Effectiveness of 18F-FDG PET/CT in detection of loco-regional recurrence of breast cancer in comparison to CT alone

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Introduction

Breast cancer affects more than 1 million women worldwide. It is the most common type of cancer and the second leading cause of cancer related death among women [(1)]. The estimated incidence in 2018 was 2.088 million of new cases in the world [(2)]. Breast cancer was the most common cancer among women and the third leading cause of cancer related death in Egypt [(3)]. In 2012; 18,660 new cases were estimated in Egypt and out of them the mortality rates was estimated at 7,161 [(4)].

Recurrence of breast cancer is a major clinical manifestation and represents the principal cause of breast cancer-related deaths [(5)].Loco-regional recurrence (LRR, ipsilateral breast or axillary lymph nodes)may occur in 5-27% of patients [(6)]. Early detection and treatment of isolated LRR before symptomatic onset may have a beneficial effect on the prognosis, by improving local treatment feasibility rate and by avoiding the situation of uncontrollable loco-regional disease [(7)].

Conventional imaging methods which reflect mainly the morphological changes are often inconclusive in differentiating local pathology from post therapeutic changes. Early detection of LRR may necessitate further invasive procedures [(8)].

Positron emission tomography (PET) with fluorine 18 (^{18}F) fluoro-deoxyglucose (FDG) has an important role in oncology. Its role in the management of breast cancer patientsis evolving. Combined PET and computed tomography (CT) (PET/CT) systems have replaced PET alone in most nuclear medicine departments [(9)].

FDG PET/CT is an imaging method that has a strong point as it enables anatomic localization of the PET signal via CT [(10)]. PET/CT is particularly useful in patients who are suspected to have or who are exhibiting a recurrence on physical examination or conventional imaging methods [(11)].

Sensitivity of PET/CT for detecting LRR or metastasis among patients with breast cancer is approximately 97%, with a diagnostic accuracy of 95% in one study, supporting the efficacy of PET/CT for patients diagnosed or suspected of having recurrent breast cancer [(12)]. However, there is a lack of evidence demonstrating the efficacy and cost effectiveness of this modality, along with the hazards of radiation exposure and the absence of specific clinical indications [(13)].

This study was designed to evaluate the effectiveness of ^{18}F-FDG PET/CT imaging in diagnosis of LRR of breast cancer in correlation to CT alone.

Patients and Methods:

This prospective study was approved by Ethical and Research committees at Faculty of Medicine, Sohag University. An informed written

consent was obtained from all participants.The study included 45 female patients with histopathologically proven breast cancer managed by mastectomy +/- chemotherapy and/or radiotherapy with post treatment tumor free interval.

Exclusion criteria:

☒ Patients with proved other malignancy (Double primary).

☒ Pregnant females.

☒ Patient with proved loco-regional and/or distant metastasis.

Study design:

I- Careful history taking: Detailed history was obtained from all patients with the help of their data sheets. Age of the patients was recorded. Data about the laterality of the cancer and the type of operationwas obtained.

The pathological reports as regards the initial type of cancer and its grading, tissue infiltration, and axillary lymph nodes involvement, as well as the expressed receptors (ER, PR, HER2, and Ki67) were documented. The post-operative therapeutic history (Chemotherapy and/or radiotherapy) was recorded.

II- Evaluation by PET/CT:

^{18}F-FDG PET/CT was done to all patients, according to the following protocol:

II. A) PET Acquisition:

FDG PET/CT study was done using a dedicated PET/CT scanner ***(GE, PET/CT Discovery)***. This camera integrates a PET scanner with a dual-section helical CT scanner (40 slice Emotion) and allows the acquisition of co-registered CT and PET images in one session.

Scanning started 60-90 min after tracer injection of 370-555 MBq of ^{18}F-FDG in the forearm. Intravenous contrast agent was administered in most patients. Pretest 6 hours fasting period was required (only water was allowed) and blood glucose level was assessed to insure proper blood glucose level (<200mg/dl).

Each patient was imaged from the skull to mid-thigh in the supine position with arms elevated, and CT scanning was started at the level of the Cervico-thoracic region with the following parameters: 400 mAs; 120 kV; slice thickness, 3 mm; pitch, 1.5. The CT scans were acquired during normal respiration reached caudally to the mid thighs.

