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^{18}FDG-PET/CT versus Contrast Enhanced CT in Detection of Loco-Regional Breast Cancer Recurrence.

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ABSTRACT:

Background: Among women cancer, cancer breast represents the most common type and the second cause of death related to malignancy. During the first 2 to 3 years after treatment the loco-regional recurrence rate is highest and then it decreases gradually. FDG PET/CT has high sensitivity and specificity in detection of breast cancer recurrence. **Aim:** Evaluation of the role of PET/CT compared to CECT in detection of loco regional recurrence in breast cancer patients during restaging and follows up. **Material and Methods:** Fifty seven female patients with treated breast cancer were included in this study. All patients underwent estimation of breast tumor markers levels, whole body FDG PET–CT and contrast enhanced CT (CECT). Correlation with the histopathological examination of the loco regional lesions was done. **Results:** Fourteen patients 14/57 (24.56%) had loco-regional recurrences most of them were hormone receptor positive and had high levels of tumor markers out of them, 2/14 patients (14.28 %) had regional recurrence, 2/14 patients (14.28%) had local recurrence (LR) with distant metastases (DM) and 10/14 patients (71.42%) had both local and regional recurrence. PET-CT detected loco-regional recurrence in 13/14 patients versus 6/14 patients for CECT. The sensitivity, specificity, PPV, NPV of both PET-CT and CECT were 92.9%, 93.0%, 81.25%, and 97.5% versus 42.9%, 100%,

100% and 84.3% respectively. PET-CT had higher sensitivity than CECT with statistically significant difference (P value 0.00001), while CECT had higher specificity with no statistically significant difference (P value 0.61). **Conclusion:** FDG-PET/CT is very sensitive compared to CECT in the detection of loco- regional recurrence of breast cancer. It has higher detection rate of metastatic lymph nodes.

Key words: Breast cancer, local recurrence, FDG PET/CT, CECT.

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INTRODUCTION:

The most common malignancy affecting women is the breast cancer. The relapse within the first 15 years after treatment is approximately 30% [(1)]. The highest rate of recurrence occurs within the first 2 to 3 years after treatment and start to decreases gradually. Isolated (loco regional) recurrences represent 10 to 20% of all recurrences while distant metastases either in one or multiple anatomical structures represent 60% to 70% [(2)]. Local or regional recurrence is defined as clinically and histologically documented relapse in the ipsilateral breast or regional nodes. Distant metastasis is defined as clinical evidence of distant disease based on clinical and/or radiographic findings [(3)]. 18F-FDG PET/CT showed a relevant impact in early diagnosis and treatment of recurrence in breast cancer patients, particularly if other investigations are doubtful [(1)].

The principal aims in the surveillance in these patients are early local relapses detection and contralateral recurrences identification [(4)]. European Society for Medical Oncology (ESMO) guidelines and National Comprehensive Cancer Network guidelines (NCCN) are suggesting that FDG PET/CT may be helpful for detecting the site of recurrence particularly if the traditional methods of imaging are suspicious or conflicting [(5)]. Moreover, in patient with recurrence and high levels of tumor markers and suspicious conventional imaging, this modality of imaging has improved the identification of isolated loco regional recurrence as well as isolated metastatic lesions [(6)]. The FDG PET/CT high sensitivity (77%–90%) and specificity (69%–80%) allows meeting of this target, with higher sensitivity (92.7%) in patients with increased serum CA15.3 levels and a radiologic suspicion of recurrence [(7)].

After initial diagnosis and treatment, follow up, examinations and investigations are required for early detection, accurate restaging and proper therapeutic planning for recurrences [8].

Aim of the work: We aim to evaluate the role of PET/CT compared to CECT in detection of loco regional recurrence in treated cancer breast patients during the restaging and follow up processes either in presence or absence of clinical, laboratory and/or radiological data.

PATIENTS AND METHODS:

Fifty seven female patients with treated breast cancer from the international medical center (IMC), National cancer Institute (NCI), Zagazig University hospitals and Helwan University hospitals were evaluated for detection of breast cancer recurrence during the restaging or follow up at the period from March 2015 to May 2017. Loco-Regional recurrence was used to indicate a recurrence in either the ipsilateral breast or regional nodal basin. All patients gave informed consent for study participation before imaging. The patients underwent clinical examination; estimation of the specific breast tumor markers levels, CECT, whole-body ^{18}FDG-PET/CT. Histopathological examination of loco-regional lesions was also done.

