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Correlation Between of PET/CT and Molecular Subtypes and in Patients with Metastatic Breast Cancer.

Moustafa, H [1]. Nasr, A[2] and Tawakol, A[1].

[1] Oncology and Nuclear Medicine Department, Cairo University and [2] Maadi Armed Force Hospital. Egypt.

ABSTRACT:

FDG PET/CT whole-body imaging has higher sensitivity, specificity and accuracy as compared to CT in detection of metastatic spread and follows up after treatment. **The aim of this study:** to assess of the impact of PET/CT in patients with metastatic breast cancer and monitoring the therapy response in relation to different molecular subtypes. **Material and Methods:** The study included 40 patients classified into 4 molecular subtypes; Luminal A like subtype (13 patients), Luminal B+ subtype (15 patients), Luminal B- subtype (4 patients) and Basal like subtype (8 patients). All patients with possible metastatic breast cancer performed PET-CT before treatment, while 34 patients perform PET-CT after the end of therapy. **Results:** on lesion based analysis the total numbers of metastatic lesions in CT and bone scan were 120 lesions (49 in LNs, 24 in lung, 8 in liver; while 39 in bone). Metastatic lesions in PET/CT were 76 lesions (46 in LNs, 22 in lung and 8 in liver and 22 in bone). During follow up after therapy, the majority of luminal A group showed complete response to therapy during follow up PET/CT scan. Also, luminal B+ subgroup showed partial response. While most of basal-like subgroup showed progressive disease. **Conclusion:** PET/CT can detect metastatic spread in breast cancer and monitor therapy response in relation to different molecular subtypes. The mean SUV max showed relation to the different molecular subtypes.

Key Words: PET/CT, Molecular Subtypes and Metastatic Lesions.

Corresponding Authors: Nasr, A. **E-mail:**dr_ahmed_nasr77@yahoo.com.

INTRODUCTION:

Breast cancer is the most prominent cancer and the second most prominent cause of mortality in women. In recent years the incidence of breast cancer has increased to 102 per 100,000 per year [(1)].

Standard imaging techniques in breast cancer include radiological examinations, such as X-ray mammography, Ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI).

Nuclear medicine techniques also play an increasing role in staging and follow up of breast cancer. Bone scintigraphy was used for follow-up of women with breast cancer to detect bone metastases [(2)].

A crucial development in the treatment of breast carcinoma has been the realization that the presence of hormone (estrogen and progesterone) receptors in the tumor tissue correlates well with response to hormone therapy and chemotherapy.

As a matter of fact; estrogen receptor status is regarded as powerful predictive marker in breast cancer management. The subtypes of breast cancers recognized by their gene signature include: luminal (type A and B), HER2/neu type and basal-like (Triple negative).

The basal-like subtype is associated with the worst prognosis.

Since the different subtypes of breast cancers exhibit specific characteristics, they would likely benefit from different approaches of treatment [(3)].

PET/CT was introduced in different types, clinical oncology and provides an effective and accurate imaging technique for a variety of diagnostic oncology. In breast cancer, main applications are detection of the response, restaging and detection of metastatic disease, and for monitoring treatment response [(4)]. However, there is evidence that breast cancer patients may benefit from an FDG-PET examination, compared with other imaging modalities to demonstrate proper extent of the disease and metastatic spread within a single investigation [(5)].

PET/CT scan can be used as a noninvasive molecular imaging of breast cancer, and prediction of therapeutic effect and prognosis of patients. Studies have revealed that luminal A subtype has a significantly lower maximum standard intake value (SUV max) than the other subtypes; triple-negative and (HER2).

Positive tumors have relatively high SUV max than luminal B subtype, but the specificity and sensitivity of SUV max in diagnosis of molecular subtypes are very low. So its clinical application is limited in predicting the effectiveness of the treatment and the prognosis of the patients, the decreased uptake of FDG may be correlated with better therapeutic effect [(6)].

Aim of the work: assessment of the impact of different molecular subtypes on FDG avidity in different metastatic lesions in patients with breast cancer undergoing PET/CT, as well as monitoring the therapy response using PET-CT in metastatic breast cancer in relation to different molecular subtypes.