PET was performed immediately after acquisition of the CT images (5-7 bed positions; acquisition time, 2-3 min/bed position). The CT-data were used for attenuation correction, and images were reconstructed as 5-mm slices applying a standard iterative algorithm (ordered-subset expectation maximization).

II. B) Image reconstruction: Maximum intensity whole body projection (MIP), sagittal, coronal and axial slices were reconstructed using dedicated PET software system. Images were interpreted at a workstation equipped with fusion software ***(advantage Window AW version 5, GE)*** that provides multi-planar reformatted images and enables display of the PET images, CT images, and fused PET/CT images was interpreted by 2 experienced nuclear medicine physicians. The analysis was conducted on per patient and per lesion based analysis.

II. C) Image analysis: PET analysis was performed qualitatively and semi-quantitatively:

II. C.1- Qualitative analysis: By visual assessment of abnormal areas of FDG uptake. Areas showing increased FDG uptake not corresponding to known areas of physiological uptake was considered positive for recurrence.

II. C.2- Semi-quantitative analysis:A region of interest was

drawn around each visually detected area of abnormal FDG uptake and SUVmax was automatically calculated.

III- Tissue biopsy: Tissue biopsy was obtained from patients whenever it was possible (Only in 14 patients). Specimens were prepared for histo-pathological examination for recurrence.

IV- Statistical analysis: Data were recorded in Excel data sheet and analyzed usingStatistical Package for Social Sciences soft ware program (SPSS, version 24). Qualitative variables were recorded as frequencies and percentages and were compared by chi-square test. Quantitative variables were presented as means ± standard deviation (SD). Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated. Agreement between results was tested using kappa test. Graphs were produced by using Excel. *P* value < 0.05 was considered statistically significant.

Results

The mean age ± SD of the patients was 58.47±9.1 years (Range= 40-77 years).The vast majority of the patients had either CBS or MRM (18/45; 40% for each). Radical mastectomy was done in 8 cases (17.8%). Around half of the cases (22 cases, 49%) had isolated left sided tumor, with 16 cases (35.5%) had isolated left sided tumor.

CT finding of the study populations:

The most commonly abnormality found was lymph node affection in one third of cases (15 cases, 33.3%). The findings of CT in the study populations are shown in table 1.

FDG PET/CT findings:

The most commonly abnormality found was lymph node affection in more than third of cases (16/45, 35.6%). The findings of PET/CT in the study populations are shown in table 2.

Finding	No of +ve cases	Percent of +ve cases
Breast nodule	14	31.1%
Breast cyst	1	2.2%
Lymph nodes	15	33.3%
Chestwall nodules	11	24.4%
Bone metastasis	9	20%
Lung deposits	4	8.9%
Liver metastasis	1	2.2%
Suprarenal metastasis	1	2.2%

Table 1: Findings of CT in the study populations (n= 45).

Finding	No of +ve cases	Percent of +ve cases	SUV max		
			Mean	SD	Range
Breast nodule	14	31.1%	6.66	3.33	2.8-12.7
Breast cyst	1	2.2%	4.5		
Lymph nodes	16	35.6%	6.39	3.27	2.5-12.5
Chest wall nodules	11	24.4%	6.45	2.11	2.5-9.5
Bone metastasis	9	20%	5.94	1.99	2.6-8.5
Lung deposits	5	11.1%	4.32	2.32	1.7-5
Liver metastasis	2	4.4%	5.7	0.71	5.2-6.2
Suprarenal metastasis	1	2.2%	4.2		

Table 2: Findings of PET/CT in the study populations (n= 45).

Comparison between CT and PET/CT performance in detecting LRR:
By comparing the CT, and PET for signs of recurrence; it was found that PET was the most accurate (81.07%), with the highest sensitivity (88.46%), and specificity (73.68%) (Table 3).

	Sonography	CT	PET/CT	Biopsy or follow up
True positive (TP), n	18	21	23	26
True negative (TN), n	14	12	14	19
False positive (FP), n	5	**7**	5	0
False negative (FN), n	8	5	3	0
Sensitivity (%)	69.23	80.77	88.46	
Specificity (%)	73.68	63.16	73.68	
Positive predictive value (%)	78.26	75.00	82.14	
Negative predictive value (%)	63.64	70.59	82.35	
Accuracy (%)	71.46	71.96	81.07	

Table 3: Comparison between CT and PET/CT in detecting LRR.

