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ORIGINAL ARTICLE

Utility of 18F-FDG Positron Emission Tomography (PET)/Computed Tomography (CT) in the evaluation of primary malignant bone tumors

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ABSTRACT

Background: The pathophysiology of bone malignancies has become better understood owing to the appearance of hybrid positron emission tomography/computed tomography (PET/CT) modality which has a huge influence on treatment strategies. The study aimed to clarify the supplementary benefits of PET/CT in the staging of primary bone malignancies and the assessment of post-therapeutic response.**Methods**Thirty-six patients with pathologically proven primary malignant bone tumors were included in this cross-sectional prospective study. Every patient had a PET/CT scan performed for staging/restaging and evaluation of therapeutic response. The gold standard reference to verify the accuracy of the study results was biopsy/histopathology.**Results:** FDG-PET/CT demonstrated higher sensitivity and specificity than CT in the evaluation of therapeutic response and follow-up of cases to detect residual/recurrent lesions with sensitivity 90.9%, specificity 100%, positive and negative predictive values of 100% and 87.5% respectively and overall accuracy 94.4%. Meanwhile, CT sensitivity was 81.8%, specificity 71.4%, positive and negative predictivevalues were 81.8% and 71.4%, and accuracy 77.8%.

Conclusions: As a promising non-invasive diagnostic method for evaluating primary bone malignancies; PET/CT is an imaging modality that offers a high specificity, sensitivity, and accuracy.

Keywords: Primary malignant bone tumors, FDG, PET, CT.

INTRODUCTION

Primary bone malignancies are rare tumors arising from bone mesenchymal cells accounting for about 0.2% of all cancers worldwide. There are many subtypes but osteosarcoma, chondrosarcoma and Ewing sarcoma are the commonest. These tumors are often aggressive and necessitate early diagnosis, using radiological imaging and tumoral histopathology. Surgical excision is the basis of curative treatment, with adjuvant chemo and radiotherapy **[1]**

Diagnostic imaging has a key role in the assessment and treatment of bone malignancies. Different imaging modalities as X-rays, CT scanning, MRI and scintigraphy rely primarily on tumoral morphological features making them incapable of staging tumors accurately and unable to distinguish between alterations that occur after therapy and residue/recurrent lesions as a result of radiation or surgery-induced deformation of the local anatomy **[2]**.

Furthermore, because positron emission tomography (PET) relies solely on functional imaging employing different radiotracers to detect metabolic avid lesions rather than anatomical localization, it has limited role in tumoral staging **[3]**.

The development of fused FDG PET/CT modality has improved our understanding of the pathogenesis of cancers, which has a major impact on how various tumors are evaluated, staged, and managed. This has led to improved treatment outcomes, quality of life, and higher survival rates **[4]**.

Also, it exhibits high specificity and accuracy with the advantage of having whole body scanning range offer a chance for more clinical purposes. In addition to the functional data provided by PET imaging, at the same scan, we can obtain significant morphological information from CT scanning **[5]**.

FDG-PET is also utilized to assess therapy response, determine recurring lesions, and stage pathologically proved malignancies more precisely. Additionally, it offers a non-invasive technique for grading malignancies based on the degree of FDG absorption; which is considered a valuable indicator for prognosis **[6]**.

It has been demonstrated that the survival of osteosarcoma can be extended to 65–70% when chemotherapy and surgery are combined. Most of metastases are found in the lung, with the remainder in bone, lymph nodes, and remaining regions of body. As a result, the prognosis for individuals with radiographically detectable distant metastases is poor. Furthermore, 13.5% of sarcoma patients experience a local recurrence following limb-salvage procedures. Thus, precise and early identification of metastatic deposits and local residue/recurrent lesions is essential for osteosarcoma treatment and risk assessment **[7,8]**.

Because PET/CT is not impacted by imaging artifacts, it is advantageous in evaluating local recurrence **[9]**.

Our study aimed to clarify the additional utility of PET/CT in staging of primary bone cancers, evaluation of post-therapeutic response as well as revealing residue or metastasis in regular follow-up studies.

METHODS

Thirty-six patients with pathologically verified primary malignant bone tumors were presented to the radiology department for this cross-sectional prospective study. The study was carried out throughout the period from March 2023 to June 2024.

Written informed consent was obtained from patients, and the study protocol was approved by the institution's medical ethics committee and faculty of medicine (with reference number ZU-IRB # 10749). The research was conducted under the World Medical Association’s Code of Ethics (Helsinki Declaration) for human research.

Inclusion criteria

Patients with histopathological proven primary malignant bone tumors with no age or gender predilection.

Exclusion criteria

All patients with blood glucose level >200 mg/dl at the time of the study, impaired renal functions, those who had recent surgery lasted less than 6 weeks or had received chemotherapy or radiotherapy within < 3 months, active infection, and pregnant females.

Patient preparation

Before the scan, all patients were instructed to fast for approximately six hours. In order to inject 18F-FDG into the patient, an IV cannula was placed in the arm. The patients were requested to void prior to scanning and were advised not to engage in any strenuous activity before or after the radioisotope injection to prevent any physiologic muscle uptake of FDG. Before receiving an 18F-FDG injection, blood glucose levels in diabetic individuals were regularly checked.

