Role of Positron Emission Tomography in Detecting Primary Tumor in Cases of Metastases of Unknown Origin

Ibrahim D[1] , Abdelghaffar A[2] , Hassan M[3], Khailfa MS[1]

[1] Nuclear Medicine Unit, Department of Clinical Oncology and Nuclear Medicine, Sohag University Hospital, Sohag University, Sohag, Egypt
[2] Department of Clinical Oncology, Sohag University Hospital, Sohag University, Sohag, Egypt
[3] Physics Department, Faculty of Science, Sohag University, Sohag, Egypt

Authors Information:
Doaa Ibrahim
Nuclear Medicine Unit, Department of Clinical Oncology and Nuclear Medicine, Sohag University Hospital, Sohag University, Sohag, Egypt
email: Doaaibrahim066@gmail.com

Alshaymaa Abdelghaffar
Department of Clinical Oncology, Sohag University Hospital, Sohag University, Sohag, Egypt
email: Drshaymaa_sharaka@outlook.sa

Mohamed Hassan
Physics Department, Faculty of Science, Sohag University, Sohag, Egypt
email: fargal33100@yahoo.com

Mai Sayed Khalifa
Nuclear Medicine Unit, Department of Clinical Oncology and Nuclear Medicine, Sohag University Hospital, Sohag University, Sohag, Egypt
email: drmai.sayed83@gmail.com

Corresponding Author:
Doaa Ibrahim
Nuclear Medicine Unit, Department of Clinical Oncology and Nuclear Medicine, Sohag University Hospital, Sohag University, Sohag, Egypt
email: Doaaibrahim066@gmail.com

Abstract:
Background: Metastases of unknown origin (MUO) have diverse clinical presentations and, unfortunately, poor outcomes in most cases. Identifying the initial tumor location is still a considerable issue in many MUO cases. Our aim in this research was to assess the ability of F18-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (^{18}F-FDG PET/CT) to detect the site of the primary tumor before starting active treatment.
Materials and methods: The study included 60 patients referred to our unit as cases of metastatic lesions with unknown primary (34 male, 26 female). PET/CT was done for all patients with its standard protocol.
Results: PET/CT could suggest primary lesion in 44 cases (73.3%) with an estimated sensitivity of 97%, specificity 57%, positive predictive value 80.9%, and negative predictive value 91%.
Conclusion: PET/CT is a very valuable tool in cases of MUO and is recommended as a diagnostic test for identification of the primary in cancer patients whose primary is unknown.

Keywords: Metastasis of unknown origin, Positron emission tomography, Primary tumor detection

Background:

Metastases of unknown origin (MUO) are defined as lesions confirmed pathologically to be metastatic, but the primary tumor site cannot be identified during classic pretreatment assessment [1, 2]. MUO constitutes about 2-5% of all cancers. The median age at diagnosis is 60–65 years, and it is more prevalent in men than in women [3]. MUO has diverse clinical presentations and, unfortunately, poor outcomes in most cases. These tumors are characterized by their aggressiveness, early disseminating lesions, and surprising metastatic pattern [4].

Identifying the primary tumor site is still a considerable issue in many MUO cases. At presentation, MUO patients usually undergo thorough diagnostic investigations including laboratory tests, non-invasive imaging studies, and invasive procedures (e.g., endoscopies and biopsies). Computed tomography

(CT), Magnetic resonance imaging (MRI), and mammography have been considered the standard imaging studies [5].

Identifying the primary tumor site is critical for appropriate, tumor-specific management and further monitoring. Additionally, it probably leads to better treatment outcomes and a decrease in treatment-associated morbidity [6]. Moreover, these imaging modalities may sadly fail to identify the primary tumor site. This dilemma necessitates the use of different noninvasive imaging methods with good diagnostic accuracy. Positron emission tomography (PET) scan has been documented to be helpful for the diagnosis, staging, and follow-up of various cancers [7, 8]. The fusion of PET with either CT (PET/CT) or MRI (PET/MRI) has a fundamental benefit as it provides more useful anatomical and functional information [9, 10]. The patient usually receives experimental chemotherapy protocols if the primary site is undiscovered. PET/CT–based treatment protocols were reported to have significantly higher patient survival than with empirical therapy [6].

The sensitivity and accuracy of PET/CT were studied for primary tumor site identification and were reported to be considerably higher than other imaging, e.g., CT/MRI [11].

In this research, our target was to assess the ability of PET/CT to identify the site of the primary tumor before starting active treatment.

