pulmonary metastasis during follow up study.

Modality	Patients	
	+ve	-ve
PET/CT	(13.7%)	(86.3%)
CT	(11.8%)	(88.2%)

Table 10: Showing the pulmonary metastasis detected by PET/CT versus CT.

Visceral metastasis

Combined PET/CT has shown metastatic visceral disease in 9 patients (including the liver, spleen, omentum and suprarenal gland), while CT alone found the disease in 8 patients with ρ value of combined PET/CT over CT alone was 0.18.

Modality	Patients	
	+ve	-ve
PET/CT	(17.65%)	(82.35%)
CT	(7.84%)	(84.31%)

Table 11: Showing the visceral metastasis detected by PET/CT versus CT.

Osseous deposits

Out of 34 patients, combined PET/CT detected osseous deposits in15 patients, with 13 patients were found to have osseous deposits by CT alone (ρ value of combined PET/CT over CT alone was 0.2).

Bone scan results were available for 8 patients of the positive patients detected by combined PET/CT, and they reveal 7 patients with osseous deposits, with one patient showing negative results for deposits (however further MRI study revealed metastatic bone disease).

Modality	Patients	
	+ve	-ve
PET/CT	(29.4%)	(70.6%)
CT	(25.5%)	(74.5%)

Table 12: Sowing the osseous deposits detected by PET/CT versus CT.

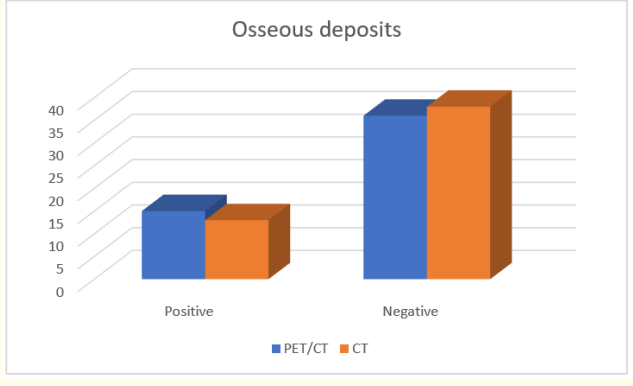

Figure 6: Showing number of patients with osseous deposits detected by combined PET/CT and CT.

TNM staging

Overall staging

Combined PET/CT upgraded the staging compared to initial CT staging.

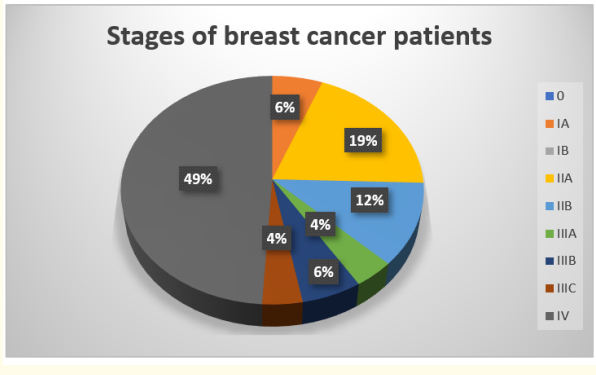

Figure 7: Showing percentage of each stage of breast cancer patients.

Overall comparison between CT versus combined PET/CT

	CT		PET/CT		P value
	Positive	Negative	Positive	Negative	
Axillary lymph nodes	23 (45%)	28 (55%)	33 (64.7%)	18 (35.3%)	0.001
Contralateral axillary lymph nodes	6 (12.25%)	43 (87.75%)	8 (16.32%)	41 (83.68%)	0.066
Internal mammary lymph nodes	4 (7.84%)	47 (92.16%)	9 (17.65%)	42 (82.35%)	0.025
Other lymph nodes	15 (29.4%)	36 (70.6%)	18 (35.3%)	33 (64.7%)	0.005
Pulmonary metastasis	6 (11.8%)	45 (88.2%)	7 (13.7%)	44 (86.3%)	0.317
Visceral metastasis	8 (7.84%)	43 (92.16%)	9 (17.65%)	42 (82.35%)	0.18
Osseous deposits	13 (25.5%)	38 (74.5%)	15 (29.4%)	36 (70.6%)	0.2

Table 13: Overall comparison between combined PET/CT versus CT alone.