Technique

- PET/CT device: GE Discovery IQ device
- Radio-isotope dose: 45–90 minutes prior to the exam, patients received an injection of 0.15 mCi/kg of 18F-FDG.
- Technique: For entire body PET image

acquisition, all cases were situated supine with their arms raised. Using same scan location, we performed post-contrast CT using a non-ionic contrast (300 mg iodine/ml) was given intravenously (2 ml/kg), at a rate 3-5 ml/s for 30 seconds after PET imaging.

- About six to seven bed positions are used in 3D acquisition mode for scanning the entire patient with 3-5 minutes acquisition per each position. Hundreds of trans-axial PET and CT images were first reconstructed. The whole acquisition time for an integrated PET/ CT scan was about 25 min. PET image data sets were reconstructed using CT data for attenuation correction and co-registered images were demonstrated using special software.
- Post-imaging instructions: patients were instructed to drink a lot of water, and stay away from children and pregnant females for twenty-four hours.

Images interpretation

Two consultant radiologists with 6 and 8 years of PET/CT experience interpreted all images independently and then final decisions reached by consensus.

A) Interpretation of the CT findings (morphological findings):

1- Osseous lesions:

Findings of primary malignant bone lesions were; medullary and cortical bone destruction, wide zone of transition, permeative appearance, aggressive periosteal reaction, tumor matrix calcification/ossification, associated extra-osseous soft tissue mass and spectrum of appearances from purely lytic to purely sclerotic.

2- Extra osseous lesions

Lymph nodes: evaluation of either loco-regional or distant lymph nodes regarding their size and morphology; and considered malignant when measuring more than 10 mm (short axis), showing central necrosis, loss of fatty hilum, and/or exhibiting similar enhancement pattern as the primary lesion and considered benign when being less than 10 mm and showing preserved fatty hilum.

Metastasis: assessment of bony skeleton for lytic, sclerotic lesions, pathological fractures and other body regions metastatic deposits, e.g. lung, liver…. etc.

B) Interpretation of the PET/CT findings (metabolic findings):

The bony lesions considered malignant when there was increased 18F-FDG-uptake compared to surrounding normal bony tissues. A region of interest (ROI) centered on the site of highest metabolic activity on each axial slice of the tumor displaying high FDG uptake was used to asses standard uptake value (SUV). The greatest pixel value corresponding to the neoplasm was identified as SUVmax.

1- osseous lesions:

Primary bone cancers have been found to display a spectrum of FDG uptakes, with lesions that exhibit less aggression tend to be less FDG avid than aggressive ones. The lesions considered cancerous on showing higher SUV value more than 2.8.

Extra osseous disease:

Assessment of lymph nodes either regional or distant and metastatic deposits is based upon their FDG uptake; the lesions considered positive on PET basis when showing higher SUV value more than 2.5.

Analysis of the findings:

In our study; true positive cases were those reported neoplastic on PET or CT studies and verified to be malignant on histopathology or further follow-up. Similarly, true negative was defined as areas reported as non-neoplastic on PET or CT scan and verified to be non-malignant on histopathology or further follow-up.

False positive was reported as malignant lesions on PET or CT studies but verified to be benign on histopathology or follow-up. Similarly, false negative was defined as areas reported non-neoplastic on PET or CT scan but were malignant on histopathology or further follow-up.

Statistical analysis

SPSS 24.0 was used to analyze the data (SPSS Inc., Chicago, IL, USA). To determine whether the data were normally distributed, the Shapiro Walk test was utilized. In order to display the qualitative data, percentages and frequencies were used. The chi-squared test ($\chi 2$) and Fisher exact were used to compare the qualitative variables. For parametric and nonparametric variables, the variation in the quantitative data between the two groups was assessed using the Independent T-test and the Mann-Whitney test, respectively. When comparing more than two dependent groups with normally distributed variables, a one-way ANOVA test was employed.

RESULTS:

Thirty-six patients had been histopathological diagnosed with primary bone cancers were included in our research, aged 12 to 70 years old, with a median age of 22.5 years. Eighteen (50%) males and eighteen (50%) females were present. The pathological types and the primary locations of the tumors were illustrated in **(Table 1).**

Patients had PET/CT studies for a pre-treatment and post-treatment TNM staging of lesions, also as a part of routine follow-up to detect any recurrent lesions or after positive clinical results raising the possibility of cancer recurrence. The studies also included evaluation of the response to treatment to identify any distant or residual lesions that may be present locally **(Figs. 1, 2, 3, 4)**.

Concerning pre-treatment and post-treatment TNM staging according to CT and PET CT studies, the results illustrated in **(Figs. S1, S2).**

In contrast to morphological CT results, TNM staging altered in 12 cases (33.3%) whose PET/CT revealed downstaging, sixteen patients (44.4 %) showed the same grade and 8 patients (22.3 %) showed upgrading based on metabolic activity **(Table 2).**

Regarding therapy, the tumors were surgically removed from sixteen patients (44.4%) without obtaining post-operative medical treatment and 6 patients (16.7 %) obtained chemotherapy following surgery. Ten patients (27.8 %) obtained only chemotherapy and 4 cases (11.1%) obtained chemo-radiotherapy.

To determine the effectiveness of therapy, PET/CT was performed four to twelve weeks following the completion of definitive chemo-radiotherapy by the work protocol and we regarded the PET/CT as follow-up rather than post-treatment evaluation if it was done more than 3 months after the start of therapy.