Methods:

The ethical agreement to perform this research was taken from the institutional ethical committee (Registration number: Soh-Med-23-09-2PD) from the medical research ethics committee of Sohag University faculty of medicine. This study was conducted at the nuclear medicine unit in Sohag Oncology Center from 3/2022 to 7/2023. The examined patients were referred to our unit as cases of metastatic lesions with unknown primary. Patients selected for this study have either pathologically proven/ radiologically diagnosed metastatic lesions, or patients referred to our unit as MUO where the primary tumor couldn't be confirmed by other conventional imaging. Patients with known primary tumors, pregnant females, and those aged less than 18 years were excluded. Being a retrospective study, written informed consent was not needed.

PET/CT imaging protocol:

Patients were fasting for 4 hours before the PET/CT scan to lower normal tissue's glucose uptake and blood insulin levels. For every patient, the blood glucose reading during the scan was less than 200 mg/dl. Depending on their body weight, patients received injections of 370–555 MBq of ^{18}F FDG and started imaging after 45-90 min. PET technique: PET emission scans of the entire body were acquired with the patient in a supine position on the table of PET/CT scanning with their arms raised overhead using the Discovery IQ PET scanner from the base of the skull to the foot, around ten to fifteen-bed positions, two to five minutes per bed position, and roughly fifty percent overlap between each bed position CT technique: Low dose CT with imaging setup of 130 kV, 248 mAs, 5-mm slice thickness, 500–600 mm field of view, and voxel size $0.98 \times 0.98 \times 5mm^3$, the patient remains in the same position. Attenuation correction of the PET data was performed using low-dose CT images.

An ordered subset expectation maximization iterative reconstruction approach was used to rebuild PET images using CT-based attenuation correction. Both qualitative and quantitative evaluations of the pictures were made.

FDG PET/CT interpretation:

All images were assessed by 2 nuclear medicine specialists; images were assessed visually for any lesions with increased FDG uptake and semiquantitative with standard uptake value (SUVmax).

Statistical analysis:

Data analysis and Statistical evaluation: IBM SPSS 26 software was used for data analysis.

Results:

60 patients were presented to our unit from the period of 3/2022 to 7/2023, 34 males (56.7%), and 26 females (34.3%) with either pathologically proven or radiologically detected metastatic lesions with unknown primary. The age ranges from 25 to 85 years old with a mean age of 60+/-12 years. The sites of metastatic lesions at initial patients' presentations are presented in Table 1& figure 1.

Table1. Sites of metastatic lesions at initial patients' presentation.

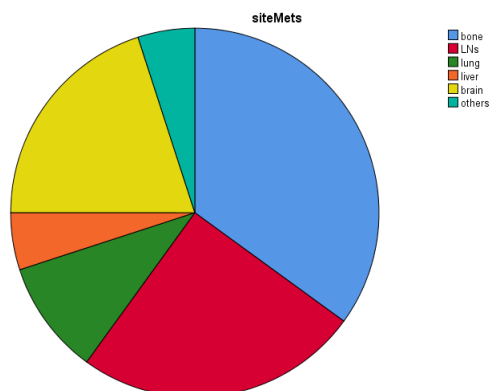| Site of metastatic lesions at presentation	Number of cases	Percentage
Bone	21	35%
LNs	15	25%
Brain	12	20%
Lung	6	10%
Liver	3	5%
Others (pleural, peritoneal)	3	5%
Total	60	100%

Figure 1. A pie chart for the distribution of metastatic lesions at initial presentation.

PET/CT could suggest primary lesion in 44 cases (73.3%), the most common site was GIT origin 12 cases (20%), lung 9 cases (15%), thyroid gland 7 cases (11.7%), prostate 5 cases (8.3%), others 11 cases 18% (muscular tumors 3 cases, gynecological 3cases, lymphoma 2 cases, pharynx 2 cases, parathyroid tumor 1 case). Of these patients, 41 were considered true positive (35 were pathologically proven to be malignant and 6 patients were diagnosed with high tumor markers), and 3 patients were considered false positive. PET/CT couldn't suggest primary lesion in 16 cases "negative for detecting primary tumor" (26.7%).