Discussion

Breast cancer is the most common cancer worldwide and one of the leading causes of cancer-related death among women. The 18F-FDG Positron Emission Tomography/Computed Tomography (PET/CT) is a non-invasive imaging technique and is widely used within the diagnostic algorithms of oncological diseases (G. Ugurluer., *et al*. 2016)

Conventional imaging cannot precisely detect axillary lymph node involvement and/or the presence of distant metastases, which significantly change therapeutic management of these patients. Whole-body 18F-FDG PET/CThas proven tobe an effective imaging modality for staging of malignant tumors (Fuster., *et al*. 2008)

Moreover, the limited specificity of PET that's due to the increased glucose metabolic activities of benign tumors and inflammatory tissues (such as those of tuberculosis) can be partially overcome by PET/CT. Therefore, the 18F-FDG PET/CT would be more informative for pre-therapeutic staging of the entire body in a single examination (Tatsumi M., *et al*, 2006). Baseline PET parameters measured before neoadjuvant treatment have prognostic values in locally advanced breast cancer patients (David Groheux., *et al*, 2017).

The co-registration of PET images with images from computed tomography (CT) allows combined anatomic and functional imaging with a single scanner. Combined PET/CT provides information that cannot be obtained with PET or CT alone and is rapidly assuming a critical role in the clinical evaluation of patients with cancer for staging and evaluating the effect of treatment. Equivocal CT findings can be evaluated better with the help of the additional functional information provided by FDG PET, especially in follow-up of cancer patients who have undergone surgery, radiation therapy, or chemotherapy. Conversely, subtle metabolic findings at FDGPET that might be confused with normal physiologic up take may allow the detection of pathologic sites of FDG accumulation when combined with findings at CT [2].

FDG PET images are generally assessed qualitatively or quantitatively for pathologically increased radio tracer uptake. The standardized uptake value SUV. The SUV tends to be higher in tumors than in benign lesions; the higher the SUV of a mass, the more likely the mass is to be malignant [2].

Serious effects arise from the mismatch between the CT and PET images due to patient respiration affecting the regions adjacent to the heart, diaphragm and lung bases which may interfere with the interpretation of lung nodules. In the current study, CT and PET scans were done during shallow breathing in agreement with Townsend., *et al*, 2004 to minimize the mis-registration artifacts.

Diabetic patients usually represent a problem because hyperglycemia leads to competitive inhibition of 18F-FDG uptake into cells, so serum glucose levels greater than 200 ng/dl result in significant changes in 18F-FDG distribution. In this study, all the patients are within the average range for injection.

The use of contrast enhanced CT in PET/CT helps in better anatomical localization and characterization of lesions but contrast-enhanced pixels can potentially generate focal artifacts in the PET image with undesirable outcome particularly for tumor imaging (Pfannenberg AC., *et al*. 2007).

We performed PET combined with low dose CT for attenuation correction and then performed contrast enhanced CT for image fusion. In accordance with Bernsdorf *et al*. [3], Wiley 2005, Cohade and Wahl 2003 and unlike Veit-Haibach., *et al*. 2007, Beyer., *et al*, 2005 and Yau., *et al*. 2005, we did not use the contrast enhanced CT for attenuation correction and thus we did not face the possible artifactual hot spots on the attenuation-corrected image or quantitative overestimation of 18F-FDG activity as mentioned by Townsend., *et al*, 2004.

Cohade and Wahl,2003 and Wiley 2005, obtained two CT scans, low dose unenhanced CT for attenuation correction and diagnostic intravenous contrast–enhanced CT at the end of the study.

Unlike Beyer., *et al*, 2005 and Yau, 2005 who had shown that the presence of intravenous contrast material actually had a little effect on the CT-based attenuation correction factors.

Multiple studies which investigated the role of IV iodinated contrast material administration in PET/CT had mixed results. Pfannenberg., *et al*, 2007 studied the additional value of contrast-enhanced multiphase CT in comparison with low-dose unenhanced CT in combined PET–PET/CT protocols for patients with different malignant tumors in a retrospective study and concluded that diagnostic multiphase CT as part of the combined PET/CT protocol has the potential to provide considerable additional value in specific clinical conditions, with resultant change of management in a substantial proportion of patients. Cantwell, 2007 showed the superior value of contrast-enhanced CT over unenhanced CT in PET/CT protocols in evaluation of patients with metastatic liver lesions from colorectal cancer.

Conversely, Rodríguez-Vigil., *et al*, 2006 showed a good correlation between unenhanced low-dose PET/CT and contrast-enhanced full-dose PET/CT for lymph node and extra-nodal disease in lymphomas, suggesting that unenhanced low-dose PET/CT might be sufficient.