MATERIALS AND METHODS:

Study design: This is a prospective study in which 40 female patients with evidence of proven metastatic breast cancer were referred for PET/CT in Department of Nuclear Medicine in Maadi Armed Forces Medical Compound in the period between March 2015 to October 2017. The protocol of the study was approved by the ethical committee in Oncology and NM department in faculty of Medicine Cairo University.

All clinical and histopathological information was extracted from the patients' clinical sheet in agreement with the referring physicians. This included the pathological data, molecular subtypes, evidence of metastatic and the current reason for FDG-PET/CT referral.

Four patients were excluded because of a lack of sufficient follow-up information (clinical data or imaging) and two patients died during the study time, leaving 40 patients for final evaluation. Follow up after therapy was done in 34 patients in view of absence of metastatic lesion in PET/CT.

Inclusion criteria include: Histologically confirmed diagnosis of breast cancer with molecular subtypes, (ER, PR, and HER2).Initially metastatic breast cancer or relapsed after primary treatment evident by abdominal ultrasound, diagnostic CT scan, bone scan or elevated tumor markers. Patients provide written informed consent before any study-specific procedure.

All patients included in the study with PET/CT on account of evaluation of metastatic breast cancer; these were evident by elevated tumor markers, equivocal findings diagnostic CT and/or positive bone scan.

FDG-PET/CT studies were performed after appearance of clinical, radiological and/or laboratory data warranting restaging and follow up during a period of 12 – 18 months. FDG-PET/CT study was performed in 34 patients after complete therapy cessation for monitoring and assessment of therapy response for a period of 6-12 months.

Whole Body PET/CT Imaging with 18F-FDG:

Patient Preparation; the patient is asked to fast for 6 hours prior to scan. Control of blood glucose in diabetic patients. Remove metallic items from the patient. Insert an I.V. catheter in the patient's arm for administration of 18F-FDG.They are instructed to avoid caffeinated fluids but can have water during this period. Patients are also 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. The patient is asked to void prior to scanning.

Dosage Administration: Inject 18F-FDG into the patient in a dosage of 0.1 mCi/kg or as prescribed by the physician. Imaging started 45 to 60 minutes after FDG administration and is instructed to remain quiet with minimal movement until the completion of the PET/CT scan.

Patient position and acquisition: They are positioned with the arms elevated. However, if the patients cannot maintain this position comfortably without moving for the entire study then the arms left by the side of the patients.

PET/CT is performed on an integrated scanner (GE discovery) that combines both CT and PET capabilities in two sequential gantries, avoiding the need for patient motion between the CT and PET components of the study and thereby leading to accurate co-registration of the CT and PET data. PET study follows an enhanced CT study.

The CT study takes approximately 60–70 seconds and the PET study takes approximately 20–30 minutes, depending on the coverage required. Attenuation correction of PET images is performed by using attenuation data from the CT component of the examination; emission data are corrected for scatter, random events, and dead-time losses by using the manufacturer's software.

PET is performed following the CT study without moving the patient. Approximately six to seven bed positions are planned in the three dimensional acquisition modes for scanning the entire patient with 2–3 minute acquisition at each bed position.

PET/CT images are analyzed both qualitatively and semi quantitatively.

Imaging interpretations at initial diagnosis: Images were interpreted by 2 experienced nuclear medicine physicians. Reviewers were blinded to the results of the other imaging modalities. PET/CT was performed with special emphasis on the site of the primary lesion, other breast; regional lymph nodes in both axilla and internal mammary group's. Also, lungs, liver and skeletal systems were evaluated for assessment of metastatic spread. Qualitative assessment for presence of hyper-metabolic lesions was evaluated on corrected PET images. Semi-quantitative evaluation was performed using the Standardized Uptake Value (SUV-max) for all abnormal foci.

Positive lesions were defined as showing true disease involvement in both PET/CT and diagnostic CT studies or dis-concordant lesions with positive PET/CT and negative diagnostic CT proved by other diagnostic imaging.

Negative lesions were defined as showing true negative disease involvement in both PET/CT and diagnostic CT studies or dis-concordant negative lesions in PET/CT and positive diagnostic CT proved by other diagnostic imaging.

Assessment of relapse of metastatic was done at 6 – 12 Months: Presence or absences of disease relapse with metastatic lesions in bone, liver, lung and adrenals using PET/CT. Correlation of sites metastatic lesions with different molecular subtypes. In equivocal new lesions, histopathological assessment or using other imaging modalities as MRI, bone scintigraphy and follow-up using PET/CT were done. Assessment of therapy was done according to WHO criteria.

