Role of PET-CT in Detection of Primary Tumor in Cases of Metastases of Unknown Primary

Mahmoud G. Tawfeek[a], Medhat Refaat[b], Khalid M. Taalab[c]

Abstract:

Background: Needing an alternate non-invasive imaging technique with a higher diagnostic value in patients with carcinoma of unknown primary (CUP), fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) emerges as an excellent problem-solving tool which can replace many other imaging modalities. This work aimed to evaluate the role of FDG-PET/CT in management of patients with carcinoma of unknown primary tumor site. **Subjects & methods:** In this work PET/CT was performed for 30 patients presented with metastasis of unknown primary, after IV injection of the radiotracer 18F-FDG. Images were evaluated and cases of suspicion of primary tumor were correlated with all clinical, pathological & follow up information. **Results:** The primary tumor site was defined in 83.4% of cases using PET/CT, with sensitivity of 89.3%, accuracy of 86.6 % and specificity of 50%. **Conclusion and recommendations:** although being a single imaging modality, FDG-PET/CT has several practical advantages in earlier detection of primary in CUP patients compared to other investigations, and thus allowing earlier proper management and better prognosis.

Keywords: PET/CT, unknown primary, CUP.

[a] Department of diagnostic radiology, Al-Agouza Charity Hospital, Egyptian ministry of health, Egypt. [b] Department of radiology, Benha faculty of medicine, Benha University, Egypt. [c] Department of Nuclear Medicine, Egyptian Military Medical Academy, Egypt.

Corresponding to: Mahmoud G. Tawfeek, Department of diagnostic radiology, Al-Agouza Charity Hospital, Egyptian ministry of health, Egypt.

Email:

mahmoud.gad.radiologist@gmail.com

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Introduction:

Carcinoma of unknown primary (CUP) is the presence of histopathologically confirmed metastases while the original cancer site is not determined at the moment of diagnosis even with extensive diagnostic workup. CUP is one of the ten commonest cancers (accounting for 3–5% of all malignancies) and is the fourth leading cause of cancer-related death ***(1).*** Although histopathological studies frequently provide information about the primary site location, not all primary tumors are identified despite extensive diagnostic work-up. This prevents therapeutic strategy optimization, which depends on tumor differentiation, location, and stage as determined by the TNM system. As a result, the patient's prognosis is negatively affected ***(2).*** Combination of positron emission tomography with computed tomography PET/CT, using 18F-fluoro-2-deoxyglucose (FDG) as a radiotracer maybe the ideal diagnostic tool in CUP patients ***(3).*** PET/CT combined imaging with 18F-FDG has gained major role in the diagnosis, staging and follow-up of cancer patients. The uptake degree of 18F-FDG by tumor tissues are valuable indices in the prognosis of cancer patients ***(4).*** Warburg effect; which is the increased glucose metabolism in various cancer phenotypes, is the rationale for 18F-FDG use in PET/CT in CUP. So 18F-FDG PET/CT offers high contrast, highly sensitive imaging modality for malignancy detection ***(5)***. Primary tumor detection will enhance treatment plan so improving the outcome. Many studies found that patients with detected primary tumor had a higher survival rate than those with primary tumor remained undetected (***6).***

Methodology

Study population:

This prospective study was conducted on 30 patients (18 males & 12 females), their ages ranged between 2nd and 8th decades with pathology proved or laboratory, clinically or radiologically suspected metastatic foci of unknown primary and referred to a private center in the period from October 2018 till April 2021 for detection of the site of the primary malignancy by whole body PET/CT scan. At referral, medical history, previous investigations, and pathology reports were recorded.

Cases were categorized according to: Site and distribution of metastases on presentation with the cause of suspicion of malignancy whether histopathology proved

metastatic lesion or clinical or radiological or laboratory suggested a potential malignancy (e.g., recent rapid weight loss and elevated tumor markers).

Equipment and instruments:

Combined PET/CT scan was done, using GE Medical Systems (Discovery 610). The integrated CT system is a 16 multi-slice scanner. Co-registered CT and PET images acquisition was performed in the same session.

Adequate patient preparations were strictly followed. The patients were asked to fast for 4–6 hours, except for glucose-free hydration, before receiving the radiotracer (18F-FDG). 60 min after IV injection of (3.7 MBq/Kg; maximum dose 370 MBq) of 18F-FDG, the scan was done. A whole-body examination was done in the supine position, from skull vault to midthigh.

A fully diagnostic CT scan was performed. IV contrast administration (120 mL of a low-osmolar iodinated contrast agent) and water as a negative oral contrast agent for bowel were used.

Images were reconstructed and viewed on workstation which provide reformatted multi-planar PET, CT, and PET/CT fusion images.

