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Frequency of skeletal metastasis on 18F-fluorodeoxyglucose positron emission tomography/computed tomography with negative computed tomography at Institute of Nuclear Medicine and Oncology

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ABSTRACT

Background: Skeletal metastasis (SM) with skeletal related events (SREs) occurs in up to 70% of breast cancer and more than 50% of malignant tumors. Whole-body 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) used to characterize the metabolic, anatomic, and morphologic status of suspected bone lesions. SMs are detected using multiple modalities; however, FDG PET/CT may offer a single investigation to detect SM combining the strength of functional imaging and radiological imaging simultaneously. **Aims and Objectives:** This study was to assess the frequency of SM on 18F-FDG PET/CT with negative CT at Institute of Nuclear Medicine and Oncology (INMOL). **Materials and Methods:** This cross-sectional study included a sample of total 50 patients with SM of known primary malignancies who underwent 18F-FDG PET/CT scan at INMOL Cancer Hospital, Lahore. **Results:** Of the 50 patients, we discovered the concordant findings between PET and CT as both PET + /CT + in 38 patients (76%) whereas in 12 patients (24%) with PET + /CT- findings were discordant. CT was unable to detect SM in at least 12 patients. The maximum standardized uptake value (SUV_{max}) of SM in patients with negative CT found to be slightly higher as 5.2 ± 4.1 (range: 2.5–7.8) than in patients with positive CT finding as 4.8 ± 2.8 (range: 3.9–5.8) with P = 0.76. P-value is insignificant this means that high SUV is not typical or conclusive evidence of metastasis. **Conclusion:** Despite limited data, this study has demonstrated high concordance between FDG PET and CT scan in detecting SM. Furthermore, the study has shown that 18F-FDG PET appears to have slightly better detection efficiency as compared to CT for identification of SM which is statistically insignificant. The study demonstrated that SUV is higher in PET and CT discordant cases; however, it does not provide conclusive information favoring diagnosis of SM.

Key words: 18 F-fluorodeoxyglucose positron emission tomography/computed tomography; Computed tomography negative; Positron emission tomography positive; Skeletal metastasis

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INTRODUCTION

Skeletal metastasis (SM) is a cancer of bone that has originated from another site. The third most frequent site of metastasis after lung and liver is bone. The breast and prostate cancer involve formation of majority of SM. Three types of SMs including osteolytic, osteoblastic, and mixed lesions. Osteolytic metastases are characterized by normal

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bone destruction and osteoblastic lesions are characterized by new bone formation whereas individual metastatic lesion containing both lytic and sclerotic components termed as mixed lesions.[1] Hematologic malignant tumors do not cause bone disease frequently, well multiple myeloma is the most frequent cancer to involve bones.[2] SMs with skeletal related events (SREs) occur in up to 70% of breast cancer and more than 50% of malignant tumours.[3]

Among solid cancers, breast, lung, prostate, kidney, and thyroid cancer account for 80% of all SMs. Although many other types of primary malignant tumors can metastasize to bones, including, not restricted to, melanoma, sarcoma, and malignant tumors of gastrointestinal tract, as well as carcinoma of uterus.[4]

Common symptoms include cancer related pain in body, hypercalcemia, pathological fractures most commonly in ribs and vertebrae, and spinal cord compression.[5] Its distribution is determined by the primary malignant tumor. The most common sites include vertebral column, pelvis, sacrum, and proximal femur.[6] Skeletal malignancies and other conditions can disturb the OPG-RANKL-RANK signaling pathway and stimulate the increased osteoclast formation, consequently accelerating bone resorption and results in bone loss.[7]

The standard imaging modality for imaging of cancer is computed tomography (CT) but it may not be able to detect metastasis that is constricted to the bone marrow or cortex and without any obvious bone loss.[8] ^{18}F-fluorodeoxyglucose positron emission tomography coupled with simultaneously obtained CT (^{18}F-FDG PET/CT) to visualize the glucose metabolism, is currently a diagnostic tool in oncology. In patients diagnosed with malignant melanoma or lung cancer, for instance, ^{18}F-FDG PET-CT has substituted other methods for SMs detection, so the metastases can be detected with high sensitivity as well as specificity because they are metabolically active tumors. Similarly, metastases can also be detected in soft tissues because of high tumor contrast. Thus for complete staging of these types of tumors among others, ^{18}F-FDG PET-CT can be used.[9] ^{18}F-FDG PET showed sensitivity and specificity of 98% and 56%, respectively, in the detection of SMs. One of the major advantages of ^{18}F-FDG PET is it's ability to compare the maximum standardized uptake value ($SUVma_x$) of metastatic bone deposits between serial studies, which provide an objective measure of the response to therapy.[10]

The purpose of the study is to assess the frequency of SM on ^{18}F-FDG PET/CT with negative CT at Institute of Nuclear Medicine and Oncology (INMOL).