Comparison of CT and PET performance in detecting breast cancer distant metastasis:
Performance of CT in comparison to PET results is shown in Table 4.

	CT	PET/CT	Biopsy or follow up
True positive (TP), n	8	11	11
True negative (TN), n	32	34	34
False positive (FP), n	2	0	0
False negative (FN), n	3	0	0
Sensitivity (%)	72.73	100	
Specificity (%)	94.12	100	
Positive predictive value (PPV) (%)	80.00	100	
Negative predictive value (NPV) (%)	91.43	100	
Accuracy (%)	83.42	100	

Table 4: Comparison of CT and PET performance in detecting distant metastasis.

Results of histopathology:
Out of the 45 patients; biopsy was taken from only 14 patients. Out of them; 10 cases (10/14; 71.4%) were positive for recurrence. Out of the 10 positive cases; 8 cases (80%) were positive recurrence by PET/CT and the other 2 cases (20%) were suspicious of recurrence by PET/CT. All the 4 negative cases were also negative for recurrence by PET/CT.

Discussion

Recurrence of breast cancer is a major clinical manifestation and represents the principal cause of breast cancer-related deaths [(5)].PET/CT may be used for early detection of LRR of breast cancer [(11)].

In the current study; FDG-PET/CT was more accurate than CT in diagnosing LRR of breast cancer (Overall accuracy= 81.07% versus 71.96% respectively). This is in agreement with previous reports of ***Radan et al.***[(14)] (81% versus 59%), ***Tatsumi et al.***[(15)] (86% versus 77%), ***Haug et al.***[(16)] (94% versus 77%), ***Dirisamer et al.***[(17)] (81% versus 70%), ***Champion et al.***[(18)] (94% versus 48%).

In the present study; FDG-PET/CT was more sensitive than CT in diagnosing LRR of breast cancer (Sensitivity= 88.46% versus 80.77% respectively). This is in agreement with previous reports of ***Radan et al.***[(14)] (85% versus 70%), ***Haug et al.***[(16)] (96% versus 95%), ***Dirisamer et al.***[(17)] (93% versus 66%), ***Champion et al.***[(18)] (94.5% versus 33%).

In this study; FDG-PET/CT was more specific than CT in diagnosing LRR of breast cancer (Specificity= 73.68% versus 63.16% respectively). This is in agreement with previous reports of ***Radan et al.***[(14)] (76% versus 47%), ***Haug et al.***[(16)] (89% versus 78%), ***Dirisamer et al.***[(17)] (100% versus 92%), ***Champion et al.***[(18)] (85.5% versus 55%),

In the present study; FDG-PET/CT was more superior to CT in diagnosing distant metastasis of breast cancer (liver metastasis, lung deposits, bone metastasis, and suprarenal metastasis). This is in agreement with previous reports [(12, 14, 17-21)].

While acknowledging the advantages of CT such as availability, costs or acquisition speed, its inferiority both on a per-patient and per-lesion basis raises doubts about its usefulness in

patients with recurrent breast cancer [19].

The study has some limitations. First, our study comprised a relatively limited patient number. Therefore, our findings should be regarded as preliminary. However, ^{18}F FDG PET/CT proved to be promising in terms of recurrent breast cancer staging, and further studies comprising larger patient cohorts seem warranted. Second limitation was the inability to use ^{18}F-FDG PET/MRI in comparison to PET/CT. Another limitation was that not all suspected lesions had confirmed pathology laboratory results.

Also; for the calculation of sensitivity and specificity, a person-based approach was used instead of one that was lesion based. This procedure reflects that treatment decisions are generally made based on the presence of recurrent or metastatic disease, rather than on the number of lesions involved. Consequently, it is clinically more relevant to consider the patient-based data rather than the lesion-based analyses.

