ONCOLOGY, Original Article

Does PET/CT Have an Additional Value in Detection of Osteolytic Bone Metastases.

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Abstract

Introduction: Although radionuclide bone scanning with technetium 99m (99mTc) methyl diphosphonate has been the standard means of evaluating individuals suspected of having bone metastases, 18F-FDG PET may be comparable in accuracy, depending on the tumor type. 18F-FDG PET has been reported as being appropriate for detecting bone metastases specially lytic and mixed lesions. More recently, integrated PET/computed tomography (CT) has revealed various implications for evaluating bone metastases.

Aim of the study: To evaluate the sensitivity, positive predictive value (PPV) of 18F-FDG PET/ (CT) in the identification of malignant bone lesions when the PET and CT findings are concordant and discordant.

Patients and Methods: Fifty four patients (25 female and 29 male patients; age range, 10–74 years) with 158 PET/CT detected bone lesions were included in this study. The sensitivity, PPVs of the integrated PET/CT and of each modality, CT and PET components of the examination were calculated.

Results: Of the 82 bone lesions with positive findings at both PET and CT, 73 bone lesions were malignant and 9 were benign lesions with sensitivity 100% and PPV of 89%. Of the 36 bone lesions with positive findings at PET
and negative findings at CT, 25 were malignant and 11 were benign bone lesions with sensitivity of 46.2% and PPV of 69.4%. Of 40 bone lesions with negative findings at PET and positive findings at CT, 29 were malignant and 11 were benign bone lesions with sensitivity of 53.7% & PPV of 72.5%.

Conclusions: PET/CT has high sensitivity & PPV for detection of bone metastases than either PET or CT as a separate modalities. FDG PET has high sensitivity & PPV in lytic lesions than the sclerotic ones.

Introduction: Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is a well-established modality for staging, restaging, and treatment monitoring in oncology patients (1–3). A key issue that is less well studied is the performance of FDG PET in accurately depicting bone metastases that would potentially have a large effect on patient treatment. Although radionuclide bone scanning with technetium 99m (99mTc) methyl diphosphonate has been the standard means of evaluating individuals suspected of having bone metastases, 18F-FDG PET may be comparable in accuracy, depending on the tumor type (4–9). 18F-FDG PET has been reported as being appropriate for detecting all types of bone metastases

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including lytic, sclerotic, and mixed lesions, however, accumulating data suggest that 18F-FDG PET is more sensitive in detecting lytic metastases than sclerotic metastases. The latter type of metastases may show uptake of lower intensity compared with lytic lesions or even no increased uptake at all (9). More recently, integrated PET/computed tomography (CT) has revealed various implications for evaluating bone metastases (10–14). First, integrated PET/CT can help better differentiate whether 18F-FDG avid lesions are truly located within bone versus adjacent soft tissue (15).

Second, the CT data are a potentially valuable addition to the 18F-FDG PET information. Bone lesions that are suspicious for malignancy at both the PET and CT portions of a PET/CT examination are likely to be malignant, however lesions that are positive at one portion of the examination but appear benign at the other are challenging lesions.

The aims of our study are to evaluate the sensitivity & positive predictive value (PPV) for 18F-FDG PET, CT and PET/CT in the identification of malignant bone lesions.

Patients and Methods

54 patients out of 632 patients with various types of malignancy were referred for PET/CT. 158 bone lesions were identified in these 54 patients. The group is formed of 29 males & 25 females with their age ranging from 10 years to 74 years. Patients had a variety of tumor types as presented in (Table 1). All bone lesions identified at PET, CT, or both PET & CT were recorded.

Table 1: Patient Characteristics of the 54 patients with bone lesions included in the study.

Parameters	
No. of Patients (n= 54)	
Tumor type	
Breast	19
Lung	15
Colo-rectal	12
Uterus	2
Osteo-sarcoma	2
Naso-pharyngeal	2
Metastasis of unknown primary	2
Sex	
Male	29
Female	25
No. of lesions (n=158)	
According to CT picture: **90 lytic** lesions & **32 sclerotic** lesions	
According to only PET: 36 lesions	
Indication of PET/CT	
Initial staging	5
Assessment of treatment response	36
Detection of recurrence	13

PET/CT Scanning

All patients fasted for 6 h prior to examination. Blood glucose level was measured and ranged from 80 to 130 mg/dl. The acquisitions started 45–60 min after intravenous injection of 18F-FDG (minimum dose 5mCi & maximum dose 15mCi 18F-FDG) according to age and weight.

