Original Article, PET/CT.

Correlation of PET/CT Metabolic Parameters of Bone Metastases in Breast Cancer Patients to Clinico-Pathological Factors.

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ABSTRACT:

Aim: To assess the relationship between different metabolic parameters of F-18 FDG PET/CT of bone metastases (BM) from breast cancer and clinico-pathological features (tumor characteristics, immune histochemical subtypes and CT appearance). **Methods:** This study prospectively enrolled 51 female patients with pathologically proven breast cancer who were referred for metastatic work-up by PET/CT and revealed BM. The metabolic parameters for the most avid BM lesion including [maximum, peak and mean standardized uptake value (SUV max, SUV peak and SUV mean respectively), total lesion glycolysis (TLG) and metabolic tumor volume (MTV)] were conducted in relation to clinico-pathological characteristics (pathology, nuclear grading, progesterone receptors (PR), estrogen receptors(ER), human epidermal growth factor receptor type 2 (HER2neu), molecular subtypes) and CT type of BM lesion. The CT appearance of the bone lesion was visually divided into osteoblastic, osteolytic, mixed lytic and sclerotic and FDG uptake with no CT correlate. **Results:** BM SUV max was significantly greater in nuclear grade II & III than in nuclear grade I (P value 0.036), Also BM SUV max was greater in invasive ductal carcinoma (IDC) than invasive lobular carcinoma (ILC) (SUV max 5.73, 3.80 respectively), BM SUV max of the osteolytic type was higher than that of other CT types of lesions (SUV max 7.13, 4.91 respectively); No significant correlations were found between different metabolic parameters (SUV max, SUV peak, SUV mean, TLG and MTV) of metastatic bony lesions and the clinico-pathological features (ER, PR, HER2, molecular subtypes, nuclear grade, histopathology and CT type).

Conclusion: SUV max of metastatic bony lesions was high in IDC, grade II&III and osteolytic lesions in patients with breast cancer and no significant correlations between different metabolic parameters of F-18 FDG PET/CT of BM from breast cancer and clinico-pathological features.

Keywords: F-18 FDG PET/CT, metabolic parameters, Breast cancer, Bone metastases, SUV max.

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INTRODUCTION:

Breast cancer (BC) is the most prevalent neoplasm in female[1]. Despite improvements in treating BC in its early stages, bone remains the most frequent site of distant metastases in patients with BC, accounting for 65–70% of cases[2, 3]. The treatment strategy and the progression of the disease are substantially affected by the diagnosis of BM[4]. With the advent of PET/CT,BC patients underwent F-18 FDG PET/CT have the advantage of a semi-quantitative modality with high accuracy and spatial resolution; it allows imaging most of the body and detecting soft tissue lesions either the primary tumor or distant metastasis beside the skeletal assessment[5]. About 15-20% of BC patients with skeletal metastases have osteoblastic or mixed lesions; however BC gives origin predominantly to lytic lesions[6].

FDG is a glucose analogue that enter the physiologic glycolytic pathway and represents the metabolic activity of the tumor itself [7].

Neoplastic cells of BC produce cellular factors that stimulate the osteoclasts function, yet inhibiting the osteoblasts resulting in a predominantly lytic lesion.

In patients with newly diagnosed BM, they mostly shows osteolytic lesions predominantly, while after treatment a reaction sclerosis occur exhibiting mixed or osteoblastic lesions on CT component. patients that did not respond to therapy showed persistence of metabolically active lytic osseous lesions with no reactive sclerosis on CT images[8].

Classification of immune histochemical features, grade, with histopathological subtypes remaining the cornerstone of characterization and a major guide to the management approach[1]. According to several previously published studies, different metabolic parameters of F-18 FDG PET/CT of the BC primary lesion represented in SUV max, TLG and MTV significantly correlated with clinico-pathological characteristics and biologic behaviour in BC [9-15].However, the clinico-pathological factors have not been established as significant predictors to the metabolic parameters of BM.

To our knowledge, this is the only study with sufficient number of patients that evaluates the relationship between F-18 FDG PET/CT metabolic parameters of bone metastases and clinico-pathological factors in BC. The objective of this prospective study was to assess the correlations between various metabolic parameters of F-18 FDG PET/CT of BM and clinico-pathological factors in BC patients.