In this study, contrast enhanced CT images were performed for the involved patients to ensure fully diagnostic CT data, and such strategy was in line with other studies as to Bernsdorf., *et al*. [3].

Performing diagnostic contrast enhanced CT provides a baseline exam in case that follow up CT alone is to be used for monitoring the therapeutic response as the cost of the PET/CT exam may not be affordable for some patients (Rodríguez-Vigil., *et al*, 2006).

There was only one patient in this study with elevated renal functions and thus the contrast enhanced diagnostic CT was not performed. There was no significant difficulty in detection of the involved mediastinal lymph nodes. However the main drawback was in the detection of the involved hilar lymph nodes as well as the hepatic focal lesions, which could be missed in the un-enhanced study and would be difficult to deicide precisely the affected segment.

The major aim of the study is to investigate the ability of 18F-FDG PET/CT to be used as a pre-operative and pre therapeutic assessment study. Several studies have assessed its role in modification of initial patients staging over the other conventional studies and it proved its superiority. Using PET/CT as metastatic work up tool is very crucial in accurate staging of the patients which is considered as the corner stone in the management plan of breast cancer patients.

In this study, regarding the assessment of the primary breast tumors in 51 patients, it has shown that combined PET/CT was superior to CT alone in detection of the primary breast cancer with sensitivity 98.11% compared to 81.7% for CT alone.

This was on agreement with previous studies by Bernsdorf., *et al*. [3] who have stated 97% sensitivity of PET/CT in identification of primary breast tumor. Moreover, Tatsumi., *et al*, 2006 have shown that PET/CT is preferable to PET or CT in the diagnosis of breast cancer. In a study performed on 60 patients by Fuster., *et al*. 2008, combined PET/CT was able to identify the primary tumor among the all patients.

Mahner., *et al*. 2008 have also reported that higher sensitivity of FDG-PET over CT alone with FDG–PET sensitivity of 93% for newly diagnosed breast cancer, compared to 88% sensitivity of CT in patientswith newly diagnosed disease.

Combined PET/CT missed only one patient with breast cancer, and that might be explained by the relatively dense patient breast parenchyma and the small size of the lesion. This explanation was supported by study done by Koolen., *et al*. [4] who have shown high sensitivity (94%) of combined PET/CT in breast tumors larger than 1 cm, with reduction of sensitivity (63%) among the breast cancer lesions smaller than 5 mm.

In this study, detection of metastatic axillary lymph nodeswas improved by combined PET/CT which detected metastatic axillary

lymph nodes in 33 patients compared to 23 patients showing positive axillary involvement by CT alone (ρ value of PET/CT over CT alone 0.001)

In the current study, there was mismatch between CT and combined PET/CT in 14 patients regarding the detection of metastatic axillary lymph nodes. In these patients combined PET/CT detected axillary lymph nodes involvement with negative results in CT alone. In 5 patients this mismatch causes no changes in the N staging, while in the other 9 patients this mismatch causes upstaging of N stage (8 patients from N0 to N1 and 1 patient from N0 to N3).

This mismatch can be explained by the small sub-centimetric lymph nodes, considered to be negative in CT, and have shown high metabolic activity in combined PET/CT study.

In studies done by Koolen., *et al*. [4], Bernsdorf., *et al*. [3] and Fuster., *et al*. 2008, combined PET/CThave shown excellent specificity (90 – 100%) and positive predictive value for detection of metastatic axillary lymph nodes with sensitivity (63 – 70%).

We agreed with study done Tatsumi., *et al*, 2006, who have revealed superiority of combined PET/CT over CT alone in detection of metastatic axillary lymph nodes. Combined PET/CT detected positive axillary lymph nodes in 25 regions with 14 positive regions detected by CT alone.

In addition to the mentioned studies, Sang KY., *et al*, 2007 have proved in their study high sensitivity and specificity of axillary PET/CT imaging in breast cancer patients. PET/CT can accurately localize and differentiate the metastatic and reactive lymph nodes when CT shows multiple enlarged lymph nodes in the axilla.

In this study, detection of metastatic internal mammary lymph nodes was improved by combined PET/CT which detected metastatic internal mammary lymph nodes in 9 patients compared to 4 patients showing positive internal mammary chain involvement by CT alone (ρ value of PET/CT over CT alone 0.025)

In the current study, there was mismatch between CT and combined PET/CT in 5 patients regarding the detection of metastatic internal mammary lymph nodes. In these patients combined PET/CT detected axillary lymph nodes involvement with negative results in CT alone. In 2 patients, this mismatch causes no changes in the N staging, while in the other 3 patients this mismatch causes upstaging of N stage (two patients from N0 to N2, and 1 patient from N0 to N3).