RESULTS

Patients characteristics of 40 patients of metastatic breast cancer were included in the study are shown in (***Table 1***).

Table (1): Patients characteristics among 40 patients of metastatic breast cancer.

Variables		N	%
Mean age of patients		54.45 ± 9.98 (30 – 71)	
Female		40	(100%)
Family history (+ve)		17	(42.5%)
Axillary LN metastasis (+ve)		15	(37.5%)
Site	Right	18	(45%)
	Left	22	(55%)
HER-2 positivity		15	(37.5%)
Pathology	Invasive ductal carcinoma	40	(100%)
Molecular subtypes	Luminal A like	13	(32.5%)
	Luminal B+	15	(37.5%)
	Luminal B-	4	(10%)
	Basal like	8	(20%)

On patient based analysis: Diagnostic CT reported metastatic LN lesions in 29 patients (72.5%); while 13 patients (32.5%) had lung metastasis. Only 5 patients had liver metastatic lesions (12.5%). Bone scan showed 12 metastatic bone lesions.

Comparison between the 4 molecular subtypes to different sites of metastases revealed (p > 0.85) ***(Table 2)***.

Table (2): Comparison between 4 molecular subtypes in relation to type of metastatic lesions.

Site of metastasis	Luminal A (N= 13)	Luminal B+ (N= 15)	Luminal B- (N= 4)	Basal like (N= 8)	p value
LNs	12 (92.3%)	10 (71.4%)	2 (50%)	5 (62.5%)	P = 0.8529
Lung	3 (23%)	6 (42.8%)	1 (25%)	3 (37.5%)	
Liver	1 (7.7%)	1 (7.1%)	1 (25%)	2 (25%)	
Bone	5 (37.5%)	5 (35.7%)	1 (25%)	1 (12.5%)	

On lesion based analysis: The total numbers of metastatic lesions in using diagnostic CT and bone scan were 120 lesions, while PET/CT they were 98 lesions. 49 lesions were metastatic LNs in CT (40.8 %) and 46 lesions were seen in PET/CT (47 %). The 3 LNs not avid to FDG in PET/CT were presented as lymph nodes measuring 1 cm with preserved hilum, but was reported as positive lesion in diagnostic CT.

There were 24 metastatic lung lesions detected in CT (20%), while 22 metastatic lung lesions were detected in PET/CT (22.4 %). The 2 pulmonary nodules not avid to FDG in PET/CT presented as sub-centmetric nodules between 6 to 8 mm as seen in CT part of the study.

The 8 liver metastatic lesions were seen in both diagnostic CT and PET/CT.

The total numbers of metastatic lesions detected by bone scan were 39 lesions (32.5%), while 22 lesions of them were seen in PET/CT (22.4%).

The 17 osseous lesions were not avid FDG and presented as degenerative bone lesions in CT part of the study. Comparative study between CT metastatic findings and baseline PET/CT findings revealed no-significant difference as regards number of metastatic lesions ($p > 0.99$) ***(Table 3)***.

Table (3) Comparison between baseline diagnostic CT, bone scan and PET/CT findings according to the type of metastatic lesions.

Variable		CT / Bone scan findings (N=120)	Baseline PET/CT findings (N=98)	p value
Site of metastasis	LNs	49 (40.8%)	46 (47.%)	P = 0.9991
	Lung	24 (20%)	22 (22.4%)	
	Liver	8 (6.6%)	8 (8.2%)	
	Bone	39 (32.5%)	22 (22.4%)	

Also, comparison between metastatic lesions in baseline and follow up PET/CT after 6 – 12 months on lesion based analysis revealed no-significant difference ($p > 0.27$) ***(Table 4)***.

Table (4): PET/CT finding in baseline and follow up in 34 patients with metastatic breast cancer on lesion based analysis.

