BENHA MEDICAL JOURNAL bmj
Print ISSN 1110-208X.
Online ISSN 2357-0016

Original article

Role of FDG PET /CT in Detection of Primary Tumors in Patients with Bone Metastasis of Unknown Origin

Ahmed F. Youssef, Hamada M. Khater, Mohammed F.Ragab, Maie E. Sabea

Abstract:

Background: the aim of this study was to evaluate the role of FDG-PET-CT in detection of the primary tumor in patients with bone lesions of unknown origin. **Patients and methods:** The study is designed as a prospective case control study. Data were obtained from 50 patients admitted to the Oncology Department of Benha University or presented to its outpatients' clinic. The study was conducted in the PET-CT Unit in (Life Scan Center) **Results:** The study included 50 patients with higher male predominance (68%). Most of patients were aged above 40 years old (76%). Most of lesions were osteolytic lesions (80%) while 30% were sclerotic and 16% were mixed. Most of lesions were multifocal (66%) while 32% were focal lesions and 4% were diffuse. Minimum SUV of the bony lesions ranged from 3to 13 with median 5 and maximum SUV ranged from 5 to 35 with median 15. PET scan was positive for 45 lesions and negative for 5 lesions. Out of 45 positive PET lesions, primary lesions outside the bone were detected in 30 patients while 15 lesions were positive to be primary lesions in the bone. **Conclusion:** PET CT is the modality of choice for optimal detection of primary tumors is cases of osseous bone lesions of unknown primary.

Keywords: Bone metastasis; primary tumors; unknown origin.

Radiodiagnosis Department, Faculty of Medicine Benha University, Egypt.

Corresponding to:
Dr. Maie E. Sabea.
Radiodiagnosis Department, Faculty of Medicine Benha University, Egypt.
Email: maiesabae288@gmail.com

Received:
Accepted:

Introduction

Skeletal metastases represent a clinical challenge regarding the diagnostic work-up for patients suffering from cancer of unknown primary. Clinical judgment and approaches borrowed from cancer of unknown primary represent a reasonable pragmatic alternative and a valid paradigm to design statistically powered clinical studies [(1)].

Indeed, minimal basic work-up for bone metastasis of unknown primary overlaps with overall cancer of unknown primary when it includes medical history, physical examination, basal blood and biochemical analysis (including bone metabolism), and computer-tomography (CT) scans of the thorax, abdomen, and pelvis [(2)].

Integrative investigation must be selected based on clinical and radiological indications, such as endoscopy and serum assessment of prostate-specific antigen (PSA), α-fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG), and chromogranin to exclude "treatable" or susceptible hormone therapy and can drive site-specific treatment. However, the tumor biopsy remains a pivotal point in the SMUP diagnostic process, providing tissue suitable for light-microscopic and immunohistochemical examination and molecular characterization. Further consequential, detailed, practical, and pathological primary and specific markers are [(3)].

Additional molecular investigations, such as gene-expression profiling (GEP) assays, hold the promise to characterize more deeply the underlying malignancies, guide a tailored therapy, and identify the tissue of origin in patients with occult primary cancers. Immunohistochemistry (IHC) and GEP offer a similar range of accuracy in tumor classification (approximately 75%) [(4)]

Nonetheless, the quality of evidence available is not strong enough to allow stringent recommendations and selected classifier assays. Approaching the differential diagnosis of suspected adenocarcinoma, PSA and mammography are two effective screening procedures for men and women, respectively [(5)]

Breast magnetic resonance imaging (MRI) and ultrasound can efficiently complete non-diagnostic screening procedures. Among additional investigations whole-body radionuclide bone scans are deemed as sensitive techniques, despite being non-specific, providing information on osteoblastic lesions and bone vascular density, with a selective signal dependent on skeletal osteoblastic remodeling, either neoplastic, inflammatory, or post-injury [(6)].