Bone metastases of unknown origin (BMUO) were detected in 21 patients. Of these patients, PET/CT could detect a primary tumor in 19 patients, with the lung being the most common primary site followed by the prostate. Figure 2 represents a bar chart for the detected primary site in patients with BMUO.
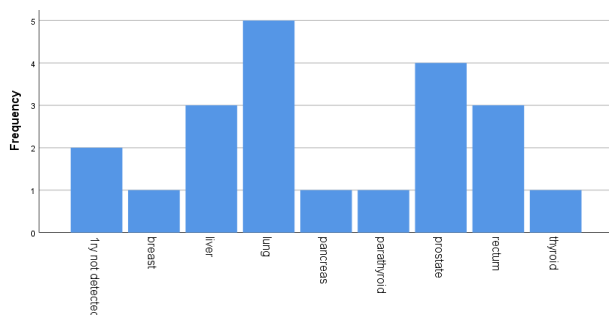
The suggested sites of primary tumors in PET/CT are shown in Table 2.

Table 2. The suggested primary sites detected by PET/CT

PET/CT results	Number of patients	Percentage
Lung as suggested primary	9	15%
Suggested GIT origin	12	20%
Thyroid as suggested primary	7	11.70%
Prostate as suggested primary	5	8.30%
Others (uterus, lymphoma, solid tumors)	11	18%
Couldn't suggest a primary	16	26.70%
Total	60	100%

Figure 2. A bar chart for the distribution of suggested primary lesions in BMUO.

Case presentation

Case 1: A 67-year-old female patient presented with multiple vertebral deposits; PET/CT revealed an FDG avid uterine mass, diagnosed as endometrial carcinoma pathologically. (Figure 3.)

Case 2: A male patient 73 years old presented with extensive sclerotic osseous deposits all over the axial skeleton, PET/CT revealed a metabolically active prostatic lesion that was not seen in CT, PSA level >100 ng. (Figure 4.)

