International Journal of Radiology Sciences

**ISSN Print:** 2664-9810
**ISSN Online:** 2664-9829
IJRC 2024; 6(2): 06-10
www.radiologyjournals.com
Received: 03-05-2024
Accepted: 08-06-2024

**Ahmed F Youssef**
Department of Radiodiagnosis, Faculty of Medicine, Benha University, Benha, Egypt

**Hamada M Khater**
Department of Radiodiagnosis, Faculty of Medicine, Benha University, Benha, Egypt

**Mohammed F Ragab**
Department of Radiodiagnosis, Faculty of Medicine, Benha University, Benha, Egypt

**Maie E Sabea**
Department of Radiodiagnosis, Faculty of Medicine, Benha University, Benha, Egypt

**Abdallah M Al-Ramzy**
Jubail Military Hospital, KSA, Saudi Arabia

**Corresponding Author:**
**Maie E Sabea**
Department of Radiodiagnosis, Faculty of Medicine, Benha University, Benha, Egypt

# 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 and Abdallah M Al-Ramzy**

**DOI:** https://doi.org/10.33545/26649810.2024.v6.i2a.22

**Abstract**
**Background:** Skeletal metastases often present a diagnostic challenge, especially in cases of bone metastasis with an unknown primary tumor. Accurate identification of the primary tumor is crucial for optimal patient management. The integration of 18F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) into clinical practice has shown promise in enhancing diagnostic accuracy. This study evaluates the effectiveness of FDG-PET/CT in detecting primary tumors in patients presenting with bone metastasis of unknown origin.
**Methods:** This prospective study included 50 patients with bone lesions of unknown primary origin, referred from the outpatient oncology clinic at Benha University between April 2022 and February 2024. Patients underwent PET/CT scanning of the neck, chest, abdomen, and pelvis. The study population comprised 30 males and 20 females, aged 6 to 70 years. All patients fasted for 6-8 hours prior to FDG injection, and scans were performed one hour post-injection. The PET/CT images were analyzed for the detection of primary tumors, with histopathological findings used as the reference standard.
**Results:** FDG-PET/CT detected primary malignancies in 41 out of 43 malignant bone lesions, yielding a sensitivity of 95.3%. Specificity was recorded at 85.7%, with 6 out of 7 benign lesions correctly identified as non-malignant. The overall accuracy of FDG-PET/CT in detecting malignant bone lesions was 94%. Additionally, PET/CT identified extraosseous lesions in 33 cases, with lymph node involvement in 21 patients, and further organ involvement in 17 of these cases. Patients aged above 40 years exhibited statistically significant differences in the presence of extraosseous lesions ($p=0.04$) and a higher frequency of multifocal bone lesions ($p=0.04$) compared to younger patients. Sclerotic lesions were more prevalent in patients older than 40 years, while osteolytic lesions were more common in those under 40 years ($p=0.03$).
**Conclusion:** FDG-PET/CT is a highly sensitive and accurate imaging modality for detecting primary tumors in patients with bone metastasis of unknown origin. It demonstrates significant potential in guiding the diagnostic work-up and management of these challenging cases, particularly in identifying extraosseous disease and specific bone lesion characteristics.

**Keywords:** FDG-PET/CT, bone metastasis, unknown primary, diagnostic imaging, skeletal metastases

## Introduction
Diagnosing patients with cancer when the primary tumor is unidentified becomes particularly complex due to the presence of bone metastases. Utilizing clinical expertise alongside methodologies tailored for cases where the primary site of cancer is unknown proves to be a practical and reliable approach for conducting clinical trials that yield statistically significant outcomes [1].
The initial evaluation for bone metastases of unknown origin parallels the extensive workup typically conducted for cancers with an unidentified primary source. This evaluation includes a thorough review of the patient's medical history, a detailed physical examination, essential blood tests, biochemical analyses (Including markers of bone metabolism), and computerized tomography (CT) scans of the chest, abdomen, and pelvis [2].
The choice of additional diagnostic tests should be guided by clinical and radiological indicators, such as endoscopic procedures and serum tests for prostate-specific antigen (PSA), α-fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG), and chromogranin.

These evaluations are instrumental in ruling out "treatable" or hormone-responsive conditions and in directing therapy towards the affected regions. Despite these tools, performing a biopsy of the tumor remains crucial in diagnosing SMUP, as it provides tissue suitable for examination under light microscopy, immunohistochemical analysis, and molecular characterization [3].