Conversely, lytic bone lesions are better characterized by conventional radiology (X-ray), CT, and MRI than by bone scan, due to the lower metabolic extent within the skeletal compartment compared to osteoblastic tumors. X-ray, CT, and MRI bone scans can also be used in case of painful lesions or bone scan positivity that requires further targeted investigation, holding the potential to clarify the etiology of weight-bearing imaging areas [(7)]

It has been shown that 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET)-scan and single-photon-emission-tomography (SPECT) can both significantly enhance the diagnostic accuracy, supporting the primary sites investigation in 37% of cases [(8)]

Aim of work:

The study aimed to evaluate the role of FDG-PET-CT in detection of the primary tumor in patients with bone lesions of unknown origin**.**

Patients and methods

Patients:

PETCT studies neck, chest, abdomen, and pelvis of 50 patients with bone lesions, were required from the outpatient Oncology Clinic at Benha University from April 2022 to February 2024 clinically suspected of having primary malignancy. The material of this work comprised patients with osseous lesions who were admitted to the oncology department of El

Mobara Hospital of Medical Insurance or followed up at the outpatient clinic. The study protocol was conducted in the PET-CT unit (Life Scan Center) and Professor Dr. Khaled Dewan's Center. Thirty of them were males and twenty were females with age group from 6 to 70 years. (n=48) and one child (n=2). All enrolled participants gave their agreement in a written consent as well as Benha Faculty of Medicine's Research Ethics Committee authorized the project {M.D. 20.4.2022}.

Examinations

All patients were scanned with a PET-CT scanner. All patients were fasted for at least 6-8 h before FDG injection. Fasting blood glucose level of less than 150 mg/dl was a requirement in all patients. The scan started 1 hour after intravenous administration of (0.07- 0.1 mCi/kg) FDG and the patient was instructed to rest. CT was performed from the skull base to mid-thigh level by CT. No oral contrast was given and water only was used to delineate bowel.

In patients with normal renal function and no previous history to hypersensitivity to intravenous contrast media we give100-130 ml of (Omnipaque 300 mg iodine/ml) was administered.

PET emission scan is 2 min per bed position. The total scanning time varied between 15 and 20 min for every patient. The CT, PET fused images were reviewed in work station in axial, coronal , sagittal and 3 D Maximum intensity projection (MIP).

Ethics

- Written and verbal consent will be obtained from every share in the study after confirmation of confidentially and personal privacy.
- The data collected from patients will not be used in other purposes rather than the present research.

Inclusion criteria:

- Patients with the following criteria were included in the study:
- Patients with osseous lesions with unknown primary malignancy.

Exclusion criteria:

Patients that had one of the following criteria will be excluded from the study:

- Known primary lesion.
- Pregnant women.
- Patients with uncontrolled diabetes mellitus.
- Extremely over-weight patients (due to presence of difficulties
- In accessing the scanner).

Statistical Methods:

Statistical analysis was conducted using SPSS (version 21, Chicago, IL, USA). Qualitative data was presented as number and percentage; while quantitative parametric data (normally distributed) was presented as mean and standard deviation and quantitative non-parametric data (abnormally distributed) was presented as median (minimum, maximum).

Results

The study included 50 patients PET scan was able to detect 41 (true positive) out of 43 malignant bone lesions but PET scan did not detect 2 malignant bone lesions (false negative) exhibiting 95.3% sensitivity. PET scan did not detect malignant bone lesions in 6 lesions (true negative) out of 7 exhibiting 85.7% specificity. PET scan had accuracy 94% of detecting malignant bone lesions. PET scan showed presence of extraosseous lesions in 33 cases. Lymph node was affected in 21 patients. Out of them, 17 lesions were extended to other organs than lymph nodes (1 kidney, 3 liver, 2 lung, 2 vessels and 9 liver and lung). 12 extraosseous lesions were detected without lymph node affection (4 hepatic lesions, 2 lung, 1 soft tissue, 5 liver and lung)