Variables		Baseline PET/CT N=98 (%)	Follow up PET/CT N=77 (%)	P value
Type of metastatic lesions	Lymph Node lesions	46 (47.%)	31 (40.3%)	P value> 0.27
	Lung lesions	22 (22.4%)	20 (25.9%)	
	Liver lesions	8 (8.2%)	8 (10.4%)	
	Bone lesions	22 (22.4%)	18 (23.4%)	

Correlation between baselines and follow up PET/CT in metastatic lesions in relation to molecular subtypes revealed significant decrease in number of lesions after therapy in luminal A group only ($p < 0.0001$). While the other groups showed no-significant difference between baseline and follow up PET/CT lesions ($p > 0.05$) ***(Table 5 and Figure 1, 2).***

Table (5) Follow up of metastatic lesions in baseline and follow up PET/CT in relation to.

Variable	Baseline PET/CT findings (N=98)	Follow up PET/CT findings (N=77)	Mc Nemar's test
			p value
Luminal A	34 (34.7%)	16 (20.7%)	< 0.0001**
Luminal B+	32 (32.7%)	29 (37.6%)	0.8252
Luminal B-	9 (9.2%)	9 (11.7%)	1.0000
Basal-like	23 (23.5%)	23 (29.9%)	1.0000

Comparison using the mean SUV max value in baseline and follow up PET/CT with different molecular subtypes revealed significant decrease in mean SUV max of LNs avidity after therapy in luminal A, B+, B- subgroups with significant difference. Also, luminal A+ group showed significant decrease in mean SUV max of bone and lung with Significant difference. Luminal B+ showed significant difference following therapy in bone lesions. On the other hand, basal-like molecular subtype showed poor response with higher mean SUV max after therapy with no-significant difference ***(Table 6)***.

Table (6) Follow up of metastatic lesions using mean SUV max of baseline and follow up PET/CT in relation to different molecular subtypes.

Variable		Baseline PET/CT findings	Follow up PET/CT findings	Paired t test
				p value
Luminal A	LNs	4.97 ± 5.6	2.9 ± 7.3	0.0461*
	Lung	2.98± 2.15	0.84 ± 2.51	0.6251*
	Liver	1.07 ± 3.88	1.73 ± 5.54	0.3370
	Bone	3.92 ± 5.09	2.68 ± 6.31	0.0376*
Luminal B+	LNs	3.89 ± 0.13	2.61 ± 0.65	0.036*
	Lung	0.98 ± 1.93	0.51 ± 0.91	0.0159
	Liver	1.01 ± 1.21	1.2 ± 1.16	0.3343
	Bone	2.8 ± 1.13	0.8 ± 1.3	0.0391*
Luminal B-	LNs	2.35 ± 3.13	1.07 ± 1.6	0.0393*
	Lung	3.75 ± 7.5	2.75 ± 7.3	0.9957
	Liver	2.2 ± 5	1.8 ± 3	0.3910
	Bone	2.85 ± 3.5	2 ± 2	0.0792
Basal-like	LNs	2.8 ± 2.67	2.75 ± 2.43	0.7850
	Lung	1.42 ± 2	2 ± 3.5	0.4828
	Liver	1.97 ± 3.72	2.2 ± 4.75	0.1803
	Bone	1.02 ± 1.95	1.35 ± 2.37	0.1735