PET/CT was done at the PET/CT unit of IMC. The protocol of the study was approved by the ethical committee of the board of Nuclear Medicine at the IMC. FDG- PET/CT and CECT studies were performed within one month.

Contrast-enhanced CT scanning: CT scanning was done using 64 multi-detectors CT scanner. Non-ionic iodinated contrast material (300 mg/ml) was used at a dose of 2.0 ml /kg body weight and injected through a large vein usually the ante-cubital vein via automated injector. All CECT images were interpreted by experienced radiologist .

PET/CT scanning and image analysis: The patients were instructed to fast for more than 5 hours before FDG injection. Patients received an intravenous injection of approximately 0.1 mCi FDG/kg, with average dose 225.0 MBq (6 mCi) for average weight patient (about70 kg). After injection, patients were required to rest for 60 minutes on a comfortable chair before undergoing the PET/CT scan. PET images will be acquired during normal breathing in the three-dimensional mode for 2 minutes per bed position 60 minutes after intravenous injection of the tracer. The scan range was from the top level of the skull to the level of the distal femur.

PET images were reconstructed using standard reconstruction iterative algorithm-ordered subset expectation maximization- (OSEM) algorithm. Attenuation correction of PET images was performed by using attenuation data from the CT component of the examination. Analysis was performed using a multimodality computer platform. For semi quantitative analysis, the nuclear medicine physician referred to the PET/CT fusion images and the CT images to set a spherical volume of interest (VOI) over the regions of interest and then recorded the peak standardized uptake value (SUV max) in the VOI. The PET/CT images were analyzed by an experienced nuclear medicine physician.

Statistical analysis: Data were coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data qualitative data represented as number and percentage, quantitative continues group represented by mean ± SD. The sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and accuracies with their respective 95% confidence intervals were calculated.

Difference and association of qualitative variables were assessed by Chi square (X^2) and (Cohen's Kappa) (K) for agreement. Inter-rater agreement Kappa test was calculated, criteria to qualify for strength of agreement were as follows: K<0.2: poor; K 0.21 – 0.40: fair; K 0.41 – 0.60: moderate; K 0.61 – 0.80: good; K 0.81 – 1.00: very good. All tests were two sided with $p < 0.05$ was considered statistically significant, $p < 0.001$ for high significant result and $p > 0.05$ was considered none statistically significant.

RESULTS:

This study included 57 female patients with breast cancer after completion of treatment with mean age 52.24±9.28 (range 31.0-67.0) years. Fifty four patients (94.7%) had unilateral disease, 26 (45.6%) right side, 28 (49.1%) left side and only 3 patients (5.3%) had bilateral disease.

All patients underwent breast surgery (35 patients modified radical mastectomy, 16 patients lumpectomy, 6 patients mastectomy) followed by chemotherapy in 55 patients (96.5%), radiotherapy in 48 patients (84.2%) and hormonal therapy in 43 patients (75.4%) as fourteen patients were hormone receptor negative so, they did not receive hormonal therapy.

High tumor markers were prevalent among the studied patients 44/57 (77.19%) patients had high tumor markers while 14/57 (24.6%) patients had hormone receptor negative breast cancer ***(Table1)***. Fourteen patients 14/57 (24.56%) had loco-regional recurrence (2 with local recurrence, 2 with regional recurrence and 10 patients with both local and regional recurrence) out of the them 6 patients (42.8%) had hormone receptor negative tumours. Thirty one patients had distant metastases in one anatomical structure or in multiple locations.

Table 1: Clinical characteristics of 57 patients with cancer breast

		N	%
Breast Cancer site.	Right	26	(45.6%)
	Left	28	(49.1%)
	Bilateral	3	(5.3%)
Operation Type	Lumpectomy	16	(28.1%)
	Mastectomy	6	(10.6%)
	MRM	35	(61.4%)
Receptors Type	Positive	43	(75.4%)
	Negative	14	(24.6%)
Chemotherapy	Yes	55	(96.5%)
	No	2	(3.5%)
Radiotherapy	Yes	48	(84.2%)
	No	9	(15.8%)
Hormonal therapy	Yes	43	(75.4%)
	No	14	(24.6%)

SUV max was used as a quantitative parameter of FDG uptake with cut off value 3. The range of mean SUV max was 4.0 - 7.1. PET scan detected 13/14 patients with loco-regional recurrence with 92.9% sensitivity, 93.0% specificity, 81.25% positive predictive value (PPV) and 97.5% negative predictive value (NPV), while CT detected 6/14 patients with 42.9% sensitivity, 100% specificity 100% PPV and 84.3% NPV***(table2)***. The Higher PET sensitivity compared to CECT for the detection of local recurrence is statistically significant (P value 0.00001). However the higher specificity of CECT is not statistically significant (P value 0.61).