Among patients aged less than 40 years, the results of PET scan were concordant with the results of the pathology. Among patients aged above 40 years old, 1 positive lesion by PET scan appeared negative by pathology (1 false positive) while 2 lesions did not appear positive by PET scan were positive by pathology (1

DOI: 10.21608/bmfj.2024.274441.2031

for renal carcinoma and 1 for ovarian carcinoma)

There were no statistically significant differences between percent of patients with either true or false positive or negative by PET scan in comparison to pathology. However, sensitivity, specificity and accuracy of PET scan appeared lower among patients aged above 40 years than patients aged below 40 years

There were statistically significant differences between both groups as regard presence of extraosseous lesions with higher frequency among group II patients (above 40 years) (p= 0.04). There was statistically significant difference between both groups as regard organ affection without LN affection with higher frequencies among group II patients (above 40 years) (p= 0.04). However, there were no statistically significant differences between both groups as regard lymph node affection either alone or with other organs.

There were no statistically significant differences between male and female bony lesions patients as regard age, type and focality of bone lesions (table 1).

There were no statistically significant differences between both groups as regard sex distribution. However, sclerotic lesions were more frequency among patients aged above 40 years old while sclerotic lesions were commoner among patients aged less than 40 years with statistically significant difference (p= 0.03) (figure 3). Also, patients aged less than 40 years had more frequent focal lesions while patients aged above 40 years had more frequent multifocal lesions with statistically significant difference (p= 0.04) (figure 1) (table 2).

As shown in table 6, 1 bone lesion appeared to be malignant as primary lesion in the bone and pathology revealed no malignancy (1 false positive out of 42 positive lesions by PET). While 2 metastatic bone lesion was negative by PET scan and appeared positive as a metastasis 1 for renal carcinoma and 1 for ovarian carcinoma by pathology (2 false negative out of 8 negative lesions by PET) (table 3).

Table (1): Comparison between male and female patients.

	Male (n= 34) **No. (%)**	**Female (n= 16)** **No. (%)**	**P value**
Age			
- Below 40 years	9 (26.5%)	3 (18.8%)	0.6
- Above 40 years	25 (73.5%)	13 (81.2%)	
Type of bony lesion			
- Sclerotic	11 (32.4%)	4 (25%)	0.3
- Osteolytic	27 (79.4%)	13 (81.2%)	
- Mixed	6 (17.6%)	2 (12.5%)	
Focality			
- Focal	12 (35.5%)	4 (25%)	0.09
- Multifocal	21 (61.8%)	12 (75%)	
- Diffuse	2 (5.9%)	0 (0%)	

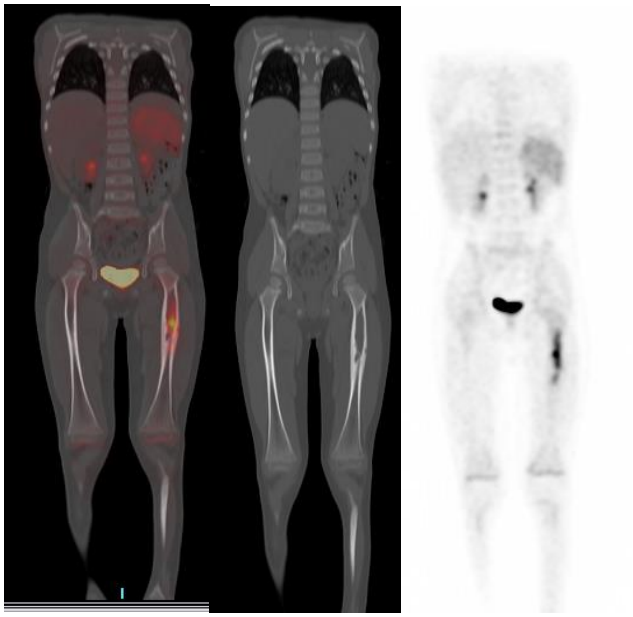

Fig 1: Coronal CT, PET Scan and PET CT both femurs showing left tibial lytic lesion with FDG uptake

Table (2): Comparison between both groups as regard sex and characteristics of bony lesions.