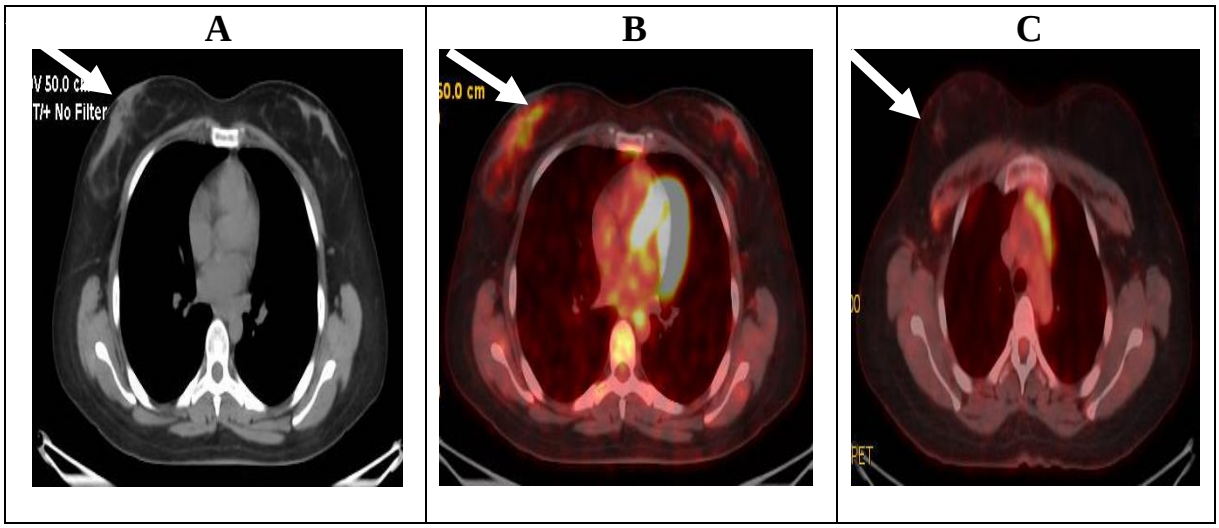

Figure 1; 30 yrs female with RT breast cancer, she received chemotherapy followed by right lumpectomy; her molecular subtype is luminal A. **(Fig 1A , B)** PET/CT showed mildly glucose avid small nodular lesion of the right lumpectomy bed with SUV max=3.5. **(Fig 1C)** Follow up PET/CT after treatment showed no evidence of avid lesion in the right breast reflecting complete metabolic response.

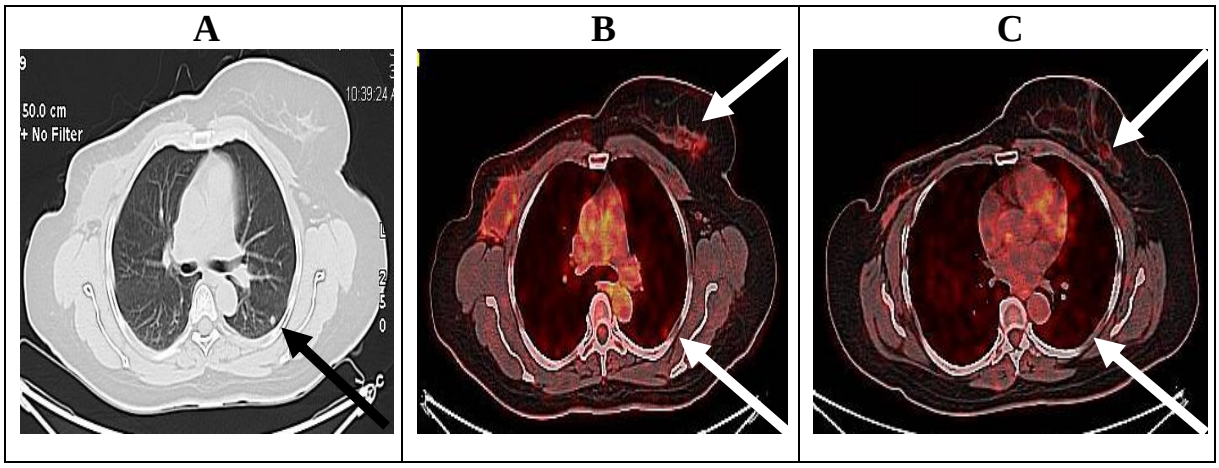

Figure 2; A 60 yrs female with history of RT MRM, her molecular subtype is luminal B+. (A) CT chest showed multiple bilateral pulmonary nodules. **(Fig 2 B) PET/CT** Residual primary lesion and bilateral pulmonary nodules with SUV max=3. (**Fig 2 C)** Follow up PET/CT after treatment showed partial regression of the glucose avid lung nodules (with SUV=2); with no avid glucose uptake in the chest wall at the site of primary lesion indicating partial metabolic response.

Comparative study between the 4 molecular subtypes in relation to response to therapy using PET/CT revealed that the majority of luminal A group showed complete response to therapy during follow up PET/CT scan. Also, the majority of luminal B+ subgroup showed partial response. While majority of basal-like subgroup showed progressive disease with highly significant difference ***(Table 7)***.

Table (7): Comparison between 4 molecular subtypes in relation to PET/CT response to therapy in 34 patients with metastatic breast cancer.