Case 3: A 65-year-old male patient presented with multiple hepatic focal lesions; PET/CT revealed an FDG avid mass related to the pancreatic tail. (Figure 5.)
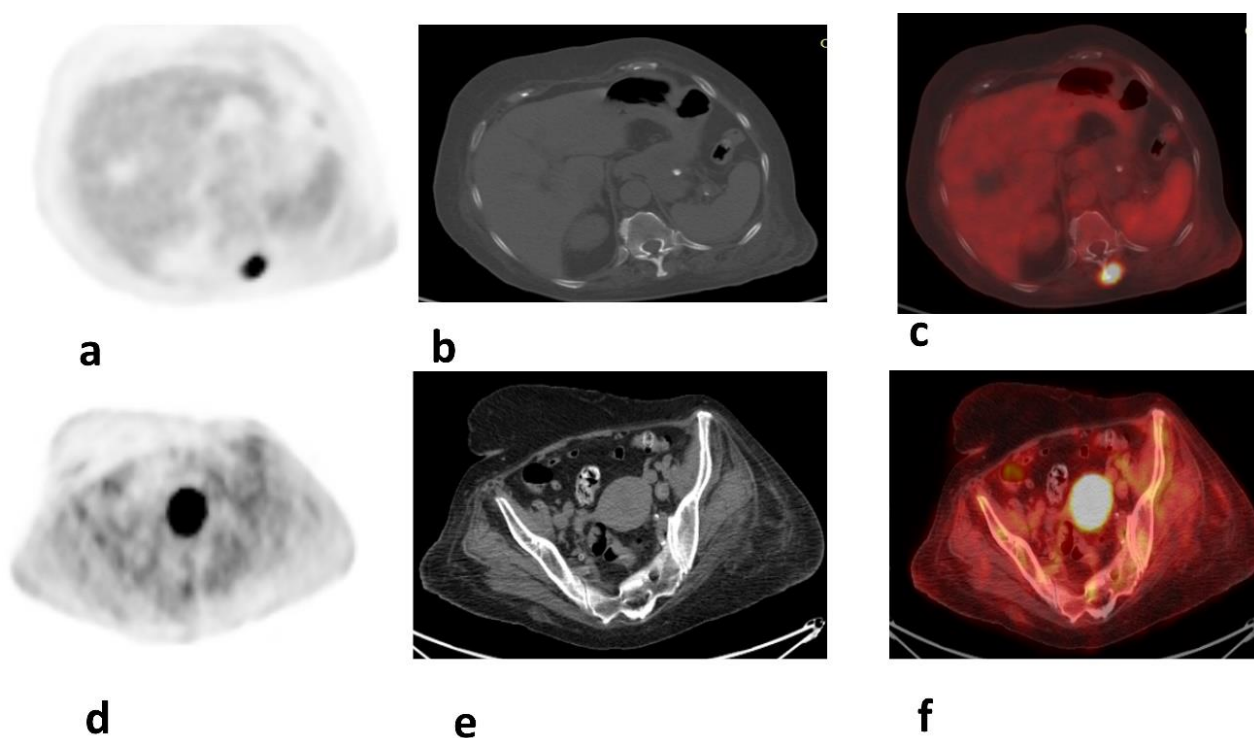
Figure 3. Case 1: axial views: a, b& c images showing metabolically active lesion at the spine of the 10th dorsal vertebra; a PET image, b CT image, c fused image, d, e& f images showing FDG avid uterine mass; d PET image, e CT image, f fused image
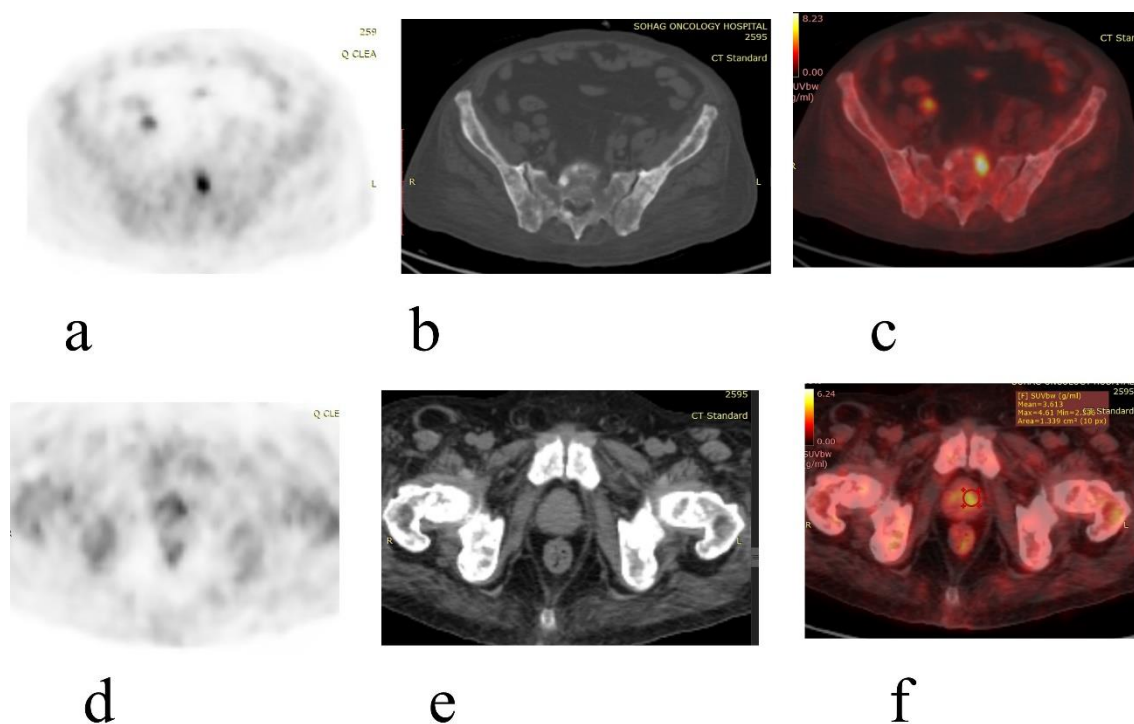