Concerning the final results of histopathology, 22 patients (61.1%) were positive for malignancy and 14 patients (38.9 %) were negative. CT detected 22 positive cases (61.1 %) and 14 negative ones (38.9 %); 18 were truly positive with proven positive lesions by biopsy with sensitivity 81.8 %, 4 false positive, 10 true negative, and 4 false negative studies with specificity 71.4%, positive and negative predicative value were 81.8% and 71.4% respectively, overall accuracy was 77.8% (Table 2). On the other hand, PET/CT detected 20 positive cases (55.6%) and 16 negative ones (44.4%); 20 were true positive with sensitivity 90.9%, 14 true negative, and 2 false negative studies with specificity 100%, positive and negative predicative value were 100% and 87.5% respectively and overall accuracy was 94.4% **(Table 3)**.

As regards to the final PET/CT results relying on the standard reference accepted criteria as: results of histopathology, radiological/PET CT follow up over 6 months, or prior radiological examinations for comparison; sixteen patients had residual/recurrent disease, 4 patients had metastasis and sixteen patients continued follow up **(Fig. S3).**

Table (1) Distribution of patients according to demographic data, pathological types and sites of tumors:

	N=36	%
Gender:		
Male	18	50%
Female	18	50%
	Median	Range
Age (year)	22.5 (15 – 55.25)	12 – 70
Pathology:		
Osteosarcoma	10	27.8%
Multiple myeloma	8	22.2%
Chondrosarcoma	12	33.3%
Ewing sarcoma	6	16.7%
Site of lesions:		
Femur	14	38.9%
Knee	4	11.1%
Tibia	4	11.1%
Humerus	2	5.6%
Wrist	2	5.6%
Vertebra	10	27.8%

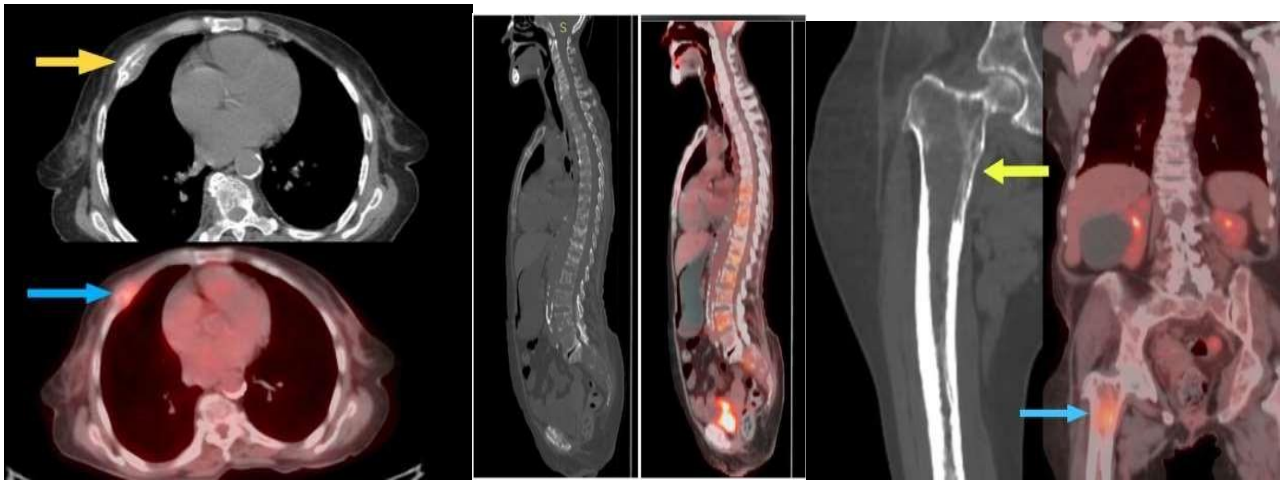
Table (2): Distribution of patients according to TNM restaging by PET/ CT as compared with CT

PET CT results as compared with CT		
	N=36	%
Downgrade	12	33.3%
Same grade	16	44.4%
Upgrade	8	22.3%

Table (3): Performance of CT and PET/CT in detection of positive tumors as proved by histopathology:

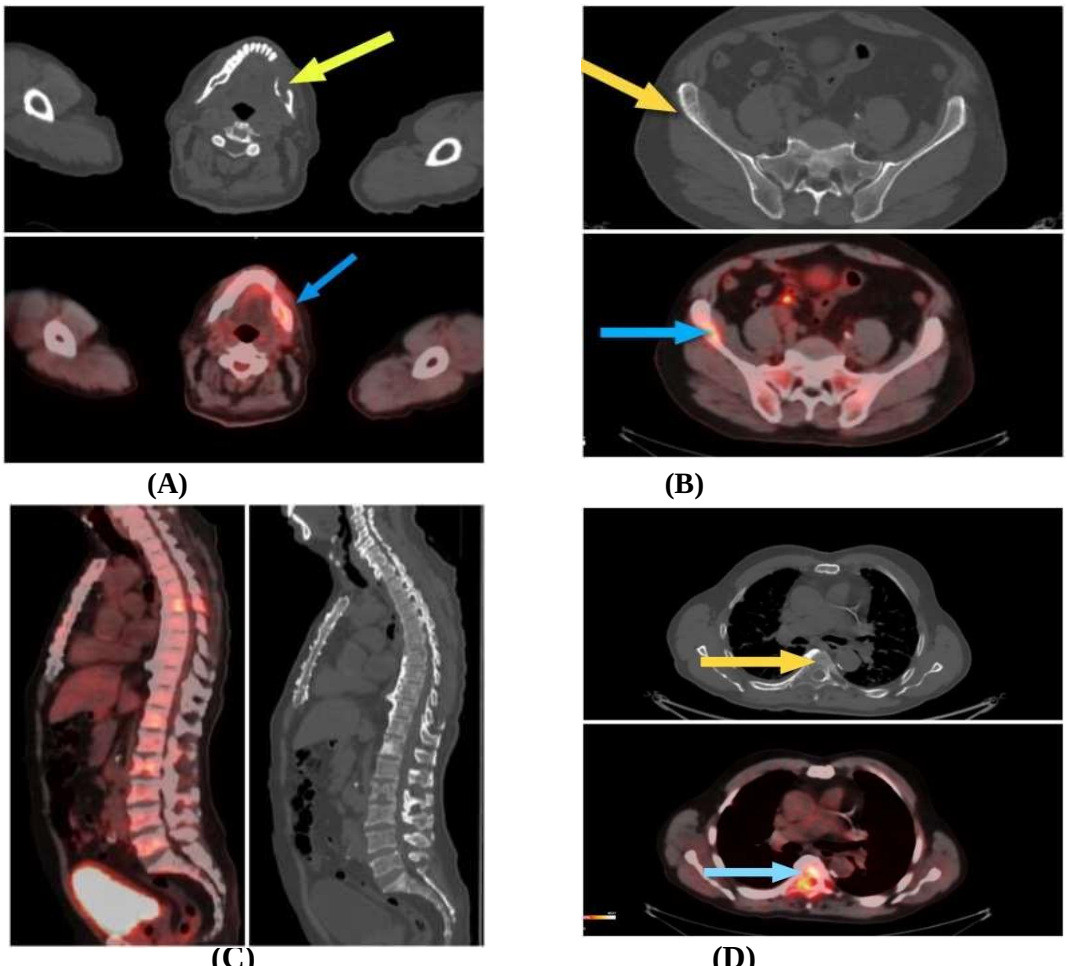
CT				
	Positive N=22	Negative N=14		Total N=36
Positive	18	4		22
Negative	4	10		14
Sensitivity	Specificity	PPV	NPV	Accuracy
81.8%	71.4%	81.8%	71.4%	77.8%
PET CT				
	Positive N=22	Negative N=14		Total N=36
Positive	20	0		20
Negative	2	14		16
Sensitivity	Specificity	PPV	NPV	Accuracy
90.9%	100%	100%	87.5%	94.4%

PPV positive predictive value NPV negative predictive value



(A) **(B)** **(C)**

Figure1:A 73 years old female presented with history of metastatic plasma cell myloma on chemotherapy for follow up. (A):AxialCT& fused PET/CT chestshowright anterior chest wall expansilelesionwithpathological ribfracture(yellowarrow)showing high FDG uptake achieving8.15 SUVmax(bluearrow). **(B): Sagittal CT& fused PET/CT** spine show generalized decrease bone density associated with compression of multiple lower dorsal and lumbarvertebraewith mixed lytic and sclerotic lesions, no associated soft tissue component, with multilevel metabolically active FDG avid lesions of the spine. **(C): Coronal CT&fused PET/CT** proximal femur showfocal expansion with bone rarefaction(yellow arrow)with increased FDG uptakeachieving up to 4.05 SUVmax (blue arrow)**.**



(A) **(B)**

(C) **(D)**

Figure 2: A 67 years old male patient histopathologically proved to be left mandibular osteosarcoma for primary staging.(A):Axial CT&fused PET/CT mandible show left mandibular ill-defined focal infiltrative destructive bony lesion (yellow arrow) achieving high FDG uptake with SUVmax up to 6.7 (blue arrow). **(B): Axial CT & fused PET/CT** pelvis show RT iliac bone ill- defined sclerotic lesion with surrounding periosteal reaction, no soft tissue component (yellow arrow) achieving high FDG uptake with SUV max upto 6.1 (blue arrow).**(C&D): Sagittal & axial CT and fused PET/CT**spine show multiple wide spread mixed lytic & sclerotic osseous lesions with metabolically active FDG avid osseous deposits with the most active lesion noted at DV6 achieving SUV max up to 9.9 (blue arrow

