

18F-FDG PET/CT for Monitoring of Treatment Response in Breast Cancer

NOHA F.A. EL-QASSAS, M.Sc.; RANIA A. MAAROUF, M.D. and ASMAA M.M. SALAMA, M.D.

The Department of Radiodiagnosis, Faculty of Medicine, Ain Shams University

Abstract

Background: Breast cancer is the most common cancer and the second leading cause of cancer mortality in women. Accurate diagnosis and staging are essential for the selection of the most appropriate therapeutic strategy and major determinants of patient prognosis and survival.

Aim of Study: The purpose of our study is to evaluate the potential role of 18F-FDG PET/CT in monitoring treatment of breast cancer and assessment of recurrence after surgical or systemic treatment.

Patients and Methods: This study is retrospective study, was conducted on (25) female patients over a period of 6 months between 2018 and 2019. Their ages ranged from 34 to 78 years with mean age of 52 years, all patients have positive history of breast cancer treatment.

Those patients were referred to the Radio Diagnosis Department & Nuclear Medicine Department in Ain Shams University.

Results: FDG-PET-CT is the investigation of choice for post-treatment follow-up of breast cancer. It has a great role in detection of newly developed lesions and detection of the disease progression.

Conclusion: FDG-PET-CT is highly useful for monitoring response to therapeutic interventions. This technique can identify response to therapy earlier than any other imaging method currently available which greatly improves patient management by allowing termination of ineffective and toxic therapies. PET-CT proved to be helpful in the evaluation of anatomic regions that have been previously treated by surgery or radiation in which the discrimination between post-treatment scar and recurrent tumor can be problematic.

Key Words: Breast cancer – Positron Emission Tomography/Computed Tomography 18F-Fluoro Deoxy Glucose.

Correspondence to: Dr. Noha F.A. El-Qassas, The Department of Radiodiagnosis, Faculty of Medicine, Ain Shams University

Introduction

BREAST cancer is the most common cancer and the second leading cause of cancer mortality in women. Accurate diagnosis and staging are essential for the selection of the most appropriate therapeutic strategy and major determinants of patient prognosis and survival [1].

The accurate staging of local, regional, and distant recurrences after initial diagnosis and treatment is critical for therapeutic planning. In general, systemic therapy is used at almost all disease stages; however, isolated local-regional disease or a single site of metastatic recurrence is also treated with surgery and radiation therapy. After treatment, follow-up examinations are required for the early detection and accurate staging of recurrences [2].

FDG PET has high accuracy for the diagnosis of recurrent or metastatic breast cancer, because it provides functional information, and it often complements conventional imaging modalities, which are more dependent on morphologic changes to depict disease recurrence. FDG PET is particularly useful for discriminating between viable tumor and post-therapy changes such as necrosis or fibrotic scarring in patients with equivocal results of anatomic imaging. FDG PET also is useful in patients in whom the only indicator of cancer recurrence is an increase in the serum levels of tumor markers such as carcinoembryonic antigen or CA 15-3 antigen [3].

Positron Emission Tomography (PET), with or without integrated Computed Tomography (CT), using 18F-Fluorodeoxyglucose (FDG) is based on the principle of increased glucose metabolism in malignant tumors and has been investigated frequently in breast cancer [4].

Skeletal metastases are the most common site of distant disease in breast cancer, accounting for 90% of all metastatic lesions as well as representing the most common site of initial metastatic involvement. The role of FDG PET and PET/CT for detection and evaluation of skeletal metastases remains unanswered. Although most lesions are mixed, with some combination of lytic and blastic components, some lesions are purely lytic or blastic, and these lesions can pose difficulties for imaging [2].

Aim of Study:

The purpose of our study is to evaluate the potential role of 18F-FDG PET/CT in monitoring treatment of breast cancer and assessment of recurrence after surgical or systemic treatment.