CT image acquisition were as follows: An initial scout view was obtained with 30 mAs and 120 kVp, followed by spiral CT at 0.8 second per rotation with 100 mAs, 149 kVp, section thickness of 4 mm.
Whole-body PET scan was acquired in overlapped bed positions from mid thigh to base of skull, 3 minutes for each bed position. The images were reconstructed by iterative algorithm. Attenuation correction was applied in all the scans by means of CT. Semi-quantitative estimation of standardized uptake value (SUV) was done for all cases. No specific preparation was given to the patients, apart from anaesthesia that was administered to pediatric patients if needed.

The following PET criteria were used in the diagnosis of a positive lesion: visual assessment of signal intensity by means of comparison to physiologic structures such as the liver; visual assessment of the focality and location of each lesion and semi-quantitative standardized uptake value measurements (SUV greater than 2.5).

The CT criteria used for the diagnosis of malignant bone lesions were identification of focal-appearing lytic or sclerotic lesions. Additional features that favored malignancy included marrow replacement, soft-tissue component, endosteal scalloping, cortical breakthrough, periosteal reaction, expansile appearance, or associated pathological fracture.

Follow-up

For benign lesions, clinical follow-up was the primary means of confirmation. Specifically, this required that the patient remained free of symptoms and/or the lesions remained stable with no changes at subsequent imaging for at least 6 months.
For malignant lesions, assessment of malignancy was based on results of histopathologic examination (3 of 158 lesions), or follow up with at least one of the following criteria: (a) Lesion progression at subsequent imaging examinations (bone scanning, magnetic resonance [MR] imaging, dedicated CT, or additional PET/CT) (101 of 158 lesions), (b) lesions were positive at the initial PET/ CT examination and then regressed after treatment with chemo or radiotherapy (16 of 158 lesions), and (c) bone disease was documented with clinical response on physical examination (9 of 158 lesions).

Statistical Analysis

We calculated the sensitivity, PPV for the stand-alone PET, CT if each was used alone and for PET/CT for correctly identifying malignant bone lesions in several different scenarios that can occur: *(a)* lesions that are positive at both the PET and CT portions of the examination, *(b)* lesions that are positive at PET and negative at CT, and *(c)* lesions that are negative at PET and positive at CT. In addition, we also considered the effect of several modifying factors i.e. the received treatment (chemotherapy, radiotherapy or hormonal), and the tumor type that could affect the PPV and sensitivity of PET/CT.

Results

The 54 patients included in this study showed 158 bone lesions suspicious for malignancy at either the PET alone (36 lesions, 22.7%), CT alone (40 lesions 25.3%) or at both PET & CT (82 lesions, 51.8%). Of the 82 lesions identified as positive for malignancy at both the PET and CT portions of the examination, 73 lesions proved to be malignant and 9 lesions were benign, 65 lesions out of the 73 malignant bone lesions are lytic and 8 are sclerotic.

The nine benign lesions include (a case of osteosarcoma with suspected bone lesion at the site of limb salvage on MRI, a case of breast cancer with solitary marrow lesion at Dv12 on MRI, a case of naso-pharyngeal carcinoma with solitary sclerotic rib lesion, the other 6 cases have equivocal lesions over dorso-lumbar vertebrae in conventional CT). These lesions were considered benign by two subsequent MRI at 3 & 6 months interval(case 1,2), whereas follow up PET/CT (the other cases) showed no change of the previously detected lesions as well as absence of clinical findings or evidence of disease progression allover the 6 months follow up.