PET/CT response to therapy	Luminal A (N= 11)	Luminal B+ (N= 11)	Luminal B- (N= 4)	Basal like (N= 8)	p value
CR(N=8)	7 (63.6%)	1 (9%)	0 (0%)	0 (0%)	= 0.0006**
PR (N=13)	1 (9%)	8 (72.7%)	3 (75%)	1 (12.5%)	
PD (N=11)	3 (27.3%)	1 (9%)	0 (0%)	7 (87.5%)	
SD (N=2)	0 (0%)	1 (9%)	1 (25%)	0 (0%)	

ROC curve analysis:

ROC curve to discriminate sensitivity and specificity using PET/CT showed high sensitivity of 85.29% and specificity of 90% to differentiate between metastatic lesions using positive and negative PET/CT ***(Fig 3.)***

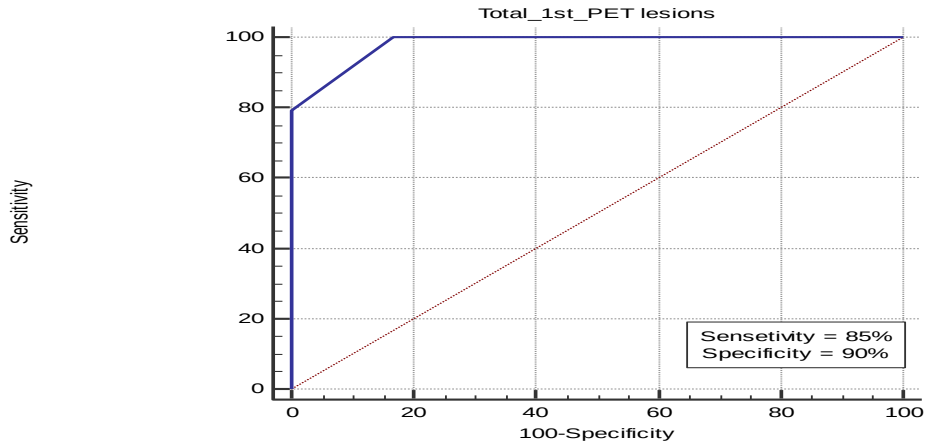

Figure (3) ROC-curve to discriminate sensitivity and specificity of patients with positive PET/CT versus patients with negative PET/CT in 34 patients with metastatic breast cancer.

ROC curve using CT assessment of metastatic lesions showed high sensitivity of 88% however it showed low specificity of 66% in relation to PET/CT ***(Fig 4)***.

Figure (4) ROC-curve, Total numbers of CT metastatic lesions to discriminated patients with positive CT lesions from patients with negative lesions in 34 patients with metastatic breast cancer.

DISCUSSION:

Breast tumors represent a collection of different histopathological types, understanding metabolic differences between molecular subtype's offers a way to identify new subtype-specific treatment strategies, especially if metabolite changes are evaluated in the broader context of the network of enzymatic reactions and pathways.

In a series of 92 primary breast cancer patients undergoing surgery at the Institute National of Tumors of Milano, they reported metabolic differences across various molecular subtypes; with luminal B subgroup represents a tumor type which preferentially relies on fatty acids for energy, whereas HER2 and basal-like ones show prevalently alterations in glucose/glutamine metabolism [(7)].

Although tumor size, lymph node metastasis and tumor grade have been widely accepted in daily clinical practice, the identification of further prognostic indicators especially in the ER+/HER2- subtype is warranted. A total of 387 operated breast cancers evaluated with FDG PET/CT at baseline in combination with molecular subtypes. Calculation of metabolic SUV max appears to be useful for selecting patients who have inferior Prognosis and need further adjuvant treatment of the ER+/HER2- subtypes [(8)].

Imaging techniques play an important role in the detection of metastatic spread in breast cancer, such early detection improves patients' prognosis, and has a substantial influence on therapy management, especially using molecular imaging with PET-CT [(9)].

Also monitoring treatment responses with PET/CT for women with metastatic breast cancer can be difficult and with the goals of therapy focused on improving quality of life and overall survival, finding a test that is safe, non-invasive and reliable to assess response is a challenge [(10)].

In this prospective study 40 patients with metastatic breast cancer were studied to detect the diagnostic value of PET/CT in metastatic breast cancer patients. Also, correlation of different molecular subtypes with PET/CT foe assessment of response therapy has been evaluated.