MATERIAL AND MEHODS:

This clinical study prospectively recruited patients with pathologically established BC referred for metastatic workup (initial staging, assessment of therapeutic response, restaging) and found to have BM by PET/CT. BC patients with benign bony lesion were eliminated from the study. Also BC patients with insufficient clinico-pathological data or non-confirmed BM were removed. The study was approved by Local Ethical Committee (IRB no. 04-2023-300217) with written informed consents were obtained from all patients. The clinico-pathological features such as Immunohistochemistry (IHC) markers including; ER, PR and HER2neuin addition to

tumor characteristics like; tumor histopathology, nuclear grade were recorded.

F-18 FDG PET/CT protocol

Following a minimum of 4 hours fasting and measurement of blood sugar<200 mg/dL, patient was injected intravenously with approximately 0.1 mCi/kg (4 MBq/kg)F-18 FDG. After injection patient lay quietly in a dim light room and plain water (1.2 Liter) only was allowed. Imaging started 60 minutes following injection. The field of imaging was acquired from skull vault to mid-thigh with arms lifted if feasible using a PET scanner (Biograph Horizon) and 16 slice CT component. The CT studies were performed first for anatomical localization and attenuation correction with subsequent parameters: 120 kV; 3 mm slice thickness; 50 to 100 mAs and beam pitch 0.9 mm. With continuous table motion and speed of 0.9 mm/s, the PET study was performed for 1-2 minutes each bed position. Healthcare syngo via workstation was utilized for processing trans-axial, sagittal and coronal images [7, 16].

Imaging interpretation

Two nuclear medicine physicians performed the visual assessment, interpretation, and data analysis of the images. Any localized osseous FDG uptake more than the adjacent tissues was deemed positive unless it is physiological or benign uptake.

1- Visual analysis: The CT type of the lesions were visually assessed and classified as osteoblastic, osteolytic, mixed, positive FDG uptake with no CT correlate and benign featuring lesion (e.g., arthritic and degenerative changes).

2- Semiquantitative analysis: was conducted by drawing volume of interest around the concerned area to generate the following values (SUV max, SUV mean, SUV peak, TLG and MTV) of the main metastatic bony lesion (the most avid one in case of multiple lesions).

Statistical analysis:

Data was collected and checked by the researcher. IBM-SPSS version 26was used for data analysis. Means, standard deviations, maximum, minimum, and range were computed in descriptive statistics. Correlations between variables were done using Pearson's correlation coefficient test. P value< 0.05was deemed significant.

RESULTS:

Fifty one histo-pathologically proved BC female patients were recruited in this study. Twenty patients with benign or non-confirmed metastatic bony lesions were excluded thus thirty one patients with proved BM lesions were eligible for analysis. Mean age was (55.52± 11.63) years, range(26 -73) years. Most of the patients 19/31 (61.3 %) had left breast cancer, 9/31 (29 %) had right breast cancer, and three patients (9.7%) had bilateral breast cancer. The clinico-pathological characteristics of patients are mentioned in **Table 1**.

PET/CT revealed BM at various sites in the axial and peripheral skeleton. 20 out of 31lesions (64.5%) were found at the axial skeleton (9 in dorso-lumber vertebrae, 5 in skull bones, 3 in sacrum and 2 lesions in the ribs).

11/31 lesions (35.5%) were detected at the peripheral skeleton (5 in pelvis, 3 in femur, 2 scapula and 1 in tibia).

The metabolic parameters of F-18FDG PET/CT for BM (SUV max, SUV mean, SUV mean, MTV and TLG) were generated and shown in **Table 2.**

Table .1 : Patients' characteristics and clinico-pathological factors.