Out of the 73 malignant lesion, 9 lesions were considered malignant through clinical evaluation(sever pain and tenderness over the demonstrated 9 vertebral lesion), 12 lesions showed healing after chemo/radiotherapy, 52 lesions proved to be malignant by other modalities(MRI, bone scan) as well as progression on the sequentional imaging. The PPV & sensitivity of combined PET/CT for detection of malignant bone lesions bone were 89 % and 100% respectively (Fig.1, Table 2). The maximum SUV for these lesions ranged from 3.9 to 13.2 with mean SUV of 9.1

The PET and CT findings were discordant in 76 lesions of the 158 bone lesions (48%). In the 36 lesions that were positive at the PET and negative at the CT portions of the integrated examination. 25 considered to be malignant (2 lesions by biopsy, 14 lesions by MRI, 4 lesions showed response to chemo/radiotherapy, and 5 lesions showed progression on subsequent imaging). Whereas 11 lesions were benign being of stationary course with no development of other lesions.

Thus the PPV and sensitivity of PET were 69.4% & 46.2 % respectively (Fig 2, Table 2).

Table 2: Sensitivity, PPV of PET, CT and combined PET/CT in evaluation of malignant bone lesions.

	PET	CT	PET/CT
Senistivity	46.2%	53.7 %	100%
PPV	69.4%	72.5 %	89%

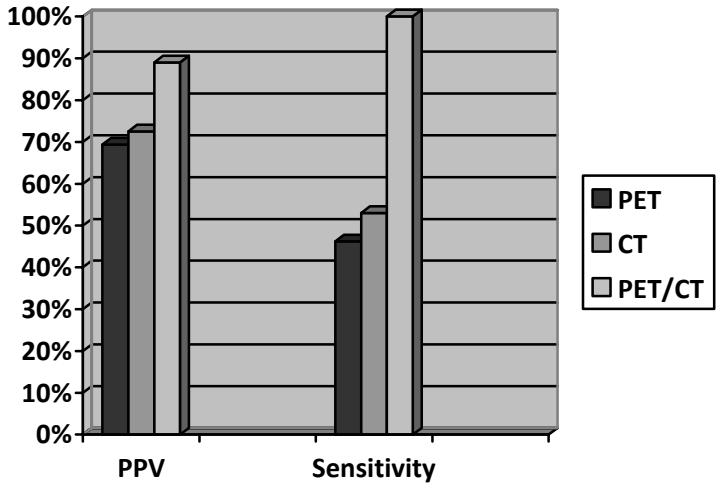


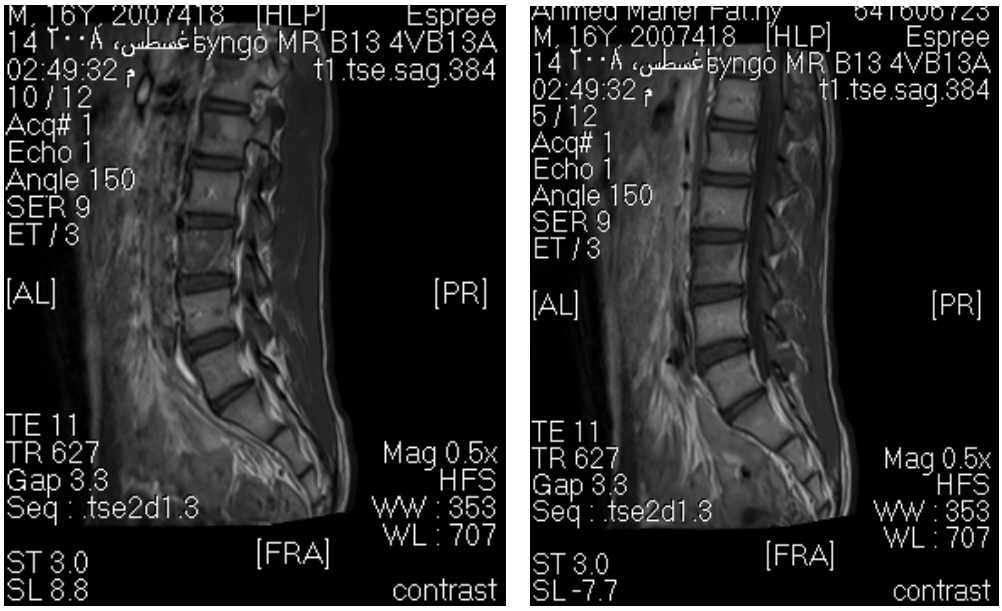
Fig. 2: Positive predictive value & Sensitivity of PET alone, CT alone and PET/CT for malignant bone lesions.