PET/CT showed three false positive cases but there were no false positives on CECT. The false positives were due to inflammatory reaction. PET/CT showed only 1 (1.7%) false negative patient while CECT showed 8 (14.1%) false negative patients ***(Table 2 & Figure 1, 2)***.

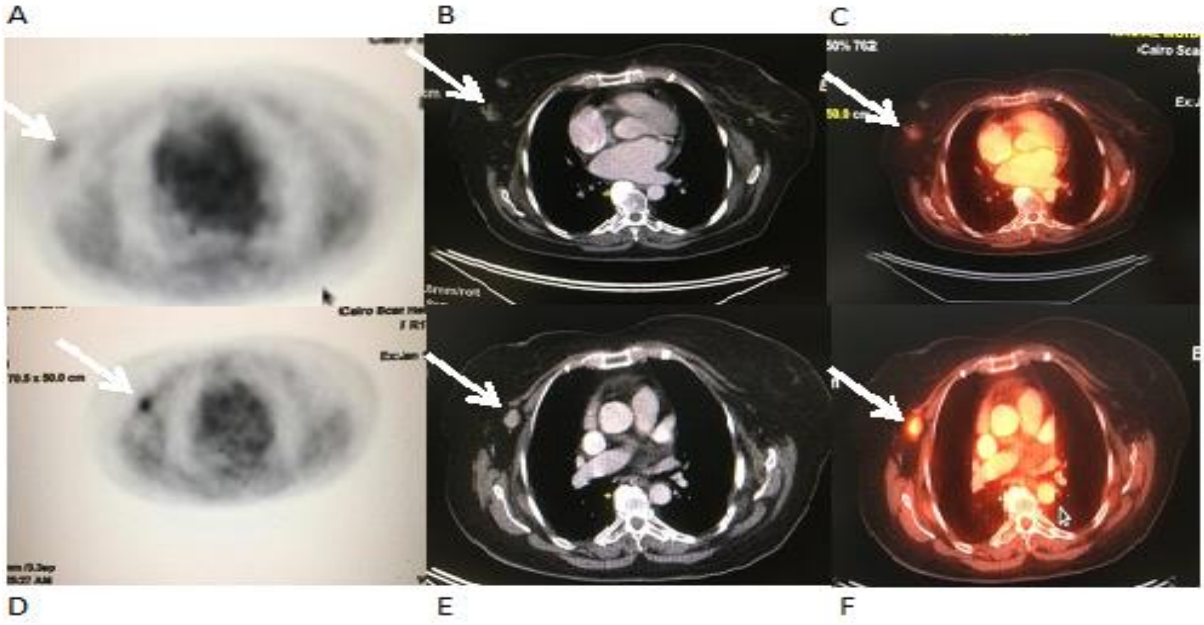

Fig 1 (A): Female patient who has got right breast cancer, small hyper metabolic soft tissue mass lesion is noticed at the right breast, it is indeterminate in CECT, while it showed increased FDG avidity supporting disease recurrence**. (B)** An equivocal pathologically enlarged right axillary nodal lesion on CECT (arrowed), I was avid for FDG with high SUV value, denoting metastatic nature.