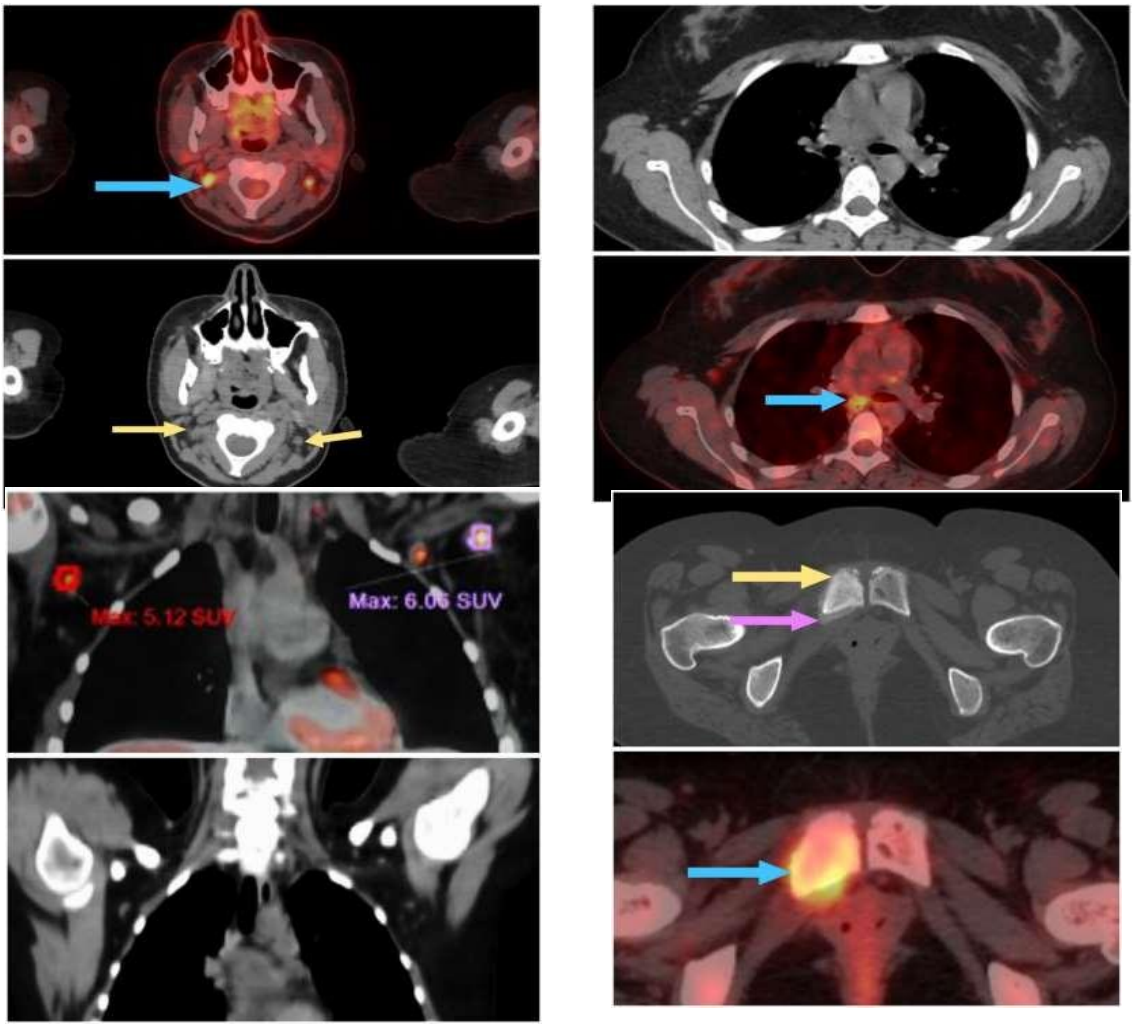


Figure 3: A 15 years old female patient with biopsy-proven left femur Ewing sarcoma, underwent surgical excision followed by chemo-radiotherapy for 3 months and refereed for follow up. (A): Axial CT & fused PET /CT neck show newly developed multiple metabolically active bilateral cervical lymph nodes (yellow arrow) with the most avid nodal lesion at the right side achieving SUV max of 5.4 (blue arrow). (B): Axial CT study of chest shows no pathologically enlarged mediastinal lymph nodes however fused PET/CT shows pre-vascular, pre-tracheal and subarinal (blue arrow) metabolically active lymph nodes achieving SUV max uptake of 2.3 denoting role of PET/CT in detection of micronodal metastasis. (C): Coronal CT & fused PET/CT chest show multiple bilateral enlarged axillary lymph nodes with high FDG uptake achieving SUV max up to 6. (D): Axial CT & fused PET/CT pelvic bones show right pubic bone ill-defined sclerotic lesion (yellow arrow) with periosteal reaction (purple arrow) achieving high FDG uptake with SUV max of 8.6.