Patients and Methods

This study is retrospective study was conducted on (25) female patients over a period of 6 months between 2018 and 2019. Their ages ranged from 34 to 78 years with mean age of 52 years all patients have positive history of breast cancer treatment. Those patients were referred to the Radio Diagnosis Department & Nuclear Medicine Departments in Ain Shams University and private center.

• *Inclusion criteria of the study:*

- 1- Patients diagnosed with breast cancer undergoing to treatment (NAC, radio, hormonal or surgical treatment).
- 2- Any age group.

• *Exclusion criteria:*

- 1- Pregnancy.
- 2- Blood glucose level greater than 140mg/dl.
- 3- Women with renal impairment.

• *Ethical considerations:*

The study will be submitted for approval of the Ethical Committee of Department of Radiology, Faculty of Medicine, Ain Shams University.

A written consent will be taken from all participants before recruitment in the study. This is done after full, simple, comprehensive explanation of the purpose, procedures and susceptible hazards- if any-of the study.

- Technique of whole-body PET/CT imaging with 18F-FDG.

I- *Physician directive:*

- 1- Clinical evaluation by complete past and present history.

2- Laboratory studies including:

- Blood glucose level.
- Blood urea nitrogen and creatinine.

II- *Patient position:* The patient lies supine either with the arms above the head or by the side. Except for patients being studied for head and neck cancer, arms above the head is the preferred position to decrease beam hardening artifact during the CT portion of the examination. However, not all patients can maintain this position comfortably without moving for the entire study (PET and CT), and arms by the side is an alternative.

III- *Dosage administration:*

1- 18F-FDG is injected in a dosage of 1 MCi/10kg followed by saline.

2- The patient waits for 60 to 90 minutes after 18F-FDG administration and is instructed to remain quiet with minimal movement until the completion of the PET/CT scan.

3- Intravenous and oral CT contrast agents are recommended in PET/CT studies. Intravenous agents are used for all body areas except the abdomen, for which oral contrast agents are used. IV contrast agents are administered 30 to 40 seconds before CT scanning. Oral contrast agents provide positive contrast by increase of CT attenuation (iodine, barium) or negative contrast by distension of the bowel (water-based contrast agents).

IV- *Examination time:* A whole body PET study (neck through pelvis) follows an enhanced whole body CT study. The CT study takes approximately 60-70 seconds to complete and the PET study takes approximately 30-45 minutes, depending on the coverage required.

IV- *Complications:* Allergy from contrast media treated by corticosteroids.

Renal impairment require nephrologist consultation for treatment according to its degree.

• *Interpretation of PET-CT scans:*

There are different methods for assessment of radiotracer uptake by normal and pathologic tissues, such as visual inspection, the Standardized Uptake Value (SUV), and the glucose metabolic rate. SUVs are used for semi quantification of FDG uptake typically; malignant tumors have an SUV greater than 2.5-3.0, whereas normal tissues such as the liver, lung, and marrow have SUVs ranging from 0.5 to 2.5.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± Standard Deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Chi-square (χ^2) test of significance was used in order to compare proportions between qualitative parameters.
- Paired sample *t*-test of significance was used when comparing between related sample.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p*-value was considered significant as the following:
 - Probability (*p*-value).
 - *p*-value < 0.05 was considered significant.
 - *p*-value < 0.001 was considered as highly significant.
 - *p*-value > 0.05 was considered insignificant.

Results

The results of the present study are demonstrated in the following tables and barographs.

Table (1): Distribution of breast cancer cases according to their demographic data regarding age (years) (n=25).

Age (years)	Statistics
Range	34-78
Mean ± SD	52.76±12.29
Median (IQR)*	53 (21)

*: Interquartile range.

This table shows that the patients ranged age was 34-78 with mean 52.76 and median 53 (21).

Table (2): Distribution of breast cancer cases according to their metastasis (n=25).

Metastasis pre-treatment	No.	%
LN	8	32
Liver	6	24
Bone	5	20
Lung	4	16
Adrenal	2	8

This table shows that site of metastasis in initial staging PET/CT was in lymph nodes accounting for 32% of cases.