	Group I (<40) (n= 12) No. (%)	**Group II (>40) (n= 38) No. (%)**	**P value**
Sex			
- Male	9 (75%)	25 (65.8%)	0.81
- Female	3 (25%)	13 (24.2%)	
Type of bony lesions			
- Sclerotic	0 (0%)	15 (39.5%)	**0.03**
- Osteolytic	10 (83.3%)	30 (78.9%)	
- Mixed	1 (8.3%)	7 (18.4%)	
Focality			
- Focal	6 (50%)	10 (26.3%)	**0.04**
- Multifocal	5 (41.7%)	28 (73.7%)	
- Diffuse	2 (16.7%)	0 (0%)	

Chi square test; Level of significance < 0.05

Table (3): Comparison between bone lesions sites by PET and by pathology.

	PET scan No. (%)	**Pathology/others No. (%)**
- Prostate	9 (18%)	9 (18%)
- Multiple myeloma	7 (14%)	7 (14%)
- Breast	5 (10%)	5 (10%)
- Bone	5 (10%)	4 (8%)
- Pulmonary/ Pancreas	6 (18%)/ 1 (2%)	6 (18%)/ 1 (2%)
- Adrenal	3 (6%)/	3 (6%) (1 by radiology)
- Renal	2 (8%)	3 (6%)
- Hepatic	2 (4%)	2 (4%)
- Sarcoma/ Pleura	1 (2%)/ 1 (2%)	1 (2%)/ 1 (2%)
- Ovarian	0 (0%)	1 (2%)
- No malignancy	8 (16%)	7 (14%) (1 no biopsy)
Total lesions:		
- Malignant	42 (84%)	43 (86%)
- Benign	8 (16%)	7 (14%)

DOI: 10.21608/bmfj.2024.274441.2031

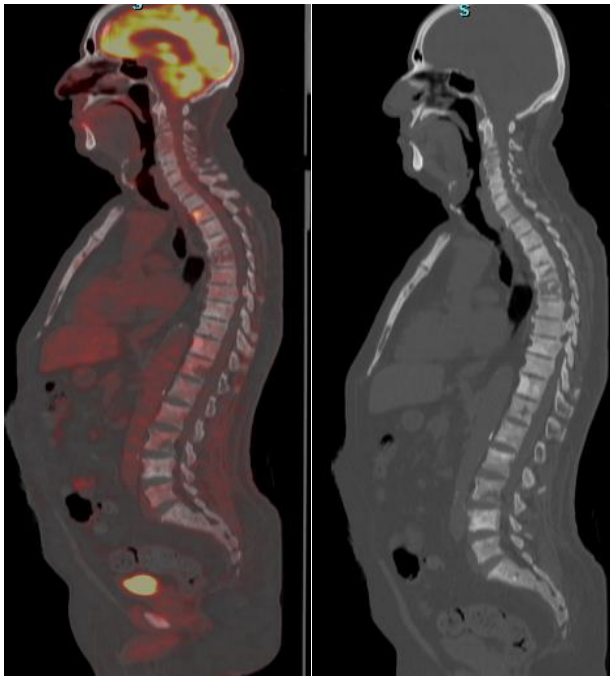

Fig 2: Sagittal view CT and PET CT lumbar spine with sclerotic lesions with variable grades of uptake

Discussion:

According to the present results, the commonest primary lesion was prostatic carcinoma (18%) (Figure 2) followed by lung cancer (12%). In agreement with the present study, another research done in 2020 [17] reported that lung and prostatic cancer had the highest frequencies however he reported lung cancer at higher frequency than prostatic cancer (52% vs. 13%). Also, it was demonstrated that lung (25.2%) and prostate (15.2%) were the main sites for primary lesions for metastatic lesions on unknown primary [9]. Also, the researchers reported lung as the main primary site for bone metastasis [10].