Further molecular assessments, including gene-expression profiling (GEP) assays, offer a deeper understanding of the underlying malignancies, assist in personalizing treatment plans, and help identify the primary source of cancer in patients with unknown primary tumors. Both Immunohistochemistry (IHC) and Gene Expression Profiling (GEP) have demonstrated comparable accuracy in classifying tumors, with an estimated accuracy of around 75% [4].

However, the current body of evidence does not sufficiently support strong recommendations for the routine use of specific classifier tests. When exploring potential causes of likely adenocarcinoma, PSA testing remains an effective screening tool for men, while mammography is useful for women [5].

Both breast MRI and ultrasonography serve as effective methods for performing non-diagnostic screening procedures. Whole-body radionuclide bone scans, though highly sensitive, lack specificity. Their primary role is to provide information regarding osteoblastic lesions and bone vascular density, which are influenced by skeletal osteoblastic remodeling processes. These processes may be triggered by neoplastic, inflammatory, or post-injury factors [6].

Compared to bone scans, conventional radiology (X-ray), CT, and MRI offer greater accuracy in characterizing lytic bone lesions. Lytic lesions, which exhibit lower metabolic activity in the skeletal compartment, are less detectable on bone scans compared to osteoblastic malignancies. X-ray, CT, and MRI scans are valuable for evaluating painful lesions or positive findings on bone scans that warrant further investigation. These imaging modalities can help elucidate the underlying causes of abnormalities in weight-bearing regions [7].

Research has indicated that combining 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) with single-photon emission computed tomography (SPECT) can significantly improve diagnostic accuracy, aiding in the identification of primary tumor sites in 37% of cases [8].

The study aims to assess the effectiveness of FDG-PET-CT in locating the primary tumor in patients with undetermined bone lesions.

## Subjects and Methods

### Patients

This study employed positron emission tomography/ computed tomography (PET/CT) imaging to investigate the neck, chest, abdomen, and pelvis of 50 individuals who displayed bone anomalies. The participants were selected from the outpatient oncology clinic at Benha University between April 2022 and February 2024. Every patient was suspected of having a primary cancer based on clinical assessment. The cohort consisted of 30 males and 20 females, with ages ranging from 6 to 70 years (n=48), including one child (n=2).

### Evaluations

Each patient was scanned using a PET-CT scanner. Patients were required to fast for a minimum of 6-8 hours before receiving the FDG injection. Every participant had to possess fasting blood glucose levels that were lower than 150 mg/dl. The scanning technique commenced one hour following the intravenous infusion of FDG at a dosage of 0.07-0.1 mCi/kg. During this period, patients were instructed to remain in a state of rest. The CT scan covered the region from the base of the skull to the middle of the thigh, and did not require the use of oral contrast. Alternatively, water was employed to emphasize the colon.

Patients with normal renal function and no history of allergic responses to intravenous contrast agents were administered a dose of 100-130 ml of Omnipaque, which has a concentration of 300 mg of iodine per milliliter. The PET emission scan was performed with a scan duration of 2 minutes every bed position, resulting in a total scanning time of 15 to 20 minutes per patient. The CT PET scans were analyzed using a computer, which presented images in the axial, coronal, sagittal, and 3D Maximum Intensity Projection (MIP) views.

### Ethics

Before receiving informed consent, every participant was guaranteed the confidentiality and safeguarding of their personal privacy, both in writing and spoken communication. The data collected from the patients will be used exclusively for the particular goals of this research study.

## Results

The study involved 50 patients. The PET scan successfully identified 41 out of 43 malignant bone lesions (True positives) but missed 2 malignant bone lesions (False negatives), resulting in a sensitivity of 95.3%. Additionally, the PET scan accurately identified 6 out of 7 non-malignant bone lesions (True negatives), achieving a specificity of 85.7%. The overall accuracy of the PET scan in detecting malignant bone lesions was 94%. Furthermore, the PET scan detected extra osseous lesions in 33 cases. Lymph node involvement was found in 21 patients, with 17 of these cases showing extension to other organs beyond the lymph nodes, including 1 kidney, 3 liver, 2 lung, 2 vessels, and 9 involving both the liver and lungs. Twelve extra osseous lesions were identified without lymph node involvement, consisting of 4 hepatic lesions, 2 lung lesions, 1 soft tissue lesion, and 5 involving both the liver and lungs.