Referrences

1. Taghipour M, Wray R, Sheikhbahaei S, Wright JL and Subramaniam RM: FDG Avidity and Tumor Burden: Survival Outcomes for Patients With Recurrent Breast Cancer.AJR Am J Roentgenol. 2016; 206(4): 846-55.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.CA Cancer J Clin. 2018.
3. Elatar I, Cancer registration, NCI Egypt 2001. Cairo, Egypt, National Cancer Institute 2002. 2002.
4. Dubey AK, Gupta U and Jain S: Breast cancer statistics and prediction methodology: a systematic review and analysis.Asian Pac J Cancer Prev. 2015; 16(10): 4237-45.
5. Moody SE, Perez D, Pan TC, Sarkisian CJ, Portocarrero CP: The transcriptional repressor Snail promotes mammary tumor recurrence.Cancer Cell. 2005; 8(3): 197-209.
6. Jung KW, Won YJ, Kong HJ and Lee ES: Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2015.Cancer Res Treat. 2018; 50(2): 303-316.
7. Kim SJ, Moon WK, Cho N and Chang JM: The detection of recurrent breast cancer in patients with a history of breast cancer surgery: comparison of clinical breast examination, mammography and ultrasonography.Acta Radiol. 2011; 52(1): 15-20.
8. Avril S, Muzic RF, Jr., Plecha D, Traughber BJ, Vinayak S: (1)(8)F-FDG PET/CT for Monitoring of Treatment Response in Breast Cancer.J Nucl Med. 2016; 57 Suppl 1: 34s-9s.
9. Blodgett TM, Meltzer CC and Townsend DW: PET/CT: form and function.Radiology. 2007; 242(2): 360-85.
10. Groheux D, Hatt M, Hindie E, Giacchetti S, De Cremoux P: Estrogen receptor-positive/human epidermal growth factor receptor 2-negative breast tumors: early prediction of chemosensitivity with (18)F-fluorodeoxyglucose positron emission tomography/computed tomography during neoadjuvant chemotherapy.Cancer. 2013; 119(11): 1960-8.
11. Pan L, Han Y, Sun X, Liu J and Gang H: FDG-PET and other imaging modalities for the evaluation of breast cancer recurrence and metastases: a meta-analysis.J Cancer Res Clin Oncol. 2010; 136(7): 1007-22.
12. Aukema TS, Straver ME, Peeters MJ, Russell NS, Gilhuijs KG: Detection of extra-axillary lymph node involvement with FDG PET/CT in patients with stage II-III breast cancer.Eur J Cancer. 2010; 46(18): 3205-10.
13. Parmar AD, Sheffield KM, Vargas GM, Han Y, Chao C: Quality of post-

treatment surveillance of early stage breast cancer in Texas.Surgery. 2013; 154(2): 214-25.
14. Radan L, Ben-Haim S, Bar-Shalom R, Guralnik L and Israel O: The role of FDG-PET/CT in suspected recurrence of breast cancer.Cancer. 2006; 107(11): 2545-51.
15. Tatsumi M, Cohade C, Mourtzikos KA, Fishman EK and Wahl RL: Initial experience with FDG-PET/CT in the evaluation of breast cancer.Eur J Nucl Med Mol Imaging. 2006; 33(3): 254-62.
16. Haug AR, Schmidt GP, Klingenstein A, Heinemann V, Stieber P: F-18-fluoro-2-deoxyglucose positron emission tomography/computed tomography in the follow-up of breast cancer with elevated levels of tumor markers.J Comput Assist Tomogr. 2007; 31(4): 629-34.
17. Dirisamer A, Halpern BS, Flory D, Wolf F, Beheshti M: Integrated contrast-enhanced diagnostic whole-body PET/CT as a first-line restaging modality in patients with suspected metastatic recurrence of breast cancer.Eur J Radiol. 2010; 73(2): 294-9.
18. Champion L, Brain E, Giraudet AL, Le Stanc E, Wartski M: Breast cancer recurrence diagnosis suspected on tumor marker rising: value of whole-body 18FDG-PET/CT imaging and impact on patient management.Cancer. 2011; 117(8): 1621-9.
19. Sawicki LM, Grueneisen J, Schaarschmidt BM, Buchbender C, Nagarajah J: Evaluation of (1)(8)F-FDG PET/MRI, (1)(8)F-FDG PET/CT, MRI, and CT in whole-body staging of recurrent breast cancer.Eur J Radiol. 2016; 85(2): 459-65.
20. Grassetto G, Fornasiero A, Otello D, Bonciarelli G, Rossi E: 18F-FDG-PET/CT in patients with breast cancer and rising Ca 15-3 with negative conventional imaging: a multicentre study.Eur J Radiol. 2011; 80(3): 828-33.
21. Evangelista L, Baretta Z, Vinante L, Cervino AR, Gregianin M: Tumour markers and FDG PET/CT for prediction of disease relapse in patients with breast cancer.Eur J Nucl Med Mol Imaging. 2011; 38(2): 293-301.