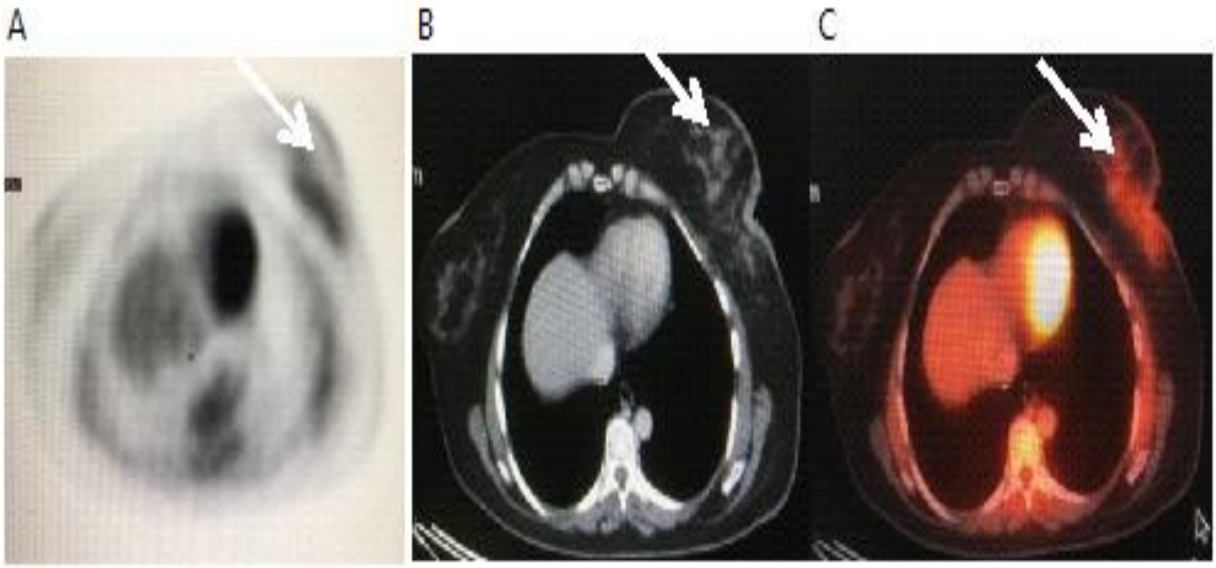

Fig 2: A case of left breast cancer showed local disease recurrence. PET-CT image showed hyper metabolic FDG avid lesion at the left breast, while the CECT images is indeterminate.

Table (2): Comparison between PET/CT and CECT in relation to histopathology in Diagnosis of loco-regional recurrence.

Findings	PET/CT No. (%)	CECT No. (%)	P Value
True Positive	13 (22.8%)	6 (10.5%)	0.03*
True Negative	40 (70.1%)	43 (75.4%)	0.67
False Positive	3 (5.2%)	0 (0.0%)	0.065
False Negative	1 (1.7%)	8 (14.1%)	0.001*
Sensitivity %	92.9%	42.9%	0.0001
SP%	93.3%	100.0%	0.61
***Positive Predictive Value* %**	81.25%	100.0%	
***Negative Predictive Value* %**	97.5%	84.3%	
Accuracy %	74.1%	59.3%	

PET/CT was concordant with histopathology for the detection of local recurrence in 53 (92.9%) patient (13 positive and 40 negative) and discordant in 4 (12.2%) patient with P value 0.00 and kappa 0.47. However CECT was concordant in 49 (85.9%) patients and discordant in 8 (14.1%) patients with P value 0.00 and K 31 ***(Table 3)***.

Table (3): Agreement between PET/CT & CECT in relation to histopathology in diagnosis of LR.

Findings	PET/CT	CECT
Concordant	53 (92.9%)	49 (85.9%)
-ve/-ve	40 (70.1%)	43 (75.4%)
+ve/+ve	13 (22.8%)	6 (10.5%)
Discordant	4 (7.0%)	8 (14.0%)
+ve/-ve	3 (5.2%)	0 (0%)
-ve/+ve	1 (1.8%)	8 (14.0%)
X^2	52.4	20.5
K	0.47	0.31
P value	0.00	0.00

X_2. Chi square test. K: Kappa test.

Overall Positive PET/CT findings were found in 45/57 patients (78.9%) that are nearly the same as CECT which showed lesions in 44/57 patients (77.2%). PET/CT was found to be more superior over CECT in detection of loco-regional recurrence; it detected 10/45 patients (22.2%) with loco-regional recurrence versus three patients (6.8%) for CECT. Both imaging methods were comparable for detection of both local recurrence and local recurrence associated with distant metastases. PET/CT detected distant metastases in 31 patients (69%) versus 38 patients (86.4%) for CECT ***(Table 4)***.

Table (4): Comparison between PET/CT and CECT in detection of LR, loco-regional and distant metastases of breast cancer.

	+ve PET/CT findings No (%)	**+ve CECT findings No (%)**
Overall No.	45 (100%)	44 (100%)
Local recurrence.	2 (4.4%)	2 (4.5%)
Regional recurrence.	2 (4.4%)	1 (2.3%)
Loco-regional recurrence.	10 (22.2%))	3 (6.8%)
Distant metastases. Only	31 (69%)	38 (86.4%)

As regarding the distant metastases, PET/CT showed higher detection rate for positive LNs and osseous lesions, while CECT is better than PET/CT in detection of the brain lesions. Both imaging methods showed no notable difference in detection of the lung lesions (13 patients each). The rate of lesions detection in the liver was comparable between PET/CT and CECT.