Table (3): Distribution of breast cancer cases according to their local recurrence (n=25).

Local recurrence	No.	%
No	21	84
Yes	4	16
Total	25	100

This table shows that there's no local recurrence in 84% of patients.

Table (4): Distribution of breast cancer cases according to their site of metastasis in follow-up pet/ct.

Follow-up	No.	%
Liver	5	20
Bone	4	16
Lung	3	12
LN	2	8
Adrenal	2	8

This table shows that the comments site of metastasis in follow-up PET/CT was Liver accounting for 20% of cases.

Table (5): Comparison between metastasis and follow up according to their SUV regarding liver, lung, LN, bone and adrenal (n=25).

SUV	Metastasis		Follow-up		Paired sample <i>t</i> -test		
	Range	Mean ± SD	Range	Mean ± SD	Mean Diff.	<i>t</i> -test	<i>p</i> -value
Liver	5.12-12	8.12±2.65	0-10.9	5.24±3.12	2.880	2.742	0.033*
Lung	2.8-12	5.90±4.31	0-11.3	6.10±4.79	0.467	0.103	0.927
LN	2.9-9.3	5.26±2.22	0-11.3	2.10±4.19	3.163	2.603	0.035*
Bone	1.6-24	11.48±8.87	0-24	8.57±8.97	2.400	2.023	0.113
Adrenal	5-5.5	5.25±0.35	3-3.4	3.20±0.28	2.050	4.556	0.138

p-value >0.05 NS. **p*-value <0.05 S.

This table shows statistically significant difference in SUV values between metastasis pre-treatment and follow-up according to liver and LN.

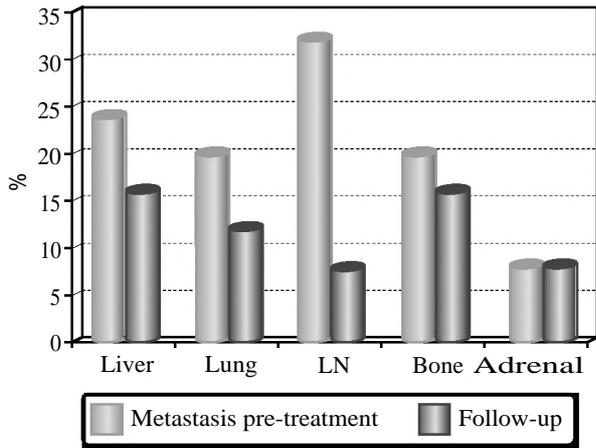


Fig. (1): Bar chart between metastasis pre-treatment and follow-up according to their site of metastasis regarding liver, lung, LN, bone and adrenal.

Table (6): Distribution of breast cancer cases according to their outcome (n=25).

Outcome	No.	%
Progression	10	40
Complete resolution	9	36
Regression	5	20
Stationary	1	4
Total	25	100

This table shows that 40% of cases show progression, 36% of cases show complete resolution, 20% of cases show regression, 4% of cases were stationary.

Illustrative cases:

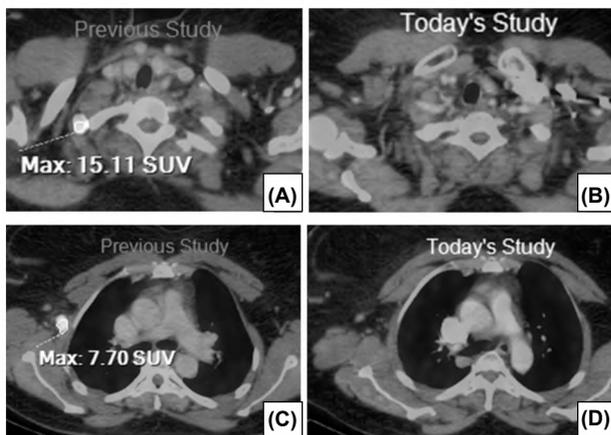


Fig. (2): 45 years old female patient with history of metastatic right breast cancer under hormonal treatment, referred for follow-up.