This result was in agreement with Tatsumi., *et al*, 2006 study which had proved FDG-PET/CT to be useful in detecting tumor involvement of the internal mammary lymph nodes compared to the CT because the smaller lymph nodes sometimes produced equivocal or negative CT findings. Therefore, PET/CT may play an important role in predicting patient outcome, as it is known that patients with metastases to these lymph nodes have a significantly worse prognosis than those without tumor involvement.

In addition to the mentioned study, Sang KY., *et al,* 2007 have proved also that the prevalence of abnormal findings for the internal mammary lymph nodes by PET/CT was about twice that of conventional CT in those patients with metastatic breast cancer.

In our study, combined PET/CT appears superior over the CT alone in detection of the extra-axillary lymph nodes. Combined PET/CT found distant lymph node metastasis in 18 patients, with 15 patients found to have positive lymph node metastasis by CT alone, with ρ value of combined PET/CT over CT alone 0.005. Contra-lateral axillary lymph node metastases were detected by combined PET/CT in 8 patients, while CT alone was able to detected in 6 patients with ρ value of combined PET/CT over CT alone 0.066.

We agree with Choi., *et al*. [5] who have reported that combined PET/CT was able to localize extra-axillary lymph nodes involvement better than contrast enhanced CT.

Another study done by Aukema., *et al*. 2010 who stated that FDG PET/CT may be useful as an additional imaging tool to assess extra-axillary lymph node metastasis, with an impact on the adjuvant radiotherapy management.

Distant metastases from breast cancer are frequently found in the lungs, liver and bones. One advantage of whole-body PET/CT imaging over conventional imaging modalities is its ability to detect metastasis at different sites and organs during a single examination (Sang KY., *et al*, 2007).

Out of 51 patients, combined PET/CT detected pulmonary metastasis in 7 patients, with 6 patients show pulmonary metastatic disease by CT alone. The one patient with mismatch was showing pulmonary nodule measuring about 1 cm in diameter with no other nodules, and it shows high metabolic activity in combined PET/CT study.

Combined PET/CT has shown metastatic visceral disease in 9 patients (11 sites including the liver, momentum, spleen and suprarenal gland), while CT alone found the disease in 8 patients with ρ value of combined PET/CT over CT alone was 0.18

One patient with mismatch between combined PET/CT and CT alone findings. In this patient combined PET/CT detected FDG-avid focal lesions within the right and left lobes with no definite CT correlate could be seen. That may be explained by the lack of contrast enhanced cuts in such patient, attributed to her elevated renal functions.

Out of 51 patients, combined PET/CT detected osseous deposits in15 patients, with 13 patients were found to have osseous deposits by CT alone (ρ value of combined PET/CT over CT alone was 0.2).

Bone scan results were available for 8 patients of the positive patients detected by combined PET/CT, and they reveal 7 patients with osseous deposits, with one patient showing negative results for bony metastasis, however further MRI study revealed metastatic bone disease.

Overall, this study have demonstrated superiority of combined PET/CT over CT alone in detection of distant metastasis.

We agree with Bernsdorf., *et al*. 2012 who have found that PET/CT is a valuable tool to provide information on extra-axillary lymph node involvement, distant metastases and other occult primary cancers. In the initial stage assessment, preoperative FDG-PET/CT has a substantial impact on staging and on clinical management and they suggest that PET/CT could be considered in the initial assessment of patients with newly diagnosed node-positive early-stage breast cancer.

This was in line with study done by Choi., *et al*, [5] stated that the overall sensitivity and specificity in detect¬ing distant metastases of the 18F-FDG PET/CT were 100% and 96.4%, respectively; whereas the sensitivity and specificity of the conventional imaging were 61.5% and 99.2%, respectively.

Combined PET/CT staged 3 patients as stage IA, 10 patients as stage IIA, 7 patients as stage IIB, 2 patients as stage IIIA, 2 patients as stage IIIB, 2 patients as stage IIIC and 25 patients as stage IV.

In this study, among 51 patients, combined PET/CT upgraded the staging of 13 patients compared to initial CT staging.

However, some limitations of our study should be acknowledged. Firstly the lack of direct clinical influence of increased sensitivity in detection of axillary, extra-axillary lymph nodes and distant metastasis in the management of the involved patients.