The 40 MBC patients in the present study were classified according molecular subtypes into 4 groups including patients with Luminal A like subtype (13 patients), patients with Luminal B+ subtype (15 patients), patients with Luminal B- subtype (4 patients) and patients with Basal like subtype (8 patients).

Vicente et al, in their study included 168 women with advanced breast cancer. PET/CT was requested in the initial staging before and after neo-adjuvant treatment. Both examinations were evaluated qualitatively and semi quantitatively with calculation of SUV max, and the percentage variation in the SUVs between PET-1 and PET-2. Biological prognostic parameters, including the steroid receptor status, were determined from primary tumor tissue. Tumor subtypes were classified following the recommendations of the 12th International Breast Conference, by Immuno-histochemical surrogates as luminal A, luminal B-HER2 (-), luminal B-HER2(+), HER2(+) or basal subtypes. Metabolic semi quantitative parameters and molecular subtypes were correlated, of the 168 tumors, 151 were classified: 16 were luminal A, 53 were luminal B-HER2 (-), 29 were luminal B-HER2 (+), 18 were HER2 (+) and 35 were basal. There were significant differences between SUV-1 and SUV-2 and the different subtypes, with higher SUVs in HER2 (+) and basal tumors. Semi quantitative metabolic parameters showed statistically significant differences among the molecular subtypes of the tumors evaluated.

Therefore, there reported that a relationship between molecular PET/CT and glycolytic phenotypes [(11)].

Niikura et al. performed a retrospective review which included 225 patients with breast cancer patients and compared the sensitivity and specificity of PET/CT and conventional imaging (CT, Ultrasonography, radiography, and skeletal scintigraphy) for the detection of distant metastases and they concluded that PET/CT was superior to conventional imaging in terms of both sensitivity and specificity [(12)].

In the present study, using PET/CT showed high sensitivity of 85% and specificity of 90% to differentiate between metastatic lesions and this result agrees with the previously reported results.

Similarly, ***Eubank et al***, reported high sensitivity, specificity and accuracy of 85%, 90% and 88%, respectively for FDG- PET in detection of metastatic spread to lymph nodes in mediastinal and intra-mammary groups. While CT was able to provide sensitivity, specificity and accuracy of only 54%, 85% and 73% in same patients groups [(13)].

In the present work, bone is the most frequent site of distant involvement in breast cancer, 39 metastatic bone lesions were detected by bone scan, Whereas, 22 lesions of them were positively detected by PET/CT.

The other 17 osseous lesions were false positive in bone scan with non-avid FDG lesions detected by CT part of study as degenerative bone lesions [(14)].

Also, ***Hahn et al***, in their results of 29 consecutive women with breast cancer were assessed with bone scintigraphy and whole-body FDG-PET/CT. A total of 132 lesions were detected on bone scintigraphy, FDG-PET/CT reported positive metastatic lesion in 70/132 lesions (53%) Whereas, 59/132 lesions (45%) were benign, and three lesions (2%) remained unclear.

The sensitivity of bone scintigraphy was 76 % compared to 96 % for FDG - PET/CT. The specificity of bone scintigraphy and FDG-ET/CT was 95% and 92%, respectively. On a lesion-basis whole-body FDG-PET/CT was more sensitive and equally specific for the detection of bone metastases compared with bone scintigraphy [(15)].

Regarding pulmonary metastasis, diagnostic CT efficiently detected sub-centmetric pulmonary nodules.

Whereas in PET imaging in view of partial-volume effect and respiratory movements had lower sensitivity for detecting smaller nodules. Combined PET/CT examination obviously improved the sensitivity of PET/CT in comparison to stand alone PET [(16)].

In the present work, 2 pulmonary nodules were not detected by PET/CT as they presented as sub-centimetric nodules between 6 to 8 mm as seen in CT part of the study with no FDG uptake. FPET/CT helped to classify doubtful findings of liver lesions on conventional imaging (angiomas and cysts), as reported by ***Garami et al*** [(17)].

In their study on 115 breast cancer patients they found that PET/CT is able to assess primary tumor size and metastatic spread more accurately than traditional diagnostic methods. It can detect distant metastases in 7-8% of those patients who were declared free of metastasis. PET/CT scan modifies the disease stage determined by traditional diagnostic modalities in almost half of the patients and leads to a change in the treatment plan in every 6th patient [(17)].