PET-CT study before treatment revealed:

- Metabolically active right retro-clavicular lymph node achieving 15.11SUV max Fig. (2A).
- Right axillary lymph node achieving 7.7SUV max Fig. (2B).

Follow-up PET/CT study revealed:

- Complete metabolic and morphological resolution of such residual hyper metabolic right retro-clavicular and right axillary nodal deposits Fig. (2C,D) with no evidence recurrent breast neoplasm or newly developed lesions.
- So follow-up revealed good therapeutic response.

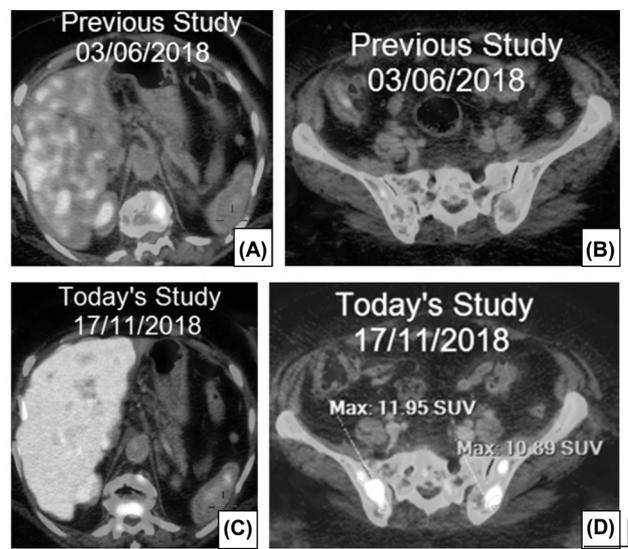


Fig. (3): 62 years old female patient with history of left breast cancer under left mastectomy referred for PET-CT for staging and follow-up after treatment.

PET-CT study revealed:

- Hyper metabolic active hepatic focal lesions ranging between 10-15mm with SUV max reaching up 6.5SUV max Fig. (3A).
- Mild metabolically active left supra-renal nodule, measuring 12mm and achieving 3.2 SUV max Fig. (3A).
- Hyper metabolic lumbar and iliac lesion with variable activity achieving up to 9.9 SUV max Fig. (3B).

Follow-up PET/CT study revealed:

- Increase in size and number of the hyper metabolic hepatic focal lesions the largest measuring about 25mm with SUV max achieving up to 12 Fig. (3C).
- Metabolic progression of the previously reported lumbar and iliac lesions, showing variable activity achieving up to 11.95 SUV max Fig. (3D).

- Stationary course of metabolic activity of the previously noted left supra renal nodule Fig. (3C).
- No PET/CT evidence of recurrent hypermetabolic breast lesions.
- So follow-up PET/CT study revealed progressive course of the disease process denoting no therapeutic response.

Discussion

Breast cancer is the most common cancer and the second leading cause of cancer mortality in women [1]. Accurate diagnosis and staging are essential for the selection of the most appropriate therapeutic strategy and major determinants of patient prognosis and survival. After treatment, follow-up examinations are required for the early detection and accurate staging of recurrences [2].

Positron Emission Tomography (PET) is a functional imaging modality that is increasingly used worldwide. F-18 FDG PET imaging is widely used in clinical oncology. Broadly, the use of FDG PET in breast cancer imaging can be discussed in terms of evaluation of the primary lesion, evaluation for distant metastatic disease, and evaluation of treatment response. PET has also been proposed as a useful modality for monitoring the response of breast cancer patients to chemotherapy, thereby guiding the choice of therapy [5].