Figure 4, Case 2: axial views: a b& c images showing metabolically active sclerotic osseous metastatic lesions; a PET image, b CT image, c fused image, d, e& f images showing metabolically active prostatic lesion; d PET image, e CT image, f fused image
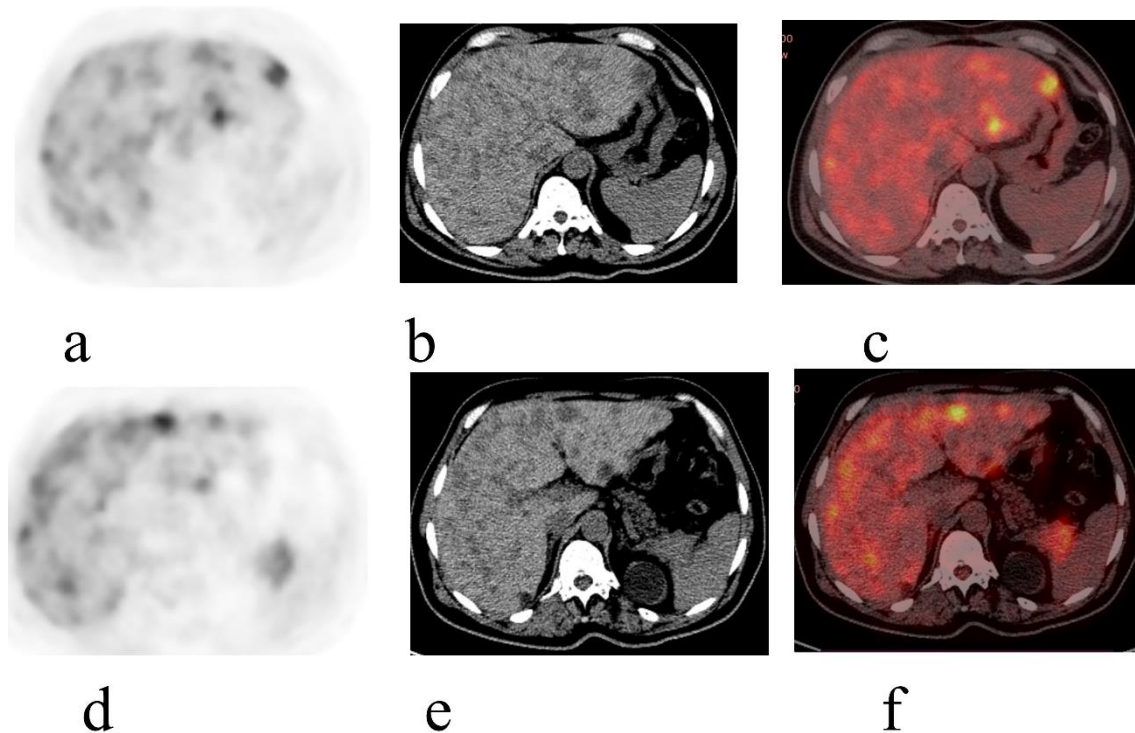
Figure 5, Case 3: axial views: a, b& c images showing multiple FDG avid bilobed hypodense hepatic focal lesions; a PET image, b CT image, c fused image, d, e& f images showing FDG avid mass related to pancreatic tail; d PET image, e CT image, f fused image

Discussion:

Early identification of primary tumors in patients with MUO enables more specific and effective treatment which leads to a better survival rate [12].

In a comprehensive review of 16 studies and 302 patients, Liu reported that the accuracy rate of FDG PET in detecting tumors of unknown primary was 78.8% [13], at the same time, Kardemir et al. could detect primary lesions in 34 of 42 patients (80%) with the lung and pancreas were the most common sites of the primary tumors followed by the liver [3]. These results go with our results where GIT and lung origin were the most common sites.

In a study conducted by Rong H et al., primary lesions could be detected in 67.7% (42 of 62 patients) with the lung being a common site of primary lesions. They also reported a change in the treatment plan according to the results of PET/CT in 21.0% (13/62) of the patients as a result of the identification of the primary tumor site or other metastatic lesions [14].

Our results also agree with the study conducted by Emine B and Ahmet Y on BMUO where they reported that lung cancer is the most common site of the primary lesion followed by prostate cancer [15].

False positive results in our current study were estimated to be about 5% and their causes were active benign thyroid lesions, colonic polyp, and inflammatory lung lesions, while the false negatives were colonic mucinous adenocarcinoma, multiple myeloma, and well-differentiated prostatic cancer.

In a similar study, false positive results were reported to be 8.6% [16] while in another study performed by Kardemir et al., false positives represented 2.8% [3]. These results were comparable with our results.

A meta-analysis by Kwee showed that the oropharynx and the lungs are the two most common locations of false-positive ^{18}F-FDG PET/CT results [17]. At the same time, possible breast cancer may be a source of false negative results on ^{18}F-FDG PET/CT, as low-grade, well-differentiated tumors and some histological tumor types such as tubular carcinoma, lobular carcinoma, and in situ carcinoma. It is important to be aware of this limitation, particularly if there is a strong suspicion of primary breast cancer (such as in the event of metastatic lesions in axillary lymph nodes). Furthermore, in the setting of head and neck cancer, tiny or superficial lesions may go unnoticed, making PET/CT scans of limited use because the resolution of FDG-PET is only around 5 mm. [18]. Additionally, It would be more difficult to identify minor and superficial lesions due to the natural absorption of FDG in the normal lymphoid tissues of the Waldeyer ring and salivary glands [19].