For patients under 40 years of age, the PET scan findings were consistent with pathology results. However, in patients over 40 years of age, 1 lesion that appeared positive on the PET scan was determined to be negative by pathology (false positive), while 2 lesions not detected by the PET scan were confirmed as malignant by pathology (1 case of renal carcinoma and 1 case of ovarian carcinoma).

There were no statistically significant differences between the percentages of true or false positives or negatives when comparing PET scan results to pathology findings. However, the sensitivity, specificity, and accuracy of the PET scan were lower in patients over 40 years of age compared to those under 40.

There were statistically significant differences between the two age groups in terms of the presence of extraosseous lesions, with a higher frequency observed in patients over 40

years of age (p=0.04). A significant difference was also found between the two groups regarding organ involvement without lymph node involvement, with the older age group showing a higher frequency (p=0.04). However, no statistically significant differences were observed between the two groups concerning lymph node involvement, whether alone or in combination with other organs.

No significant differences were found between male and female patients with bone lesions regarding age, type, or focality of the lesions (Table 1). Similarly, there were no significant differences in sex distribution between the two age groups. However, sclerotic lesions were more common in patients over 40 years of age, while osteolytic lesions were more prevalent in those under 40, with statistically significant differences (p=0.03). Additionally, focal lesions were more frequent in patients under 40, whereas multifocal lesions were more common in those over 40, with statistically significant differences (p=0.04) (Table 2).

As illustrated in Table 3, one bone lesion initially suspected to be malignant based on PET scan results was found to be non-malignant upon pathological examination (1 false positive out of 42 positive lesions detected by PET). Conversely, two metastatic bone lesions that were not identified by PET scan were confirmed as metastatic by pathology (1 case of renal carcinoma and 1 case of ovarian carcinoma) (2 false negatives out of 8 negative lesions identified by PET) (Table 3).

Coronal images from CT, PET, and PET/CT of both femurs demonstrate a lytic lesion in the left tibia with significant FDG uptake, suggesting metabolic activity. The CT image shows the structural details of the bone lesion, the PET scan highlights areas of increased metabolic activity, and the fused PET/CT image confirms the location of the FDG-avid lytic lesion within the tibia. Figure 1.

Sagittal views from CT and PET/CT of the lumbar spine demonstrate sclerotic lesions with varying degrees of FDG uptake. The CT image shows the structural characteristics of the sclerotic lesions, while the PET/CT fused image reveals metabolic activity associated with these lesions, indicating their heterogeneity in metabolic behavior. Figure 2.

## Discussion

According to the present results, the most common primary lesion was prostatic carcinoma (18%), followed by lung cancer (12%). This finding aligns with the study by Budak & Yanarates (2020), who also reported that lung and prostatic cancers had the highest frequencies, although they observed lung cancer more frequently than prostatic cancer (52% vs. 13%). Additionally, another study [15] demonstrated that lung (25.2%) and prostate (15.2%) were the main sites for primary lesions in cases of metastatic lesions of unknown primary origin. Similarly, another report [6] identified lung cancer as the primary site for bone metastasis.

In a study involving 9,505 patients [8], it was found that prostate cancer (19.6%) was the most common primary site, followed closely by breast cancer (18.9%). In another study [15], the primary malignancy was detected in 88% of patients during antemortem examinations and in 92% at autopsy among 64 patients with bone metastases of unknown origin (BMUO). The most commonly identified primary malignancies were lung cancer (n = 23), prostate cancer (n = 11), and both breast and hepatocellular cancers (n=5 each).

Conversely, one study [9] demonstrated that lung cancer had the highest frequency, followed by pancreatic and esophageal cancers. Another study [10] found that lung cancer accounted for 31.3% of metastatic bone lesions (1,456 out of 4,646 lesions), with gastric cancer coming in second, followed by liver and breast cancers. Skovlund *et al*. (2019) reported that breast cancer represented 24.6% of metastatic bone lesions, followed by lung cancer (18.8%). In yet 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].