Secondly, histopathological confirmation of imaging metastatic results could not be obtained in all patients.

We did not compare PET/CT with separately performed dedicated CT studies. Thus, the advantage of PET/CT in real clinical settings may not have been properly assessed.

In conclusion, our study results show that combined PET/CT is a single valuable tool provides whole-body overview evaluation of recently diagnosed breast cancer patients, providing valuable information on axillary and extra-axillary lymph node involvement as well as distant metastases. PET/CT proved to bean efficient, accurate and non-invasive imaging technique in detecting metastatic disease with subsequent modification of the initial patient staging which is reflected on the patients' management planes [6-46].

Case 1

62 year-old Female patient, Known metastatic breast cancer to bone. She received radiotherapy and on hormonal treatment.

Findings

Review of fused PET/CT images revealed

Loco-regional

- Subcutaneous nodules are noted at left breast measuring 1.7x1.4cm showing mild FDG activity of SUVmax~2.2.
- Other scattered variable sized subcutaneous nodules are seen along the both scapula and left side of the back more numerous, larger and most active opposite the left scapula, measures 2.6x1.7cm and exhibiting FDG uptake of SUVmax~3.4.
- Moreover, the subcutaneous layer at the root of the neck also show multiple nodules distributed in scattered manner anterior as well as posterior around the thoracic cage. The largest is noted on the right side measuring 1.9x2.2cm, with SUVmax~2.2.
- No FDG avid axillary nodal lesions detected.

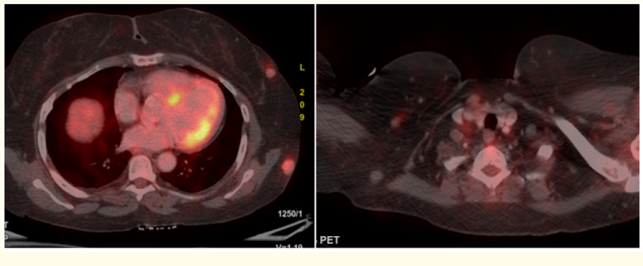

Figure 8

Distant disease

Pulmonary lesions

- Both lung fields are seat for multiple variable sized pulmonary nodules, the largest seen on the right side, medial segment of right lower lobe measuring 2.1x1.2cm, they show minimal FDG activity of SUVmax~2.1, suggestive of metastatic deposits.

Figure 9

Osseous metastases

Evidence of multiple lytic and sclerotic osseous lesions are seen within:

- The right pubic bone, with SUVmax~1.7
- Right acetabulum with SUVmax~3.1
- Both iliac bone with SUVmax~4.
- Sacrum with SUVmax~4.
- Lower dorsal and whole lumbar vertebral bodies with the highest activity opposite
- LV4 with SUVmax~4.7
- Sternum and few right sided ribs with SUVmax~2.1
- Two parenchymal hypo-metabolic Non FDG avid hepatic focal lesions, one is located at segment VIII, measuring 1.9x1.7cm while the second one appears lobulated outline, implicating segments VI and to lesser extent segment VII. They show no contrast uptake.