Researches globally recommended CT, bone scan, and FDG-PET/CT for diagnosis, staging, and therapy response of cancer with bone metastases. Use of PET/CT in cancer diagnosis and staging is less due to high cost of scan and less work done on this modality in Pakistan. This study will assess the frequency of bone metastases detected in patients undergoing FDG-PET and its comparison with CT for characterization. So that the radiation dose can be reduced in patients by using FDG-PET only without additional diagnostic CT.

Aims and objectives

This study was performed at INMOL with aim to assess the frequency of SM on 18F-FDG PET/CT with negative CT.

MATERIALS AND METHODS

After obtaining FMH College of Medicine and Dentistry Institutional Review Board (IRB) approval under the letter number of FMH-03/12/2021-IRB-1047, this study was conducted at INMOL Cancer Hospital, Lahore. The duration of the study was between October 2021 and February 2022. A sample of 50 patients with bone metastases was selected.

Sample size (n)= 50[11]

$$n = \left(\frac{Z\, \alpha/2}{d} \right) p\,(1-p)$$

Adult patients who provided informed consent and complete medical record, underwent ^{18}F-FDG PET/CT at INMOL Cancer Hospital, Lahore, were included in the study. Whereas, children less than 18 years of age and patients without CT scan were excluded from the study.

According to the European Association of Nuclear Medicine procedure guidelines, 250–350 MBq ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) radiopharmaceutical was injected in this scan with recommended interval of 45–90 min between injection and start of acquisition.^{18}F-FDG was obtained from onsite cyclotron GE PET trace and administered to patient after passing through quality control test. The examination was performed at PET-CT scanner (Discovery ST) with 16 slice-CT and bismuth germinate PET scanner. The patient was instructed to fast for at least 4 h and blood sugar level was checked before receiving the radiopharmaceutical dose. The patient was asked to lie supine on examination table with arms elevated and supported above head. For PET scanning, standard six-bed position scan was acquired from thighs toward top of skull at the rate of 3 min for one bed position. A low-dose CT was acquired earlier form vertex to thighs using 120–140 kVp and 80 mAs for anatomic localization and attenuation correction purposes.

Attenuation correction was done on PET images according to CT data and using iterative algorithm reconstruction was done and reformation in transaxial, coronal, and sagittal views.[12] PET/CT images were reviewed in analysis at processing workstation using ADW 4.1 GE software.

Lesions were semi-quantitatively analyzed using SUV_{max}, defined as the ratio of maximum regional FDG concentration to injected radioactivity per gram of patient body weight.

$$SUV = K \times [b.w/A_{inj}] \times 1000\ g/kg$$

Where, K shows calibrated pixel value, b.w is patient body weight, and A_{inj} is injected radioactivity.

SUV_{max} was determined for region of interest drawn around suspected skeletal lesion on PET/CT images which were attenuation -corrected. An increased FDG -uptake was taken as positive finding at visual analysis while the absence of uptake was taken as a negative finding. Lesions with SUVmax >4.5 were considered as abnormal lesion whereas less than this value considered as normal. CT images were evaluated using CT planes corresponded to planes on FDG PET. CT scans were displayed with bone and soft-tissue window. CT determined the morphological changes of bone.

Statistical analysis

A patient-based analysis was performed, and data were entered using IBM-SPSS v-23 software. The continuous data such as age and SUV_{max} were expressed as mean±SD, while categorical data such as gender and metastatic sites as frequency and percentage. A *t*-test was applied to evaluate the ^{18}F-FDG uptake intensity (SUV_{max}) differences in different groups of SMs. $P<0.05$ was taken as statistical significance.