Variable	Number	Percentage %
Pathological subtypes		
invasive duct carcinoma	27	87.1
invasive lobular carcinoma	2	6.5
Mixed	2	6.5
Nuclear grade		
I	3	9.7
II	20	64.5
III	8	25.8
Estrogen Receptors		
Positive	24	77.4
Negative	7	22.6
Progesterone Receptors		
Positive	20	64.5
Negative	11	35.5
Her2 receptors		
Positive	6	19.4
Negative	25	80.6
Molecular Subtypes		
Luminal A	14	45.2
luminal B (Her -ve)	9	29.0
Luminal B(Her +ve)	1	3.2
Her2 Enriched	5	16.1
Triple negative	2	6.5
CT type		
mixed	5	16.1
sclerotic	17	54.8
lytic	8	25.8
no CT correlate	1	3.2

Table .2 Parameters of F18 FDG PET CT for bone metastases

PARAMETER	Mean ± SD	Maximum	Minimum	Range
SUV max	5.4874 ± 2.65984	10.73	1.39	9.34
SUV peak	4.0361 ± 1.98587	8.97	1.23	7.74
SUV mean	3.2806 ± 1.62869	6.51	0.91	5.60
TLG	21.0194 ± 21.66766	93.22	1.67	91.55
MTV	6.9245 ± 7.05755	25.64	0.84	24.80

The BM SUV max compared between different groups according to histopathology, nuclear grading and CT types. BM SUV max was significantly greater in nuclear grade II & III than in nuclear grade I (P value 0.036)

Also BM SUV max was greater in invasive ductal carcinoma (IDC) than invasive lobular carcinoma (ILC) (5.73, 3.80 respectively),

BM SUV max of the osteo-lytic type was higher than that of other CT types of lesions (7.13, 4.91 respectively); as shown in **Table 3.**

So it should be taken into consideration during interpretation of images otherwise, lesions with low metabolic activity may be missed or confused with benign lesions, thus changing stage and management of patients.

Correlations between metabolic parameters of BM and the clinico-pathological factors were calculated and demonstrated in **Table 4**.

Table .3 comparison of BM SUV max in different groups according to nuclear grade, histology and CT type for bone metastases

	No.	Mean	P value
Grade 1	3	3.433	
Grade 2 and 3	28	5.7075	0.036
Invasive ductal carcinoma	27	5.7370	
Invasive lobular and mixed	4	3.8025	0.702
CT type: Osteolytic	8	7.1325	
Other types	23	4.9152	0.987

Table .4 correlations between different metabolic parameters of bone metastases and clinico-pathological risk factors.

	SUV max	SUV mean	MTV	TLG	Peak
Estrogen Receptors	0.363	0.464	0.225	0.199	0.426
progesterone Receptors	0.751	0.562	0.043	0.080	0.793
Her2/neu-receptors	0.746	0.706	0.178	0.311	0.800
Luminal subtype	0.285	0.342	0.298	0.247	0.322
laterality	0.570	0.678	0.588	0.659	0.623
grade	0.312	0.404	0.424	0.548	0.628
Histopathology	0.402	0.329	0.209	0.898	0.407
CT type	0.537	0.455	0.185	0.497	0.434

SUV max: Maximum SUV, SUV mean: mean SUV, MTV: Metabolic Tumor Volume and TLG: Total lesion glycolysis.

No significant correlation was noticed between SUV max and PR (P value 0.75), ER (P value 0.36), Her2 (P value0.74), molecular subtype (P value 0.28), nuclear grading (0.31), histopathology (P value 0.4) and CT type (P value 0.53).

There was no significant correlation between SUV mean and ER (P value 0.46), PR (P value 0.56), Her2 (P value0.71), molecular subtype (P value 0.34), grading (0.4), histopathology (P value 0.32) and CT type (P value 0.45).

The SUV peak showed no significant correlation with clinico-pathological factors; ER (P value 0.42), PR (P value 0.79), Her2 (P value 0.8), molecular subtype (P value 0.32), grading (0.62), histopathology (P value 0.4) and CT type (P value 0.43).

Also there was no significant correlation between MTV and TLG respectively and the tumor characteristics; ER (P value 0.22, 0.19), PR (P value 0.04, 0.08),HER2(P value 0.17,0.31),molecular subtype (P value 0.29, 0.24), grading (0.42, 0.54), histopathology (P value 0.2, 0.89) and CT type (P value 0.18, 0.49).