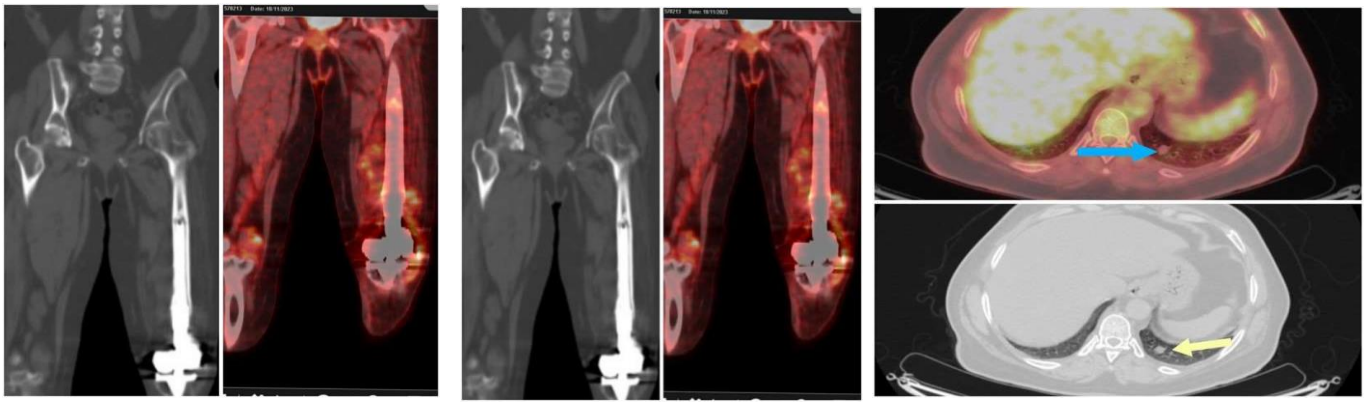


Figure 4: **A 54 years old female patient with biopsy-proven left knee chondrosarcoma underwent surgical excision followed by chemotherapy for 3 months and referred for follow-up.(A): Coronal CT & fused PET/CT** left knee show metallic prosthesis with clear surgical bed with mild surrounding regional FDG uptake but no sizable metabolically active destructive osseous lesions denoting local inflammatory changes and no local residual or recurrent tumor. **(B)**: **Axial CT& fused PET/CT** chest show multiple RT middle lobe pulmonary nodules with no FDG uptake denoting no metabolic activity. **(C)**: **Axial CT& fused PET/CT** chest

show newly developed left lower lobe pulmonary nodule (yellow arrow) with no FDG uptake denoting no metabolic activity (blue arrow).

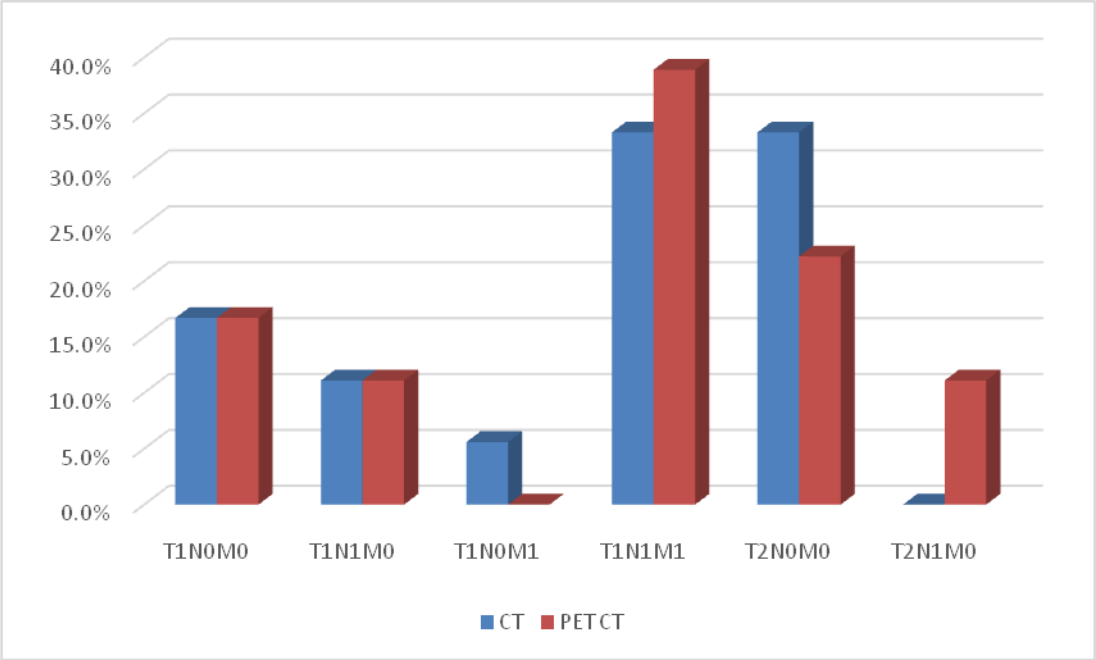


Figure (S1): Multiple bar chart showing pre-treatment TNM staging using CT and PET/CT