The maximum SUV of the malignant lesions ranged from 6.4 to 12.3 with mean SUV 8.9, While that for benign lesions ranged from 2.3 to 4.8 with mean SUV 3.2.

Of the 40 lesions proved malignant at CT (15 sclerotic, 25 lytic lesions) that were negative at PET 29 lesions of them were malignant as they showed progression on subsequent imaging, The other 11 lesions were benign bone lesions as they showed stationary course with no development of other lesions.Thus the PPV & sensitivity of the stand-alone CT were 72.5% & 53.7 % respectively (Fig 2, Table 2). Among 29 malignant CT lesions, 19 lesions appeared as lytic and 10 lesions appeared sclerotic. Also, 5 of the 11 benign lesions were lytic and 6 lesions were sclerotic.

The PET/CT and the stand alone CT detected 122 malignant bone lesions (82 lesions were detected by PET/CT and 40 lesions by CT alone). 90 were lytic lesions and 32 were sclerotic lesions. PET/CT was able to detect 65 malignant lytic lesion out of the 90 lytic bone lesions (72%). While it was able to detect only 8 sclerotic lesions out of the 18 malignant sclerotic lesions (44.47). False positive uptake was evident in 9 sclerotic benign bone lesions. Accordingly the PPV & sensitivity of PET/CT in lytic bone lesions were 100%, 72% and in sclerotic bone lesions were 47.5 % & 44.4% respectively (Table 3).

A.



B.

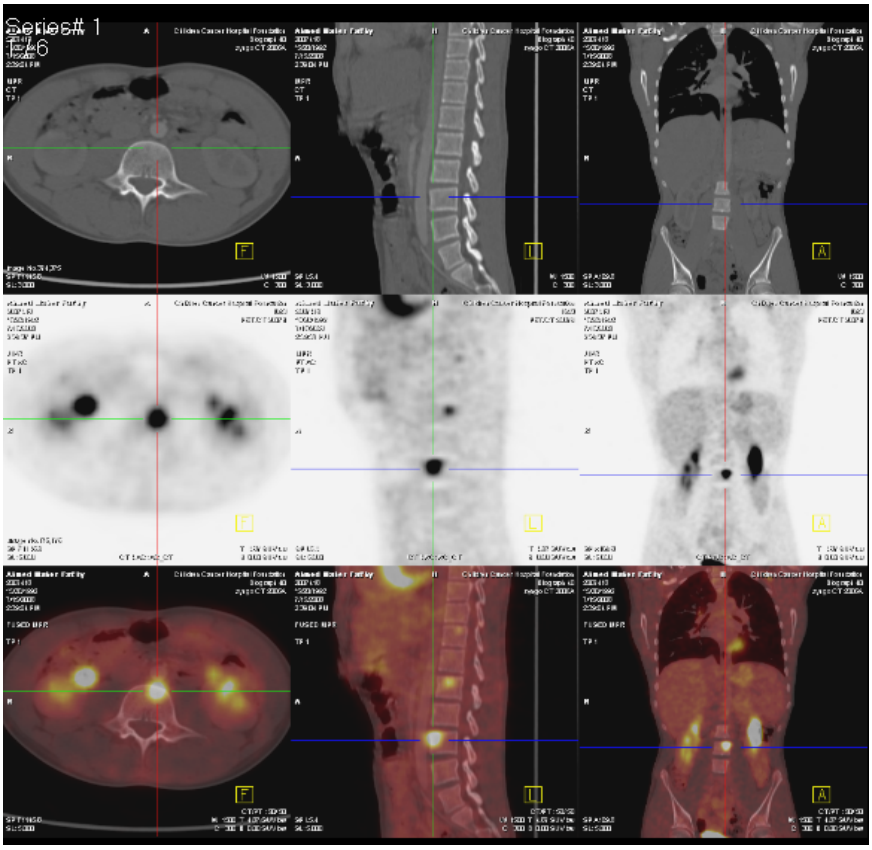


Fig. 1(A, B): MRI & PET/CT images showing focal marrow lesions in LV1,3 as well as active FDG uptake with no underlying CT changes in the stand alone CT.

Table 3: Sensitivity, PPV of PET/CT in lytic and sclerotic bone lesions.