Similarly, in the study performed 2012 on 9505 patients it was reported that prostate cancer (19.6%) was the main primary site followed by breast cancer (18.9%). In another study done 2015 [9], the primary malignancy could be detected on an antemortem examination in 88% and at autopsy in 92% of 64 patients with BMUO. The most detected primary malignancies were lung cancer (n = 23), prostate cancer (n = 11), and breast (n = 5) and hepatocellular cancer (n=5) [11]

On the other hand [12] it was demonstrated that lung cancer had the highest frequency followed by pancreas and esophagus cancer. Other studies also showed that lung cancer represented 31.3% of metastatic bony lesions (1456 out of 4646 lesions) [10]. Gastric cancer came second, and liver and breast cancer came 3rd and 4th in that study. In a study by breast cancer represented 24.6% of metastatic bone lesions followed by lung (18.8%). In another study, lung cancer was identified as the most common primary malignancy in 75 patients with BMUO (75%) followed by gastric, hepatobiliary, and prostate cancers [11].

The commonest primary site for bony metastasis was lung followed by breast. [7 & 12] Showed that breast cancer as a primary lesion had the highest frequency among bone metastasis patients. A study reported that colorectal (38%) followed by gastric (30%) and pancreatic cancers (15.2%) were the commonest primary lesions for bony metastatic lesions [12].

Histopathological findings

In the current study, biopsy was taken from 48 patients and the most detected lesions were acinar adenocarcinoma

(16%), multiple myeloma (14%) and adenocarcinoma (12%).

In agreement with the present study, a study [12] reported that adenocarcinoma was shown in 66.3% of histopathological results of patients with bony metastasis. Adenocarcinoma was the most common histopathological subtype identified in 60 patients among all those in whom the primary origin of the tumor was detected (62.6%) in a study by Budak & Yanarates, (2020).[17] Also showed that the histopathology 75% of primary tumors for bony metastasis was adenocarcinoma [13].

In 2016 a study was done [14] and revealed that out of the 47 detected primary tumors, 45 were further confirmed by histopathology. Thirteen (27.6%) were adenocarcinoma)(2015) . Most of lesions were adenocarcinoma showed that adenocarcinoma is the commonest pathological type of the primary lesions (15) in his study on 9306 bony lesions of unknown primary.

In the present study, about 26% of lesions were multiple myeloma.. In agreement with the other study, it was reported that 17.5% of bone lesions were part of multiple myeloma. It. [13]

Other studies found that multiple myeloma represented 17% of bony lesions of unknown primary.

On the other hand, demonstrated that most of primary bony lesions were multiple myeloma and represented a higher percent of all bony lesions (63.2%) of all examined bony lesions while metastasis was represented in 36.8% only [11]. In a study done [16], multiple myeloma represented 29.5% of primary bony lesions. The controversial results are attributed to the differences in nature of bony lesions as only osteolytic lesions were included while in the present study, all types were included.

Conclusion:

The results indicate that PET CT is a sensitive imaging modality for detection of primary tumors in patients of bone lesions of unknown primary