RESULTS

Out of total sample of 50 patients, majority subjects were male 68% and females 32% with mean age of 58.7±11.207 (Table 1).

Of those 50 patients, 38 (76%) were found to be positive for skeletal lesions on both PET and CT while the remaining 12 were PET positive/CT negative for bone lesions with primary malignancies such as lung (n=8), prostate (n=2), breast (n=1), and renal cell carcinoma (n=1) (Table 2).

DISCUSSION

In this study, we examined the association between ^{18}F-FDG uptake on PET and the structural changes of SM on CT of the PET-CT. SM is a major complication of several malignancies and related with increased risk of SREs such as spinal cord compression and pathological bone fractures which, in turn, reduce the quality of life. It is estimated that majority of those deaths resulting from metastatic cancer involves the skeleton. ^{18}F-FDG PET/CT plays a significant role in the identification and staging of tumors by showing metabolic activity of tumors, which makes it better than other imaging methods.[11] A study conducted by Du et al., suggests that ^{18}F-FDG uptake indicates tumor activity of bone metastases of breast cancer independent of morphological features while X-ray morphology changes differ enormously with time within the patients.[13] A study done by Abd-Elkader et al., revealed that FDG-PET/CT was capable of identifying SMs at an early stage, even when there is no structural change identified on CT.[14] In

Table 1: Characteristics of patient population

Patients	n (%)
n (total)	50
Gender	
Male	34 (68)
Female	16 (32)
Primary malignancy	
Lung cancer	21
Breast cancer	10
Renal cell	9
Prostate	7
MUO	2
Thyroid cancer	1
Metastatic sites on ^{18}F-FDG PET/CT	
PET findings	**n (%)**
Multiple metastatic sites	29 (58)
Single region	21 (42)
Pelvis	8
Rib cage	5
Thoracic spine	5
Lumbar/sacral spine	2
Appendicular skeleton	1
CT findings	**n (%)**
Multiple metastatic sites	18 (36)
Single region	20 (40)
Pelvis	10
Rib cage	4
Thoracic spine	3
Appendicular skeleton	2
Lumbar/sacral spine	1

Table 2: Comparison of FDG PET and CT for Detection of Skeletal Metastasis and SUV distribution

FDG-PET/CT findings	PET+/CT+	PET+/CT-
Total n=50	38	12
% of total	76%	24%
PET SUVmax		
Mean±SD	4.8±2.8	5.2±4.1
Range	3.9–5.8	2.5–7.8

P=0.76, PET: Positron emission tomography, CT: Computed tomography

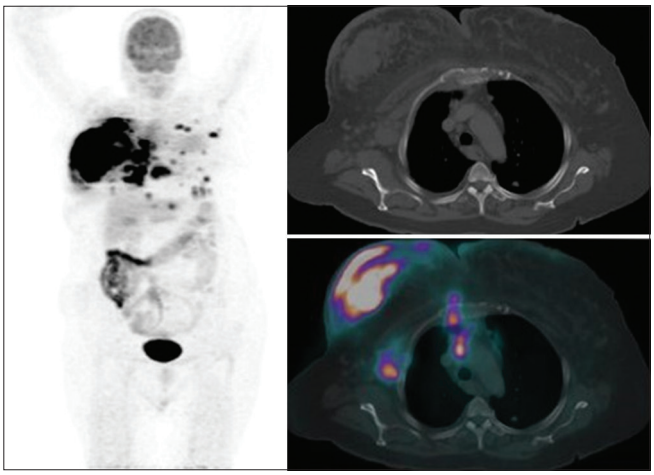

Figure 1: 18F-fluorodeoxyglucose positron emission tomography/computed tomography of patient with the right breast carcinoma demonstrating hypermetabolic right breast mass, axillary and mediastinal nodes, and metastatic deposit in sternum