	Lytic lesions	Sclerotic lesions
PPV of PET/CT	100 %	47.5%
Sensitivity of PET/CT	72 %	44.4%

Correlation of the PET/CT results with bone scan was feasible in 23 patients with 55 bone lesions (47 lytic and 8 sclerotic) detected on PET/CT. Bone scan was able to detect 41 lesions(16 in cases of breast cancer, 8 in colorectal carcinoma, 11 in bronchogenic carcinoma, 6 in others).Of the 41 lytic bone lesions detected by PET/CT, bone scan has sensitivity of 87.2 % , however it detected all the 8 sclerotic lesions.

Tumor Type

PET/CT detected 24 bone lesions(20 lytic lesions & 4 sclerotic lesions) in the 17 cases of breast cancer, 12 bone lesions(10 lytic lesions and 2 sclerotic) in the 8 cases of colorectal carcinoma 16 bone lesions, (14 lytic lesions and 2 sclerotic) in the 12 cases of bronchogenic carcinoma.

We attempted to compare the PPVs of the different primary tumor type. However, because of the small sample sizes these differences were not statistically valid.

Discussion

When interpreting a PET study, differences in 18F-FDG avidity may be found in coexisting lytic and sclerotic lesions in the same patient ***(Petren-Mallmin et al;1998)***. It is assumed that the greater avidity of 18F-FDG in lytic metastases reflects the high glycolytic rate and the relative hypoxia characterizing this type of lesion, in contrast to sclerotic metastases, which are relatively acellular, less aggressive, and not prone to hypoxia[17].

Using integrated PET/CT systems, each lesion may be characterized by its uptake and morphologic appearance. ***Metser et al; 2004*** reported an increased 18F-FDG uptake in 100% of metastases presenting as lytic lesions on the CT part of the PET/CT study and in 88% of the metastases presenting as sclerotic lesions(18). In our study we found that PET/CT has 100% PPV & 72% sensitivity in detecting lytic lesions and 47.5 % PPV & 44.4 % sensitivity in sclerotic lesions.

Cook et al.;1998 compared 18F-FDG PET with 99mTc MDP bone scintigraphy in twenty three patients with skeletal metastases from breast cancer. They concluded that 18FDG PET is superior to bone scintigraphy in the detection of osteolytic bone lesions, on the other hand osteoblastic metastases show lower metabolic activity and are frequently undetectable by PET. (Cook et al; 1998). In the current study PET/CT was able to detect 24 bone lesions (20 lytic lesions & 4 sclerotic lesions) in 17 cases of breast cancer [20].

Also,Cook and Fogelman ; 2001 reported a generally higher detection rate of bone metastases by 18F-FDG PET compared with bone scan in patients with breast cancer(9). In our study, PET/CT was able to detect 24 bone lesions (20 lytic lesions & 4 sclerotic lesions) in 17 patients with breast cancer as compared to bone scan which was able to detected only 16 lesions of these 20 lytic lesions and all the 4 sclerotic lesions, in addition to 3 more lesions that were only detected on bone scan as they showed lower level of FDG uptake.

In the present study,73 out of 82 bengin lesions that were positive by PET/CT were

malignant with sensitivity 100 % and PPV 89%. 25 lesions had positive findings at PET and negative findings at CT were malignant and 11 lesions were benign with sensitivity of 46.2 % and PPV of 69.4. 29 lesions with negative findings at PET and positive findings at CT, were malignant and 15 lesions were benign with sensitivity of 53.7% & PPV of 72.5 %.

Also,Taira et al.;2007 studied 59 patients with 113 bone lesions at detected on PET alone, CT alone and PET/CT. 46/47 lesions detected by PET/CT were malignant with PPV 98% . 19/31 lesions with positive findings at PET and negative findings at CT, were malignant and 12 were benign, for a PPV of 61%. 6/35 lesions with negative findings at PET and positive findings at CT, six were malignant and 29 were benign, for a PPV of 17%. Independently, the PPV of all lesions with positive findings at PET was significantly higher than that of all lesions with positive findings at CT.

Conclusions

- PET/CT has high sensitivity & PPV for detection of bone metastases than the stand alone PET or CT.
- F-18 FDG PET has high sensitivity & PPV in lytic Lesions than the sclerotic ones.

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