In our work, we found similar detection rate of metastatic spread to the liver for both diagnostic CT and PET/CT in the 8 patients evaluated. Histopathological prognostic parameters, such as the tumor size, grade, lymph node involvement, lympho-vascular invasion, estrogen (ER), progesterone receptors (PR) and HER2 status were determined from the primary breast tumor tissue.

The FDG uptake of metastatic sites was evaluation as the SUV max relation to the molecular subtypes and survival.

Cokmert et al, using Cox regression analysis to evaluate the associations between SUV max measurements and overall survival (OS), the mean SUV max of 176 tumors was 8.0. Among the subtypes 49 (28.8%) were luminal A, 51 (28.9%) luminal B, 35 (19.8%) HER2-overexpressing, and 41 (23.2%) triple-negative, and the corresponding means of SUV max were 5.6, 7.4, 11.4, and 11.0, respectively [(18)].

A cut-off value of ≤8.4 yielded 80% sensitivity and 57.1% specificity with an area under the receiver operating characteristics curve of 0.731 for predicting that a tumor was of the luminal A subtype.

A cut-off value of SUV max ≥10.05 yielded 62.9% sensitivity and 67.4% specificity with an AUC of 0.648 for predicting a HER2 over expressing subtype. A cut-off value of SUV max ≥9.25 yielded 61% sensitivity and 64.4% specificity with an AUC of 0.660 for predicting a triple-negative subtype. The SUV max could not effectively differentiate patients with luminal B subtype. Cox regression analysis showed that in patients with MBC, a SUV max ≤7.55 acted as an independent negative prognostic factor for OS (hazard ratio/HR = 1.552). Finally they found that the SUV max of metastatic sites on pretreatment 18F-FDG PET/CT may be an independent prognostic factor for the diagnosis of molecular phenotypes and survival in MBC patients [(18)].

In our study, there was marked decrease in mean SUV max in luminal A, B + subtypes in LNs and bone lesions.

On the other hand, Basel like subgroup showed no response as reflected with high mean SUV max after treatment.

Similarly, ***Koo et al***., in their study involved 548 patients of breast cancer reported with correlation between SUV max with immuno-histochemical defined molecular subtypes (luminal A, luminal B, HER2 positive and triple negative). FDG uptake was independently associated with subtypes of invasive breast cancer. Triple-negative and HER2-positive breast cancers showed higher SUV max values than other luminal tumor subtypes [(19)].

Whereas, ***Pan et al***., reported that luminal A subtype has a significantly lower SUV max than the other subtypes; triple-negative and (HER2) positive tumors have relatively high SUV max than luminal B subtype. However, the specificity and sensitivity of SUV max in diagnosis of molecular subtypes were very low in predicting the effectiveness of the treatment and the prognosis of the patients, the decreased uptake of FDG is correlated with better therapeutic effect. In addition, patients with high FDG uptake have worse survival outcomes [(20)].

In the present work, 34 patients with metastatic breast cancer were monitored after therapy with complete metabolic response in (23.5%), partial metabolic response to therapy in (38.2%); while (32.3%) had progressive disease.

The majority of luminal A group showed complete response to therapy during follow up PET/CT scan and also luminal B+ subgroup showed partial response; while most of Basal subtype showed progressive disease.

Also, ***Perez et al***, in their retrospective study conducted on 1380 patients with a diagnosis of metastatic breast cancer have been classified by immuno histochemistry into four subtypes: luminal A, triple negative, luminal B and HER2. An analysis was performed on the association with age, risk factors, and the clinical and histopathological features of the tumor.

The frequency was luminal A (65%), triple negative (14%), luminal B (12%), and HER2 (9%). the most frequent sub-type was luminal A, and together with the luminal B are those which have better prognosis compared with the triple negative and HER2 [(21)].

CONCLUSIONS:

PET/CT is whole body single imaging which can detect metastatic spread in breast cancer as well as monitoring the therapy response in relation to different molecular subtypes. The mean SUV max is markedly decreased in luminal A and B+ subtypes reflecting good response to therapy. On the other hand, the majority of basal-like group showed no response to therapy with any change in mean SUV. The majority of luminal A group showed complete response to therapy. Also, the majority of luminal B+ groups showed partial response, while most of the Basel like subgroup showed progressive disease.

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