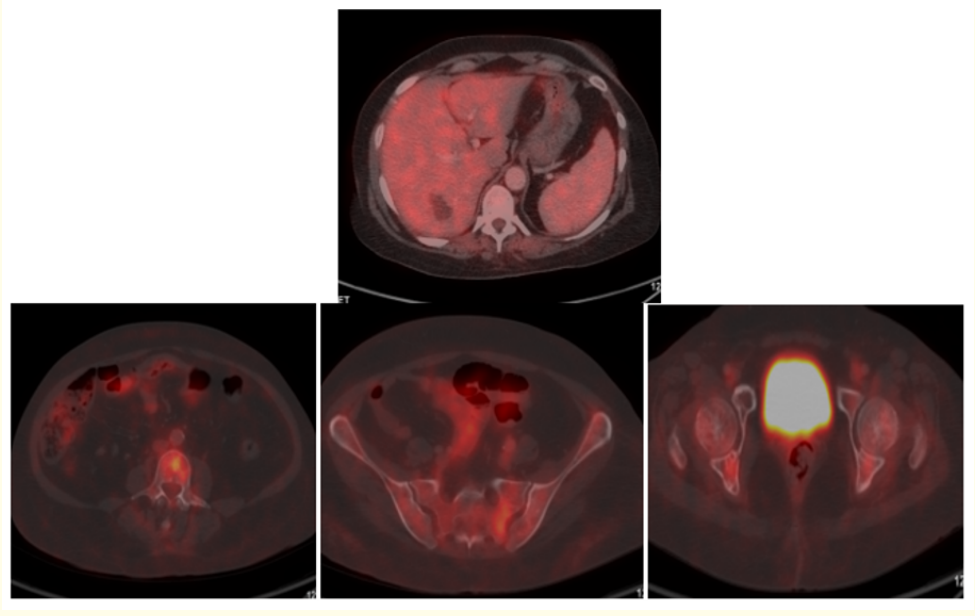

Figure 10

PET/CT diagnosis

PET/CT for a known case of metastatic breast cancer shows

- Multiple subcutaneous nodules at the left breast, chest wall posteriorly as well as root of the neck, likely neoplastic.
- Metabolically active FDG avid multiple metastatic osseous deposits and pulmonary lesions.
- Hypo-metabolic Non FDG avid hepatic focal lesions, as described.

Case 2

46 year-old female patient, suffered from left breast cancer, underwent mastectomy with implant.

Review of fused PET/CT images revealed

Loco-regional

- Evidence of left mastectomy and implant is noted.
- A well defined globular mass lesion is seen at the postero-lateral aspect of the left breast implant extending caudally posterior the implant. It measures 38x54x38mm, exhibits homogenous contrast uptake and non uniform FDG activity with SUVmax~7.1.
- Inter-pectoral nodal lesion is seen, measuring 15x13 mm in two maximum axial diameters, showing metabolic activity of SUVmax~4.8.

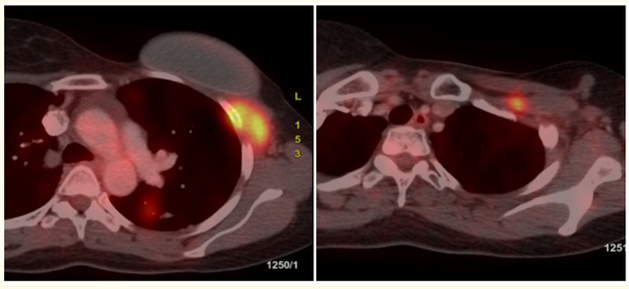

Figure 11

Distant metastases

Pulmonary metastases

The left lung shows multiple scattered FDG avid pulmonary nodules located

- Anterior segment of the its upper lobe, largest is measuring 11mm with SUVmax~4.1
- Apical segment of the lower lobe showing speculated outline and veiling, interstitial thickening of the surrounding parenchyma, measuring 22x12mm with SUVmax~3.1.
- Tiny nodules at anterior segment of lower lobe measuring 11x10mm and lingula lobe measuring10mm with SUVmax~2.2

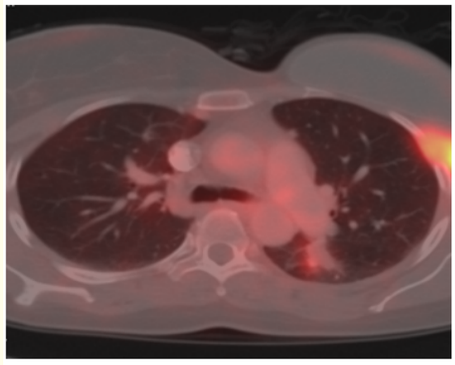

Figure 12

Osseous metastases

- Evidence e of multiple metabolically active lytic/sclerotic lesions are seen
  1. Postero-lateral aspects of left 3rd and 4th ribs with SUVmax~4.8
  2. Left side of D7 body with SUVmax~6.6
  3. Body and left pedicle of L1 vertebral body with SUVmax~8.7
  4. Postero-superior aspect of the right iliac bone and right ischium with SUVmax~6.8
  5. Neck of right femur with SUVmax~5.3
  6. Mid shaft of the right femur, associated with intramedullary soft tissue mass lesion with anterior cortical thinning, with SUVmax~7.7.