Cengiz *et al*. [12] found that the most common primary site for bone metastasis was the lung, followed by the breast. Another study [13] showed that breast cancer was the most frequent primary lesion among patients with bone metastasis. A different study [14] reported that colorectal cancer (38%), followed by gastric (30%) and pancreatic cancers (15.2%), were the most common primary lesions for bone metastases.

### Histopathological Findings

In the current study, biopsies were taken from 48 patients, revealing that the most commonly detected lesions were acinar adenocarcinoma (16%), multiple myeloma (14%), and adenocarcinoma (12%). These findings are consistent with a study [14] that reported adenocarcinoma in 66.3% of histopathological results in patients with bone metastasis. Budak & Yanarates (2020) also identified adenocarcinoma as the most common histopathological subtype in 62.6% of the 60 patients whose primary tumor origin was detected. Another study [11] similarly showed that 75% of primary tumors associated with bone metastasis were adenocarcinomas.

In another study [12], out of the 47 detected primary tumors, 45 were further confirmed by histopathology, with 13 (27.6%) being adenocarcinomas. Pavlidis *et al*. (2015) also reported that most lesions were adenocarcinomas. Similarly, a study [15] on 9,306 bone lesions of unknown primary origin found that adenocarcinoma was the most common pathological type. In the present study, approximately 26% of lesions were primary or part of primary lesions, with multiple myeloma accounting for 14% of these cases. Skovlund *et al*. [11] reported that 17.5% of bone lesions were associated with multiple myeloma. Another study [17] found that multiple myeloma represented 11.1% of bone lesions, while a separate study reported that 15.8% of bone lesions were due to multiple myeloma. Yet another study [16] found that multiple myeloma accounted for 17% of bone lesions of unknown primary origin.

On the other hand, one study [18] demonstrated that the majority of primary bone lesions were multiple myeloma, which constituted a higher percentage (63.2%) of all bone lesions examined, with metastasis representing only 36.8%. In another study [19], multiple myeloma represented 29.5% of bone lesions. The variation in results can be attributed to differences in the nature of the bone lesions studied, as the latter study included only osteolytic lesions, whereas the present study included all types.

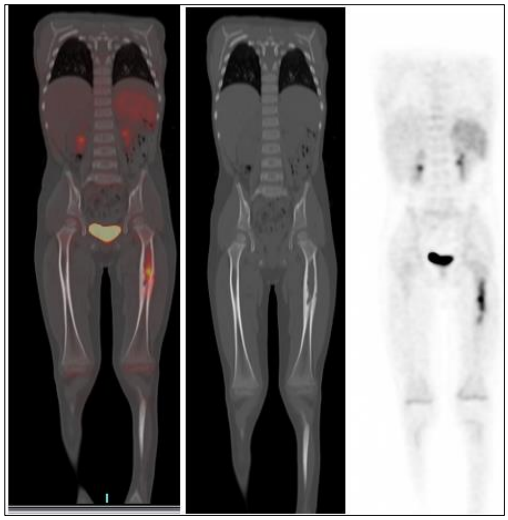

**Fig 1:** Coronal CT, PET Scan and PET CT both femurs showing left tibial lytic lesion with FDG uptake

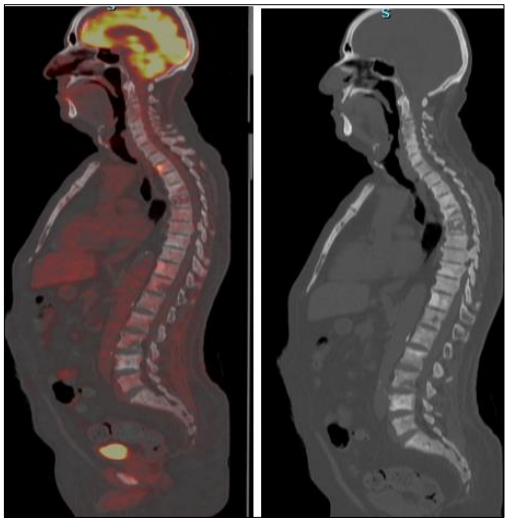

**Fig 2:** Sagittal view CT and PET CT lumbar spine with sclerotic lesions with variable grades of uptake

**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%) | |

**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%) |

## Conclusion

The findings of the current work suggest that PET CT is a highly responsive imaging technique for identifying primary malignancies in individuals with unknown main bone lesions.

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