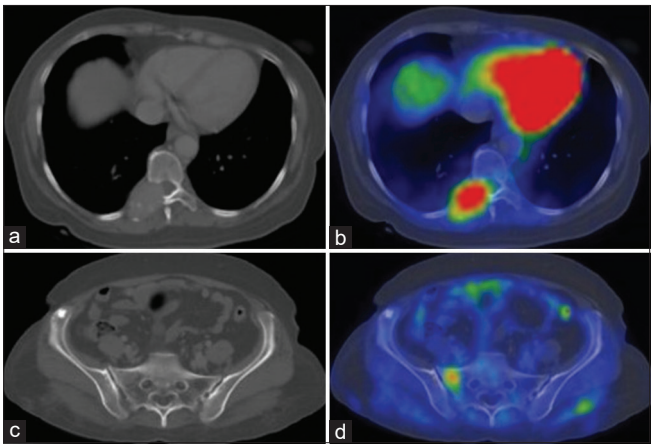

Figure 2: A diagnosed patient of lung carcinoma. (a) Computed tomography (CT) bone window demonstrating destructive lesion in the right pedicle and transverse process of T-10 vertebra, (b) Fused axial positron emission tomography CT (PET-CT) image showing metastatic deposit in the right pedicle and transverse process of T-10 vertebra, (c) CT finding negative for right sacral ala, and (d) fused axial PET-CT demonstrating metastatic deposit in the right sacral ala

our study, we included a sample of 50 patients with SM of various malignancies. In this study population, we found that 68% of male and 32% of females with mean age of 58.7 having SMs with primary diagnosis such as lung cancer (n=21), breast cancer (n=10), renal cell carcinoma (n=9), prostate (n=7), MUO (n=2), and thyroid cancer (n=1). In our study, we correlated the difference between PET and CT of ^{18}F-FDG PET/CT in SMs detection to the process by which radiotracer uptake occurs in metabolically active tumors. We found the concordant findings between PET and CT as both PET+/CT+ in 38 patients (Figure 1). In 12/50 patients, the findings between two modalities were discordant with PET positive and CT negative pattern. It means that CT was unable to detect SMs in at least 12 patients (24%) with primary malignancies such as lung (n=8), prostate (n=2), breast (n=1), and renal cell (n=1). Our findings are similar to the findings of retrospective study conducted by Ahmed et al., in which they found that PET showed the FDG-avid SM with normal CT in at least 25% of patients. Hence, their conclusion was that ^{18}F-FDG PET is sensitive in detection of SMs.[11]

Our results showed that PET demonstrated multiple metastatic sites in 58% of patients and single regions in 42% of patients whereas CT showed multiple metastatic sites in 36% of patients and single regions in about 40% of patients. This shows the strength of PET scan that it identifies SMs which may be missed on CT, further augmenting hypothesis that PET-CT alone may replace full dose diagnostic CT, thus preventing patient from excessive radiation exposure. CT showed appendicular SM in 4% of patients, lumbar/sacral spine in 2%, pelvis in 20%, rib cage in 8%, and thoracic spine metastases in 6% of patients. PET showed (Figure 2) appendicular SM in 2% of patients, lumbar/sacral spine in 4% (Figure 2), pelvis in 16%, rib cage in 10%, and thoracic spine metastases in 10% of patients. Also for single region SM, the performance of PET was better than CT. SUV of SM in patients with negative CT found to be slightly higher as 5.2±4.1 (range: 2.5–7.8) than in patients with positive CT findings as 4.8±2.8 (range: 3.9–5.8) with P=0.76. P value is insignificant this means that high SUV is not typical or conclusive evidence of metastasis. Our SUVmax findings are similar to results of study conducted by Evangelista et al.[15]

Limitations of the study

Our study has a limitation that we included the patients with positive PET findings of all FDG-PET/CT scans. Another limitation is that we did not compare the PET/CT with other imaging modalities.

CONCLUSION

Despite limited data, this study has demonstrated high concordance between FDG PET and CT scan in detecting SM. Furthermore, the study has shown that 18F-FDG PET appears to have slightly better detection efficiency as compared to CT for the identification of SM which is statistically insignificant. The study demonstrated that SUV is higher in PET and CT discordant cases; however, it does not provide conclusive information favoring diagnosis of SM.

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Authors' Contributions:
MF- Literature survey, implementation of study protocol, data collection, data analysis, prepared first draft of manuscript, manuscript preparation, and submission of article; **MNY-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **SDH-** Design of study, statistical analysis, and interpretation; **SZA-** Review manuscript and preparation of tables; **RB-** Review manuscript and literature survey; and **MWA-** Manuscript revision and preparation of figures.

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