References

1. Argentiero, A., Solimando, A. G., Brunetti, O., Calabrese, A., Pantano, F., Iuliani, M., et al. Skeletal metastases of unknown primary: biological landscape and clinical overview. Cancers. 2019;11(9), 1270
2. Bochtler, T., & Krämer, A. Does cancer of unknown primary (CUP) truly exist as a distinct cancer entity? Frontiers in oncology.2019; 9, 402
3. Krämer, A., Bochtler, T., Pauli, C., Baciarello, G., Delorme, S., Hemminki, K., et al., .Cancer of unknown primary: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆. Annals of Oncology.2023; 34(3), 228-246..
4. Minaguchi, T., Shikama, A., Akiyama, A., & Satoh, T. ,Molecular biomarkers for facilitating genome directed precision medicine in gynecological cancer. Oncology Letters.2023;26(4), 1-9
5. Vallabhajosula, S. Molecular Imaging Molecular Imaging (MI) in Oncology. In Molecular Imaging and Targeted Therapy: Radiopharmaceuticals and Clinical Applications2023; (pp. 303-373). Cham: Springer International Publishing
6. Ballhause, T. M., Jiang, S., Baranowsky, A., Brandt, S., Mertens, P. R., Frosch, K. H., et al. Relevance of notch signaling for bone metabolism and regeneration. International journal of molecular sciences,2021; 22(3), 1325...
7. Shojaie, P., Afzali, M., Nischal, N., Iyengar, K. P., Yousef, M. M. A., & Botchu, R. Bone Tumor Imaging: An Update on Modalities and Radiological Findings. Journal of Arthroscopy and Joint Surgery, 2023;10(3), 131-138
8. Rachh, S. S., Basu, S., & Alavi, A. Fluorodeoxyglucose PET/Computed Tomography in Evaluation of Prosthetic Joints and Diabetic Foot: A Comparative Perspective with Other Functional Imaging Modalities. PET clinics, 2022;17(3), 517-531.
9. Takagi, T., Katagiri, H., Kim, Y., Suehara, Y., Kubota, D., Akaike, K., et al., Skeletal metastasis of unknown primary origin at the initial visit: a retrospective analysis of 286 cases. PloS one, 2015;10(6), e0129428.
10. Han, A., Xue, J., Hu, M., Zheng, J., & Wang, X. Clinical value of 18F-FDG PET-CT in detecting primary tumor for patients with carcinoma of unknown primary. Cancer epidemiology.2016; 36(5), 470-475

DOI: 10.21608/bmfj.2024.274441.2031

11. Li, S., Peng, Y., Weinhandl, E. D., Blaes, A. H., Cetin, K., Chia, V. M., et al., Estimated number of prevalent cases of metastatic bone disease in the US adult population. Clinical epidemiology.2012;87-93..
12. Soni, N., Ora, M., Aher, P. Y., Mishra, P., Maheshwarappa, R. P., Priya, S., & Graham, M. M. Role of FDG PET/CT for detection of primary tumor in patients with extracervical metastases from carcinoma of unknown primary. Clinical Imaging.2021;78, 262-270
13. Park, S. B., Park, J. M., Moon, S. H., Cho, Y. S., Sun, J. M., Kim, B. T., & Lee, K. H. Role of 18F-FDG PET/CT in patients without known primary malignancy with skeletal lesions suspicious for cancer metastasis. PLoS One, 2018;13(5), e0196808
14. Riaz, S., Nawaz, M. K., Faruqui, Z. S., Kazmi, S. A. S., Loya, A., & Bashir, H. Diagnostic accuracy of 18F-fluorodeoxyglucose positron emission tomography-computed tomography in the evaluation of carcinoma of unknown primary. Molecular Imaging and Radionuclide Therapy, 2016;25(1), 11.
15. Hemminki, K., Riihimäki, M., Sundquist, K., & Hemminki, A. Site-specific survival rates for cancer of unknown primary according to location of metastases. International journal of cancer.2013; 133(1), 182-189..
16. Xu, Q., T. Gao, B. Zhang, J. Zeng and M. Dai . "Primary osteosarcoma in elderly patients: a report of three cases." Oncology Letters. 2019;18(2): 990-996.
17. Budak, E., & Yanarateş, A. Role of 18F-FDG PET/CT in the detection of primary malignancy in patients with bone metastasis of unknown origin. Revista Española de Medicina Nuclear e Imagen Molecular (English Edition), 2020; 39(1), 14-19.

To cite this article: Ahmed F. Youssef, Hamada M. Khater, Mohammed F.Ragab, Maie E. Sabea. Role of FDG PET /CT in Detection of Primary Tumors in Patients with Bone Metastasis of Unknown Origin. BMFJ XXX, DOI: 10.21608/bmfj.2024.274441.2031.