Many patients with stage II/III breast cancer receive Neoadjuvant Chemotherapy (NAC) [7]. This strategy allows more patients to undergo breast-conserving surgery and increases the likelihood that surgery can be performed in patients with inoperable primary disease [8]. Several studies have shown the potential of 18F-FDG PET/CT in the early assessment of response to NAC [9]. This is in part due to a lack of consensus that early evaluation of response can be used to direct change in therapy in breast cancer in the neoadjuvant setting, and there are only limited data showing that response adaptive therapy leads to improved outcomes [10].

There are different methods for assessment of radiotracer uptake by normal and pathologic tissues, such as visual inspection, the Standardized Uptake Value (SUV), and the glucose metabolic rate. SUVs are used for semi quantification of FDG uptake typically; malignant tumors have an SUV greater than 2.5-3.0, whereas normal tissues such as the liver, lung, and marrow have SUVs ranging from 0.5 to 2.5. Some studies suggested a benefit of using semi-quantitative analysis (mainly the change in SUV max or SUV mean between two PET scans)

rather than visual analysis only [8]. The SUV is most commonly used to give a semi quantitative measure of response, and SUV max is considered to be a significant prognostic indicator in breast cancer in concordance with Yang [11].

The qualitative evaluation (visual) included the description of all the hyper metabolic lesions defined as positive scan that attain/focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, (other causes of false-positive scans should be ruled out) with regard to the localization and size (maximum diameters) by CT.

Our study revealed that 5 out of 25 patients (20%) had bone metastasis. Bone scintigraphy is considered the most sensitive method for detecting and determining the extent of skeletal metastases however, purely osteolytic lesions or metastases confined to the marrow cavity may be difficult to detect on bone scintigraphy, because of lack of sufficient osteoblastic response [12].

Unlike Nakai et al., [6] which demonstrated that bone is the most common site of distant metastasis in breast cancer; nearly 70% of patients who have advanced disease have bone metastasis. In the study by Nakai et al., [6] 23 breast cancer patients who had known skeletal metastases underwent both bone scintigraphy and FDG-PET. FDG-PET detected more lesions than bone scintigraphy, except in a subgroup of patients who had osteoblastic metastases. Moreover, the level of FDG uptake in osteolytic lesions was significantly greater compared with osteoblastic lesions, and the prognosis of patients who had osteolytic-predominant disease was significantly worse.

Interpretation of the PET CT findings in our study were matching with the results of Andrei et al., [13] study of 18F FDG PET/CT in the management of breast cancer, demonstrating that PET/CT with overall sensitivity of 85% has an important role in detecting distant metastasis of breast cancer, helping to plan surgical and medical treatment, and monitoring response to treatment. Our study showed that 8 out of 25 patients (32%) had nodal metastasis, 6 out of 25 patients (24%) have liver metastasis, 5 out of 25 patients (20%) had bone metastasis, 4 out of 25 patients (16%) had lung metastasis and 2 out of 25 patients (8%) had adrenal metastasis.

Follow-up after treatment revealed decreased number of patients with nodal metastasis from 8 to 2 patients (8%), decreased number of patients with liver metastasis from 6 to 5 patients (20%),

decreased number of patients with bone metastases from 5 to 4 patients (16%), decreased number of patients with lung metastasis from 3 to 2 patients (12%), and no change in number of patients with adrenal metastasis 2 patients (8%).

Our results agree with the study of Groheux et al., [14] on 11 patients with 26 metastatic lesions revealed a statistically significant reduction in tumor metabolic activity and decreased number of patients with nodal and bone metastasis after the first and second cycles of first-line chemotherapy in lesions that responded [14].

Our result revealed that that's statistically significant difference in SUV values in pre-treatment and follow-up PET/CT according to liver and lymph node metastasis.

Assessment of treatment response in our study showed 10 out of 25 patients (40%) had progressive course with poor therapeutic response, 9 out of 25 patients (36%) showed complete resolution denoted good therapeutic response, 5 out 25 patients (20%) had regressive course with good therapeutic response and 1 out of 25 patients (4%) had a stationary with no effect of treatment.