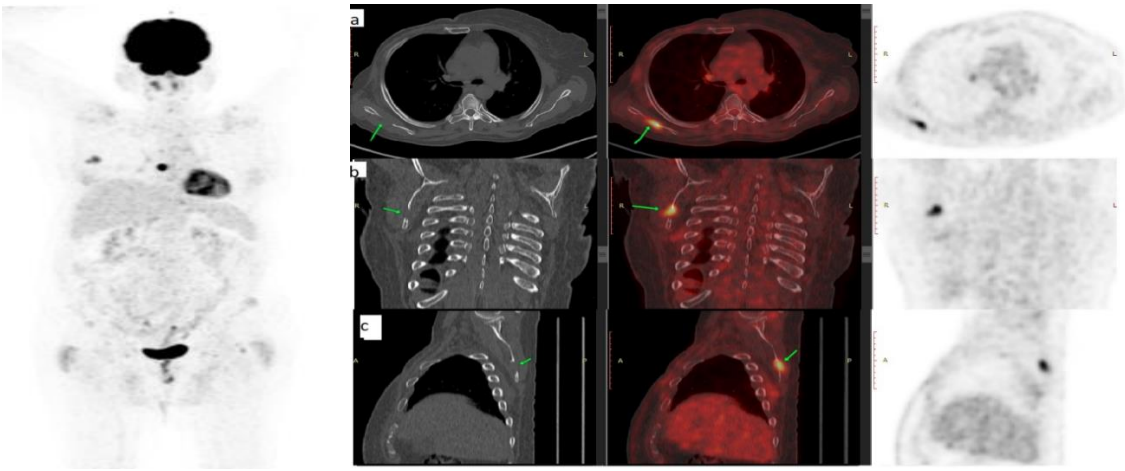

Figure.1 A 64 yrs.-old female with right breast cancer ***PET/CT*** (a: axial, b: coronal, c: sagittal) images showed lytic lesion at right scapula with metabolic parameters (SUV max 5.1, SUV mean 3.07, SUV peak 3.52, MTV 3.2, TLG 9.81)

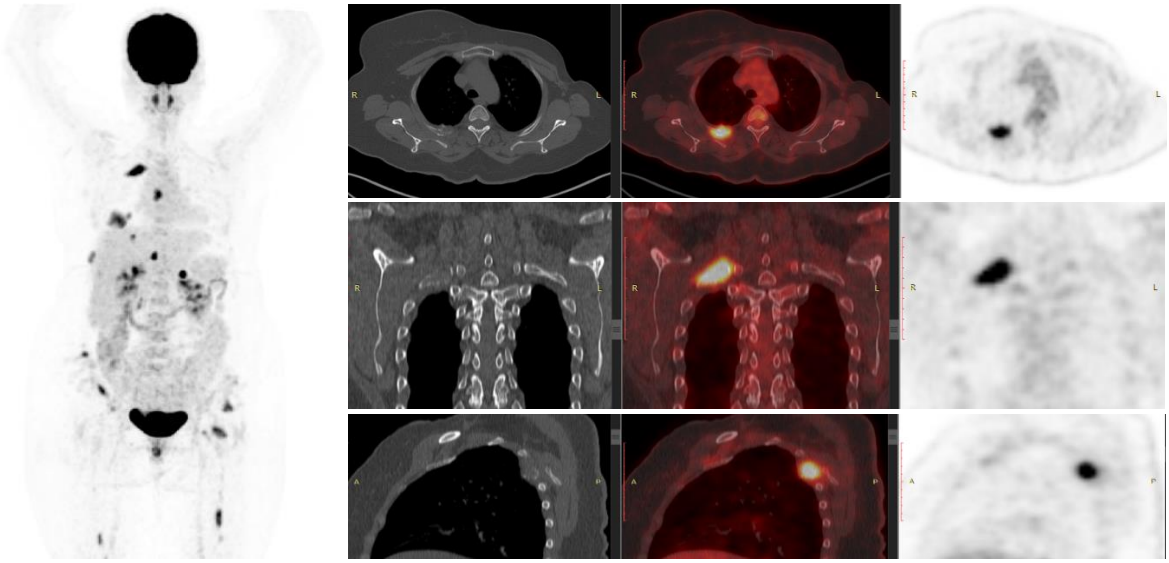

Figure 2.A 43-yrs-old female with left sided infiltrative ductal carcinoma of the breast, underwent PET/CT scan (a: axial, b: coronal, c: sagittal) demonstrates metastatic lytic osseous lesion in right 3rd rib posteriorly, its metabolic parameters (SUV max 8.5, SUV mean 5.3, MTV 5.7, TLG 30.2, peak 6.7).