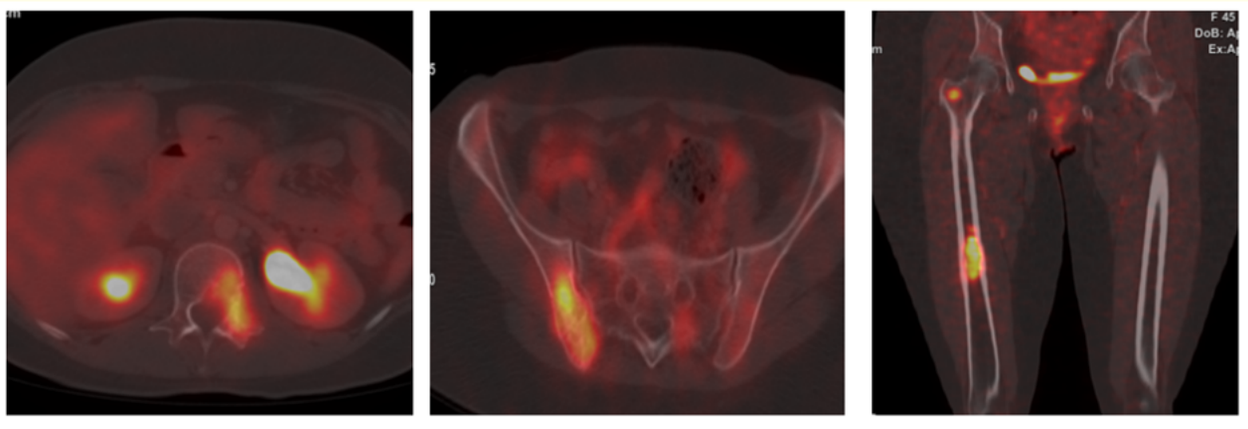

Figure 13

Opinion

Post mastectomy status for a known case of breast cancer PET/CT shows

- FDG avid hyper-metabolic soft tissue mass lesion posterior to the breast implant, keeping with local tumor recurrence associated with FDG avid left inter-pectoral nodal lesion, as described.
- Multiple FDG avid metastatic pulmonary and osseous deposits.

Case 3

Clinical data

76 year-old female patient, with recently diagnosed locally advanced left breast cancer.

Review of fused PET/ CT images revealed

I-Loco-regional disease

- The left breast is the seat of irregular sizable speculated outline soft tissue mass lesion(s) seen at the lower outer quadrant, associated with mild skin thickening, it roughly measures 5.2x5 cm in diameter, showing intense FDG avidity of SUVmax~18.7.
- Large globular speculated outline mass lesion involving the ipsilateral axillary region is seen measuring 8.6x5.8x5.3cm in maximum diameters, associated with active FDG uptake of SUVmax~27.3.
- Other few discrete small sized right axillary LNs are seen, the largest of them measures 1.4 cm with SUVmax~11.8

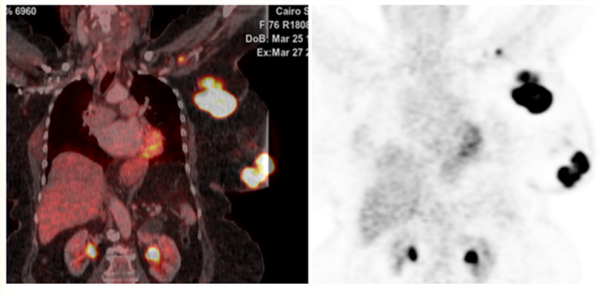

Figure 14

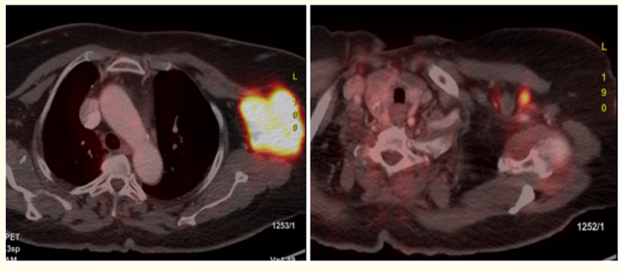

Figure 15

Distant disease

- Evidence of multiple variable sized right sided pulmonary nodules , the largest are seen within the anterior as well as the posterior basal segments measuring 1.4x1 cm and 1.7x1.2cm respectively, showing variable grades of FDG activity with SUVmax~6.9, likely metastatic deposits.
- Left upper lobe fibrotic bands with dense calcified nodule, likely old granulomatous sequel.

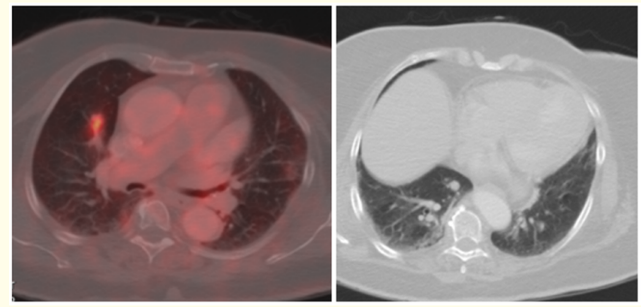

Figure 16

Opinion

PET/CT study for a newly diagnosed left breast cancer shows

- Hyper-metabolic FDG avid left breast malignant soft tissue lesion at lower outer quadrant, associated with metastatic left axillary nodal deposits, as described.
- FDG avid bilateral pulmonary nodules, likely metastatic.