Our results agree with Constantinidou et al., [15] stating that PET/CT is equally specific and more sensitive than other imaging modalities in detecting small lesions (5-10mm), particularly lymph nodes as well as visceral and bone disease. A significant proportion of their patients had PET/CT scans for staging in the recurrent and metastatic disease; PET/CT provided accurate assessment of the metastatic disease in all these cases. It was more accurate than bone scintigraphy in detecting metastatic osteolytic disease. One of the most important findings in our study is that PET/CT is useful in accurate assessment of response to therapy. They stated that there is a strong relationship between the response to therapy and decrease in FDG signal even at an early stage of therapy.

Conclusion:

FDG-PET-CT is highly useful for monitoring response to therapeutic interventions. This technique can identify response to therapy earlier than any other imaging method currently available which greatly improves patient management by allowing termination of ineffective and toxic therapies. PET-CT proved to be helpful in the evaluation of anatomic regions that have been previously treated by surgery or radiation in which the discrimination between post-treatment scar and recurrent tumor can be problematic.

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فائدة التصوير المقطعي بالإصدار البوزيتروني لتقييم الإستجابة للعلاج في سرطان الثدي

سرطان الثدي هو أكثر أنواع السرطانات تشخيصاً، كما أنه هو المسبب الأول - بين أنواع السرطانات المختلفة - لوفيات النساء في العالم. ويعتبر التصوير المتتابع بالأشعة المقطعية بالإصدار البوزيتروني هو طريقة حساسة لتقييم الإستجابة للعلاج في المرضى الذين يعانون من سرطان الثدي. فقد أثبتت النتائج أن التصوير بالأشعة المقطعية بالإصدار البوزيتروني أكثر دقة من التصوير المقطعي فقط، وهذا يبرز فائدة استخدام الأشعة المقطعية بالإصدار البوزيتروني المؤقت في إستراتيجيات العلاج "المبنية على الإستجابة"، حيث يمكن تكييف العلاج وفقاً لإستجابة الفرد للعلاج حيث يمكن لعدة طرق للتقييم الكمي التنبؤ بإستجابة أو نتائج العلاج. وتعتبر قيمة الإمتصاص الموحدة هي الأكثر شيوعاً لإعطاء قياس كمي شبه إستجابة، ولكن يعتبر الحد الأقصى لقيم الإمتصاص الموحدة مؤشراً هاماً للتنبؤ بالإستجابة في سرطان الثدي.

تعتمد تقنية التصوير بالإنبعاث البوزيتروني المدمج بالأشعة المقطعية أو بدونها وبإستخدام مادة 18 فلورودايوكسى جلوكوز على قياس عملية إمتصاص الجلوكوز وأيضه في الخلايا السرطانية، فهي لا تعتمد على التغيير في الشكل ولكن في وظائف الخلايا. يتم عمل فحص الإنبعاث البوزيتروني المدمج بالأشعة المقطعية حين تكون نتائج الفحوصات المتعارف عليها غير كافية للتشخيص الدقيق أو لمتابعة ما بعد العلاج. كما أن لهذا الفحص دور رئيسي في تحديد مراحل الأورام السرطانية المختلفة سواء في مكان ظهور الورم أو عند ظهور ثانويات في أماكن أخرى من الجسم وهو يساعد في وضع إستراتيجية العلاج.

أظهرت النتائج الفائدة التي أضافها الإنبعاث البوزيتروني على الأشعة المقطعية العادية في تحديد الثانويات في المناطق المختلفة من الجسم ومراقبة ظهور ثانويات جديدة فائتاء وبعد العلاج كل ذلك أثر بشكل مباشر على تحديد مدى تقدم المرض وإختبار العلاج المناسب لكل مريض حسب الحالة.

يعتبر التصوير بالإنبعاث البوزيتروني الدمج بالأشعة المقطعية واحد من أفضل طرق الفحص بالإشعة لمتابعة أورام الثدي بعد عمليات الإستمصال.