DISCUTION:

In BC patients, bone is the most frequent location for distant metastases with a prevalence of 65-70% [2, 3].The progress of the disease and the strategy to treatment are greatly influenced by early diagnosis of BM[4]. In the era of PET/CT, researches always seek for improving the patient's quality of life which is achieved by early diagnosis of BM to reduce the consequent skeletal-related events as spinal cord compression and fractures, and aiming to prolong the median survival duration after the diagnosis of BM which has been reported to be approximately is 2.1- 6 years[8].

Classification of immuno-histochemical features, grade, with histo-pathological subtypes remaining the cornerstone of characterization and a major guide to the management approach[1].

There is a considerable association between clinic-pathological characteristics and biologic behaviour in breast cancer and the metabolic PET parameters of the original breast lesion, as represented by SUV max, MTV and TLG according to several previously published studies [9-11]. However, the clinico-pathological factors have not been proved to be reliable predictors of the metabolic parameters of bone metastases. There is lack of information evaluating this issue.

To our knowledge, only one study assessed the relation between BM metabolic parameters and clinico-pathological factors with small number of patients (13 cases of metastatic BC to bone).

Abd El-kareem et al., assessed the relation between the clinico-pathological risk factors and metabolic parameters of different types of metastatic lesions in BC including bone metastases.13 cases of metastatic BC to bone showed no significant correlation to clinico-pathological risk factors; PR (P value 0.056), Her2 (P value 0.667), molecular subtype (P

value 0.439), nuclear grading (0.39) which agreed with our study[17].

In our study there was no significant correlation between histo-pathological subtypes, immuno-histochemical features and the BM metabolic values.

Sugihara *et al*, also agreed with our results that there is no significant difference in BM SUV max between different histological types; IDC and ILC (P value 0.103). However, SUV max was significantly lower for nuclear grade 1 than nuclear grade 2–3 (P = 0.011).These results comes in agreement with our results, where BM SUV max was significantly greater in nuclear grade 2 and 3 than in grade 1 (P value 0.36) while between IDC and ILC there was no significant difference in BM SUV max (P value 0.702)[3].

Dashevsky et al In contrast to our study,. showed that SUV max of BM was significantly greater in IDC patients (median 6.6, range 2.1 – 23.0) than ILC patients (median 3.4, range 1.6 – 12.4, $p = 0.008$), this might be greatly assigned to the more common sclerotic nature of ILC BM. Although in our study BM SUV max was greater in IDC than ILC, the difference was non-significant [18].

Few studies have assessed the relation between PET/CT metabolic parameters and dynamic contrast enhanced MRI perfusion parameters in bone metastases and reported positive correlation between them.[19, 20]

Park et al investigated the relationship between F-18 FDG PET/CT metabolic parameters (SUV max, SUV mean, MTV, and TLG)and intra voxel incoherent motion (IVIM) diffusion-weighted MRI parameters in 19 patients with vertebral bone metastases and positive moderate correlation was found between IVIM parameters and two metabolic parameters (SUV mean and SUV max; ρ = 0.499 and 0.413 respectively, *P value*< 0.01)[19]

Limitation of the study: The breast cancer patients were referred for various study indications some of them received treatment which may affect the study results. Further studies with larger population and homogenous characteristics are recommended to validate our results.

Recommendations: Further future studies are recommended to assess the relation between different metabolic parameters and other types of distant metastases in BC patients like liver and lymph nodes in addition to primary tumor lesion.

CONCLUSIONS:

The different metabolic parameters of F-18 FDG PET/CT for BM showed no significant correlations with clinico-pathological features in BC patients.BM SUV max was significantly greater in nuclear grade 2 and 3 in contrast to grade 1, while no statistical difference in BM SUV max between ILC and IDC as well as in osteolytic lesions and other CT types.

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