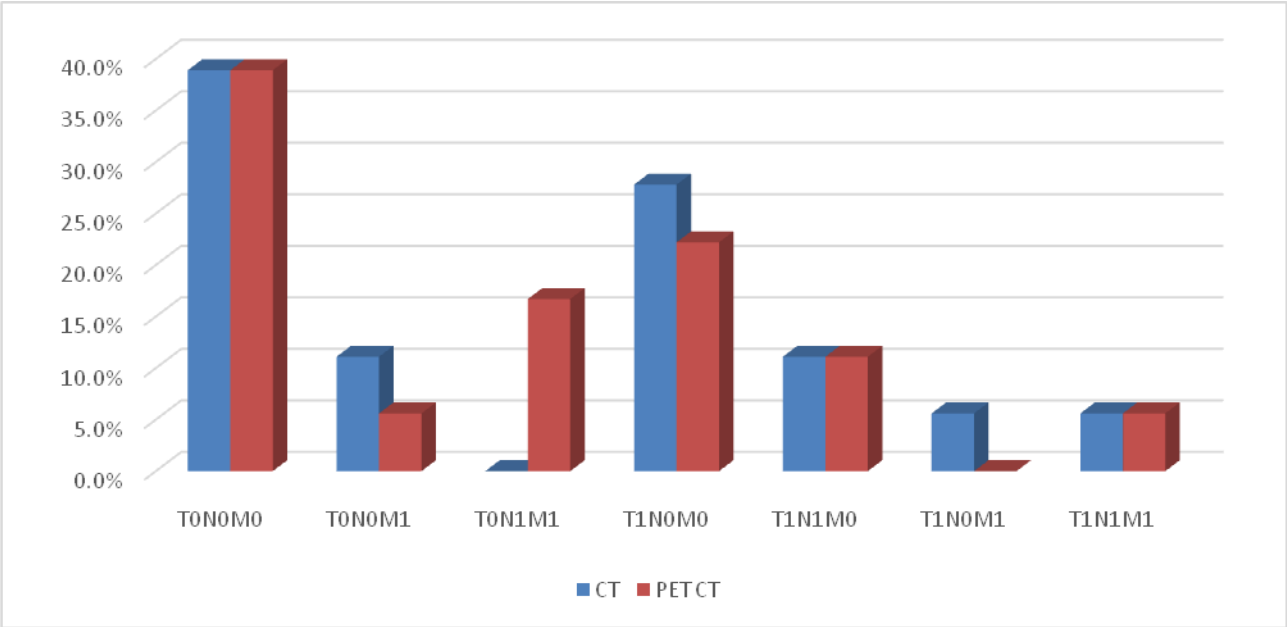


Figure (S2): Multiple bar chart showing post-treatment TNM staging using CT and PET/CT

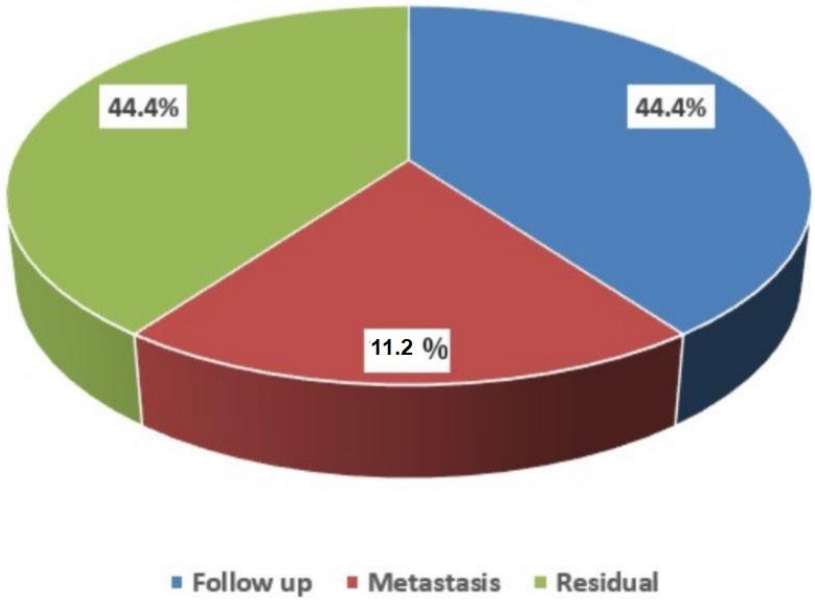


Figure (S3): Distribution of patients according to type to response after therapy

DISCUSSION:

It has been discovered that a higher SUVmax is correlated with the greatest dimension and tumor grade. Notably, studies have demonstrated a robust link between SUV and cancer grade. Because of this, PET/CT can discriminate between various grades with accuracy; a correlation coefficient of up to 0.94 has been shown. Additionally, other research has distinguished between low- and high-grade sarcomas using average lesion SUV (SUVmean) [10].

PET/CT studies in our research have been performed for pre- and post-treatment TNM staging, evaluation of treatment response, and to rule out the existence of residue/recurrent lesion, lymphadenopathy, and metastasis distally. Treatment options included radiation, chemotherapy, combined chemo-radiotherapy, and surgery. First line of treatment is surgical removal; regardless medical treatment is received afterwards. Of included patients, sixteen (44.4%) had prior surgical excision of the tumors.

Osteosarcoma accounted for 27.8% of the patients' tumor types, multiple myeloma for 22.2%, Ewing sarcoma for 16.7% and chondrosarcoma for 33.3%. While in a study by Abdella et al. [11], they observed that osteosarcoma affected 30% of patients, chondrosarcoma affected 27.5%, Ewing sarcoma affected 22.5%, fibrosarcoma affected 15%, and angiosarcoma affected 5% of patients.

In regards to lesion sites, femur accounted for 38.9% of tumors, vertebrae for 27.8%, knee for 11.1%, tibia for 11.1%, humerus for 5.6%, and wrist for 5.6%.The primary sites of lesions in the patients under study varied, according to Abdella et al.'s [11] report, the femur was the most affected, accounting for 25% of cases. Other affected sites included the ribs, iliac bone, tibia, fibula, humerus, scapula, mandible, foot, and wrist.

In the pre-treatment TNM staging, CT showed that 33.3% had T1N1M1, 33.3% had

T2N0M0, 44.4% had lymph node invasion and 38.9% had distant metastasis. Meanwhile, PET/CT showed that 38.9% had T1N1M1, 22.2% had T2N0M0, 16.7% had T1N0M0, 61.1% had lymph node invasion and 38.9% had distant metastasis. As a result, compared to CT, PET/CT significantly altered the overall TNM staging in 22.3% of patients who had an upgrade and 33.3% of patients who had a downgrade. Similarly, it was discovered that PET/CT was helpful in altering the overall TNM staging in 28.6% of sarcoma patients, according to Abdella et al.'s [11] study.

PET/CT is considered a non-invasive technique for accurately characterizing lesions that aids in therapeutic decision-making, for example, PET/CT found no corresponding FDG avidity, meanwhile CT identified lymph nodes that were thought to be neoplastic [12].