Conclusion:

For cancer patients whose primary is unknown, PET/CT is advised as a diagnostic test for primary detection. It is an extremely useful tool in MUO situations.

List of abbreviations:

^{18}F-FDG PET/CT: F18-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography
BMUO: Bone metastases of unknown origin
CT: Computed tomography
GIT: Gastrointestinal tract
LN: lymph node
MRI: Magnetic resonance imaging
MUO: Metastases of unknown origin
SUV: standard uptake value

Conflict of interests:

The authors affirm that there isn't any conflict of interest among them.

References:

1. Greco FA, Hainsworth JD. Cancer of Unknown Primary Site. In: DeVita VT, Lawrence TS, Rosenburg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology (ed 10th). Philadelphia: Lippincott Williams & Wilkins: 1720-1737; 2014.
2. Losa F, Iglesias L, Pané M, et al. Consensus statement by the Spanish Society of Pathology and the Spanish Society of Medical Oncology on the diagnosis and treatment of cancer of unknown primary. Clin Transl Oncol. 2018 Nov;20(11):1361-1372.
3. Kandemir O, Kandemir F. The role of PET CT in cancer of unknown primary Bozok Tıp Dergisi, 2003;13(2), 8-13.
4. Pavlidis N. Cancer of unknown primary: biological and clinical characteristics. Ann Oncol. 2003;14 Suppl 3:iii11-8.
5. Krämer A, Bochtler T, Pauli C, et al. Cancers of unknown primary site: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Ann. Oncol. 2022.
6. Reinert CP, Sekler J, la Fougère C, et al. Impact of PET/CT on clinical management in patients with cancer of unknown primary-a PET/CT registry study. Eur Radiol. 2020 Mar;30(3):1325-1333.
7. Chen K, Chen X. Positron emission tomography imaging of cancer biology: current status and future prospects. Semin Oncol. 2011 Feb;38(1):70-86.
8. Demir H, Berk F, Raderer M, et al. The role of nuclear medicine in the diagnosis of cancer of unknown origin. Q J Nucl Med Mol Imaging. 2004 Jun;48(2):164-73.
9. Podoloff DA, Ball DW, Ben-Josef E, et al. NCCN task force: clinical utility of PET in a variety of tumor types. J Natl Compr Canc Netw. 2009 Jun;7 Suppl 2:S1-26.
10. Townsend DW, Carney JPJ, Yap JT, et al. PET/CT today and tomorrow. J Nucl Med. 2004 Jan;45 Suppl 1:4S-14S.
11. Lee JR, Kim JS, Roh JL, et al. Detection of occult primary tumors in patients with cervical metastases of unknown primary tumors: comparison of (18)F FDG PET/CT with contrast-enhanced CT or CT/MR imaging prospective study. Radiology. 2015 Mar;274(3):764-71.
12. Zytoon AA, Elsayed EE, Nassar AI, et al. Pivotal role of PET/CT in characterization of occult metastasis with undetermined origin. Egypt J Radiol Nucl Med 2020;51:240.
13. Liu Y. FDG PET/CT for metastatic squamous cell carcinoma of unknown primary of the head and neck. Oral Oncol. 2019 May;92:46-51.
14. Huang R, Zhang Y, Hu Y, et al. Utility of 18F-FDG PET/CT in treatment strategies for patients with cancer of unknown primary, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-3184210/v1]; 2023
15. Budak E, Yanarateş A. Role of ^{18}F-FDG PET/CT in the detection of primary malignancy in patients with bone metastasis of unknown origin, Rev Esp Med Nucl Imagen Mol (Engl Ed). 2020 Jan-Feb;39(1):14-19.
16. Soni N, Ora M, Aher PY, et al. Role of FDG PET/CT for detection of primary tumor in patients with extra cervical metastases from carcinoma of unknown primary, Clin Imaging. 2021 Oct;78:262-270.
17. Kwee TC, Kwee RM. Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis. Eur Radiol. 2009 Mar;19(3):731-44.
18. Kwee TC, Basu S, Cheng G, et al. FDG PET/CT in carcinoma of unknown primary. Eur J Nucl Med Mol Imaging. 2010 Mar;37(3):635-44.
19. Nikolova PN, Hadzhiyska VH, Mladenov KB, et al. The impact of ^{18}F-FDG PET/CT in the clinical management of patients with lymph node metastasis of unknown primary origin. Neoplasma. 2021 Jan;68(1):180-189.