Case 4

Clinical data

60 year-old female patient suffered from left breast cancer underwent mastectomy on 2013 followed by radiotherapy. Recently presented with pathologically proven right breast invasive duct carcinoma.

Review of fused PET/CT images revealed

Loco-regional disease

- The right breast is seat for speculated ill-defined mass lesion measuring 1.8x1.95cm exhibiting intense enhancement with FDG avidity of SUVmax~5.3.
- Ipsilateral enlarged FDG avid axillary lymph nodes are noted, the largest measuring 1.9x1.2cm exhibiting low grade activity with SUVmax~1.7, keeping with metastatic deposits.
- Evidence of left partial mastectomy showing post operative changes yet with no evidence of current FDG avid local tumor recurrence detected.

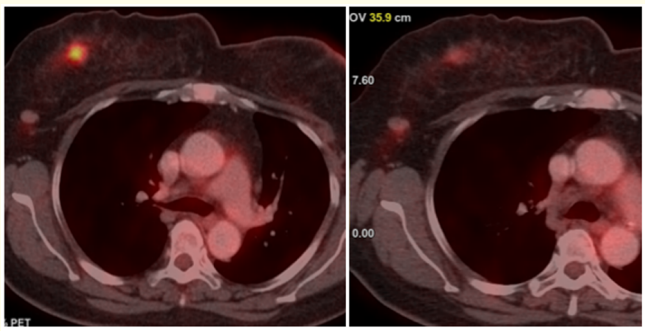

Figure 17

Opinion

PET/CT study for a known case of bilateral breast cancer show

- Hyper-metabolic FDG avid right breast malignant soft tissue lesion associated with metastatic right axillary nodal deposits, as described.
- Post left mastectomy shows no evidence of local left breast recurrence.
- NO evidence of FDG avid distant metastases.

Case 5

Clinical data

60 year-old male patient, known double primary (left breast invasive ducto-lobular carcinoma) underwent MRM in Oct. 2017, followed by 2 cycles of chemotherapy. Then recently she presented with colon mass that proved moderately differentiated adenocarcinoma by colonscopic biopsy.

Review of fused PET/CT images revealed

Loco-regional

- The left splenic flexure is the seat of well-defined soft tissue lesion measuring 2.5x2.5cm eliciting homogenous contrast uptake, it shows intense tumoral avidity of SUVmax~26.
- Right hypo-chondrial colostomy.
- No FDG avid pathologically enlarged abdominal lymph nodes detected.
- Post left mastectomy status showing clear operative bed with no evidence of definite FDG avid local tumor residue/recurrence or axillary nodal lesions detected.

Figure 18

Distant metastases

- Multiple variable sized pulmonary nodules mostly peripherally located, the largest is seen at the apical segment of the left upper lobe measuring 1.6 cm, showing no significant FDG activity, for close follow up.
- No other FDG avid lesions detected allover the rest of the surveyed body to account for distant metastases.

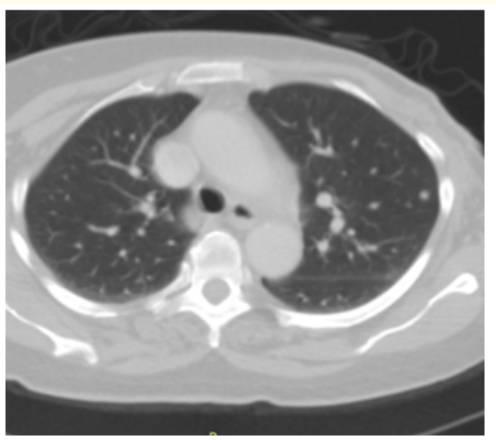

Figure 19

Opinion

A known patient of double primary (breast and colon cancer) PET/CT shows:

- Metabolically active FDG avid left splenic flexure soft tissue mass, keeping with site of primary colonic neoplasm with no evidence of nodal or peritoneal deposits.
- Post mastectomy status shows No evidence of FDG avid local tumor residue/recurrence.
- Non FDG avid bilateral pulmonary nodules? likely metastatic, for close follow up.

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