In a research by Tateishi et al. [13] on 50 cases with sarcomas that had been histologically confirmed; 48 patients (96%) with PET/CT had nodal metastasis accurately identified, compared to 46 patients (92%) with CT. In a different study, Tateishi et al. [13] were able to accomplish appropriate staging in 60 out of 69 cases (87%), upstaging in 12%, and downstaging in 1% of sarcoma patients by incorporating conventional imaging results with PET/CT findings.

According to El-Galaly et al. [14], the benefits of PET/CT in the discrimination of various bone tumor grades included precise lesion localization, detection of smaller lesions, and differentiation of benign, malignant, and various tumor stages. Research illustrated by Fuglo et al. and Gerth et al. [15, 16] revealed that PET/CT had substantially greater total TNM staging and M staging accuracies than traditional imaging.

For assessing how effectively therapy interventions perform, PET-CT is a very beneficial technique. It can detect response to treatment more quickly than any other imaging modality, which enhances patient care by enabling the discontinuation of unsuccessful treatments. It made it possible to more accurately assess anatomic areas that had undergone radiation or surgery in the past, where it might be challenging to discriminate among a recurring tumor and a post-treatment scar [17].

We concluded that PET/CT was more sensitive than CT in identifying local tumor recurrence or residue; additionally, it was not impacted by metallic artifacts that reduced the clarity of the CT picture and was better able to distinguish post-operative tissue alterations from tumoral recurrence.

In our study, FDG-PET/CT demonstrated higher sensitivity and specificity than CT in evaluation of therapeutic response and follow-up of cases with sensitivity 90.9%, specificity 100%, positive and negative predicative values 100% and 87.5% respectively and overall accuracy 94.4%. Meanwhile, CT sensitivity was 81.8%, specificity 71.4%, positive and negative predicative value were 81.8% and 71.4% and accuracy 77.8%. According to Abdella et al. [11], PET/CT revealed 94.4% sensitivity and 86.7% specificity with 90.9% accuracy, whereas CT demonstrated 88.2% sensitivity and 81.2% specificity with 84.8% accuracy.

In addition, our findings are in line with a meta-analysis conducted by Liu et al. [18], which illustrated that PET/CT had 91%

sensitivity, 90% specificity, and 94% accuracy in identifying recurrence and the establishment of metastases in osteosarcoma observations.

Our findings agrees with a research by Schulte et al. [19] that investigated 44 cases with malignant bone tumors and found that PET/CT could detect recurring lesions and restaging patients with primary bone tumors with a sensitivity of 93%, specificity of 76.7%, and accuracy of 81.7%.

According to Kumar et al. [20], increased FDG uptake can result from post-operative alterations and granulations, which makes PET/CT study interpretation extremely challenging. Additionally, according to Schöder [21], false-positive results can still arise from PET/CT scans done 12 weeks after completion of chemo and radiotherapy. These results can be attributed to edema, scarring, tissue planes alterations, and existence of inflammation following treatment which may lead to increased FDG uptake and wrongly identified as tumoral reside.

However, a remarkable missed (false negative) lesions on CT images were discovered in a study by Wafaie et al. [22] on the effectiveness of PET/CT in evaluating skeletal deposits, this was because the lesions had a high metabolic activity in PET/CT but no discernible structural abnormalities in CT. This is explained by PET ability to identify bone marrow deposits early in the lack of morphologic alterations in CT images, increasing CT sensitivity.

According to studies by Tateishi et al. and Gerth et al. [13,16], PET/CT showed significant sensitivity and specificity up to 98% and 97% for the identification of metastasis, whereas for both bone and STS, the predictive value of a positive or negative test was 97% and 98%, respectively. Additionally, Fuglo et al. [15] observed that, regarding the detection of lymph node metastases, the sensitivity and specificity were, respectively, 100% and 90%.

However, the lungs are most vulnerable to distant metastases in patients with bone sarcoma. Franzius et al. [23] noted that, because of breathing movements during the PET acquisition, PET alone is insufficient for detecting tiny lung metastases. The other explanations include the possibility of small size and lower FDG avidity in FDG-negative lung metastases.

In a study conducted on eighteen sarcoma patients before and after chemotherapy, Rashad et al. [24] discovered that SUVmax and overall tumor SUV on post-treatment PET/CT scans were more reliable indicators of therapy response than alterations in tumor size.

According to our research, 33.3% of patients had their PET/CT status downgraded and 22.3% of patients had it upgraded. According to a research by Roberge et al. [25], out of the 14 positive scan results, 6 cases had metastases identified before, 3 were false positives, and 5 had new metastatic findings with a 79% positive predictive value (PPV). FDG-PET/CT revealed that these 5 patients (4.5%) were upstaged.

Among the strongest benefits of FDG PET/CT is its capability to predict treatment response by early detection of non-responder patients. This provides an opportunity to adjust or prolong preoperative chemotherapy without having to wait for surgery or the histologic examination of the removed specimen to be completed [26].

Our study's principal weakness was limited number of cases because of expensive cost of the technique. Further multicenteric research

with large patient numbers is necessary to confirm the outcomes of our study.

CONCLUSIONS:

PET/CT could be an imaging modality that exhibits a high specificity, sensitivity, as well as accuracy in assessment of the tumor, nodal and metastatic staging and serves as a promising non-invasive diagnostic tool in assessment of primary bone cancers and provides a more comprehensive and functional assessment of therapy leading to more accurate management strategies for patients

Conflictsof Interest

The authors report no conflicts of interest.

FUNDING INFORMATION

None declared

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