DISCUSSIONS:

In the present study we evaluated the role of FDG-PET/CT versus CECT for detection of cancer breast recurrence and found that FDG-PET/CT is an accurate modality for detection of recurrence that is consistent with Moon et al who found FDG PET is a highly accurate method in the diagnosis of recurrent and/or metastatic cancer breast [(9)]. It usually complements other conventional imaging methods, which depend more upon the morphological changes of the suspected lesions because it provides functional information [(10)].

In the same way FDG PET can easily discriminate between viable and non-viable tumors remaining after therapy. These non-viable masses are composed of necrotic tissues and/or fibrosis, but not viable malignant cells, and give equivocal results if the conventional methods that depend upon anatomical changes are used. FDG PET is also useful in recurrent cases with only high levels of serum tumor markers as the only indicator of recurrence [(10-11)]. It has been shown that integration of PET/CT in patients with cancer breast improve the accuracy of restaging over that possible with PET alone, through the accurate localization of functional data on anatomic CT images [(12)].

In the current study 14 patients (24.56%) had loco regional recurrence that is in agreement with the reported figures in different studies that found near to 30% of patients develop recurrence after initial treatment.

Also, **Jemal et al** stated that around 40% of cancer breast patients developed a recurrence [(13)]. This is approximately consistent with **Hristiansen et al and Kamby et al** who found that 10% to 20% of all recurrent cases are isolated loco regional recurrences, and from 60% to 70% are distant metastases in one anatomical structure or in multiple locations [(14, 15)].

However **Freedman et al** reported higher rate of loco-regional recurrence (75%) and less distant recurrences (15%) in their studies [(16)]. This difference in the site and incidence depends upon initial tumor stage, received therapy, biology of the tumor, and the diagnostic sensitivity [(2)].

The present study revealed higher FDG-PET/CT accuracy and sensitivity than CECT 74.1% ,92.9% versus 59.3% and 42.8% respectively with comparable specificity 93.0% versus 100% this is consistent with **Dirisamer et al**, who found that PET had accuracy of (85%),

CECT (73%) and PET/CT (96%). Sensitivity and specificity of lesion detection of PET, CT and PET/CT were 84%, 66% and 93%, and 100%, 92%, and 100%, respectively [17].

In contrast **Hagay et al** reported high CECT sensitivity of 91% for diagnosis of breast cancer LR [18].

The relatively lower FDG-PET/CT specificity in the current study could be due to the high FDG uptake in areas of post treatment inflammation. On the other hand the false negative cases were due to the small size of lesions. The evaluation of local recurrence in the breast, skin or chest wall with FDG-PET can be problematic**.**

Eubank et al [19] reviewed a number of studies evaluating FDG-PET and PET/CT and found that both false positive and false negative cases of recurrent neoplasm were found in the skin, residual breast and chest wall which are consistent with our study (3 false positive and one false negative). Inflammation in these previously treated areas can be a source of FDG avidity, leading to a false positive result. False negative results could be attributed to either too small tissue volume or too low FDG avidity of the recurrent lesion (particularly in cases of lobular carcinoma) [20]**.** FDG-PET reported average sensitivity and specificity of 96% and 77%, respectively in detection of recurrent breast cancer, compared to that of a combination of conventional imaging methods [21]**.** Sixteen publications involved more than 800 patients using meta-analysis indicated that PET had mean sensitivity and mean specificity of 93% and 82% respectively for diagnosis of recurrence of cancer breast [22]**.**

Murakami et al in their study on forty seven patients detected recurrent breast cancer in 25 (53%) patients with overall sensitivity, specificity, PPV, NPV, and accuracy of PET/CT were 96%, 91%, 92%, 95%, and 94%, respectively [23].

Mohamed et al reported comparison between CT alone and PET/CT in detection of recurrent breast cancer and found the sensitivity and specificity for CT 83.3% and 84.25%, respectively versus 83.3% and 100% for PET/CT [24].

In the present study, compared with CECT results, PET/CT improved the sensitivity, NPV and accuracy. The limitations of this study are the lake of pathological confirmation of suspected DM lesions and the use of routine criteria such as traditional imaging and regular clinical follow up to determine the nature of findings.

CONCLUSION:

FDG PET/CT is very sensitive compared to CECT in the detection of loco-regional recurrence of breast cancer. It also has higher detection rate of distant metastases in lymph nodes. However adding CECT to PET studies increases its PPV and specificity.

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