Dual time point imaging was taken by imaging at two time points and evaluating the max. SUV change in between. Dual point PET scan was obtained two hours following the IV injection of the radio pharmaceutical.

Images & Data analysis:

3D MDCT images were examined for qualitative assessment for existence of hypermetabolic foci evaluated on both corrected and uncorrected PET images in the Invert Grey Scale. The malignancy criteria were: radiotracer (18F-FDG) uptake at the areas of pathological changes seen on CT images or significant focal uptake at areas suggestive of malignancy even if pathological changes at those sites are absent on CT images. Using the formula: SUV = (μCi/gram in tissue)/ (total μCi injected) body weight, to calculate the Standard Uptake Value (SUV) to quantitatively evaluate the lesions and Max. SUV values of more than 2.5 were considered significant. Only after being confirmed histopathologically, a diagnosis of the primary site of malignancy is classified as true positive (TP). If the finding was confirmed as benign the diagnosis was classified as false positive (FP). If neither 18F-FDG-PET/CT nor histopathology could determine the site of the primary, then the

evaluation was considered as true negative (TN). A false negative (FN) result was considered when the site of the primary was proven histopathologically or by follow up using other imaging studies but was not identified by 18F-FDG-PET/CT.

Statistical Analysis:

The accuracy of FDG-PET/CT was expressed in terms of sensitivity and specificity, accuracy, positive & negative predictive values. The Chi-square test was used to test the difference in accuracy. P value less than 0.05 was considered significant. P value more than 0.05 was considered insignificant.

Ethical considerations:

The study approval was taken by the ethical review committee of medical research, Faculty of Medicine, Benha University, Egypt and informed consent forms were obtained from all participants.

Results

The most affected age group was the 7^{th} decade with 36% of cases followed by 5^{th} then 6^{th} decades **(Table R1 & Fig. R1)**, males represent 60% of cases **(Table R2 & Fig. R2)**. According to the lesions on presentation, 63% cases presented with organ metastases and 17% with only lymph node lesions **(Table R3 & Fig. R3)**, hepatic metastatic lesions were the most common followed by bone lesions **(Table R4. & Fig. R4)**. Primary tumors proved pathologically in 29 cases of 30; pulmonary tumors were the most common followed by colonic carcinoma **(Table R5 & Fig. R5)**.

PET-CT have suggested the site of primary malignant tumors in 26 out of 30 patients (83. 4 %), 25 pathologically proved to be malignant (**True Positive**). The commonest site of the malignant primary lesion was in GIT followed by lung **(Fig. R6)**. However, 1 case was suggested by PET-CT as lymphoma but proved pathologically as breast carcinoma (**False Positive**).

PET-CT couldn't detect the site of primary malignancy in 4 out of 30 patients (13.3%). 1 of them PET-CT suggested the lesion as non-specific inflammatory lesion which is later confirmed pathologically being benign (**True negative**); while 3 were diagnosed falsely as negative for the primary malignancy then proved pathologically as primary ovarian and breast malignancies (**False negative**)

Hence, the total true positive pathologically proved primary tumor sites by PET/CT were

25 patients (83.4%), 1 false positive patient (3.3%), 1 true negative patient (3.3%) and 3 false negative patients (10%) (**Table R6).**

In the search for an occult primary, a sensitivity of 89.3% was achieved, with a specificity of 50%. Accuracy of 18F-FDG-PET/CT in the search for a primary malignancy was 86.6%. The presence of primary malignancy was correctly diagnosed in 25 patients, and correctly excluded in 1 patient. Examination was falsely negative in 3 patients. Positive predictive value (PPV) was (96%) and the negative predictive value (NPV) was (25 %) (**Table R7**).

Table R1: Age Distribution

Age in decades	**No. of cases**	**%**
2nd	0	0%
3rd	0	0%
4th	2	7%
5th	8	27%
6th	7	23%
7th	11	36%
8th and above	2	7%
Total	30	100 %

Table R2: Sex Distribution

Sex	**Male**	**Female**
No. of cases	18	12
%	60%	40%

Table R3: Lesions on presentation

Metastases	No. of cases
Organ metastases	19
Nodal metastases only	5
Malignant ascites/ effusion	6
Total	30

Table R4: Anatomical Site of Lesions on Presentation

Anatomical Site of lesions on presentation	No. of cases
Liver	8
Bone	6
Ascites	5
Brain	4
Cervical LNs	3
Axillary LNs	2
Adrenal gland	1
Pleural effusion	1

Table R5: 1^{ry} Tumors

1ry Tumor	No. of cases	%
Pulmonary	7	24%
Colon	6	21%
Breast	3	10%
Ovarian	3	10%
Renal	2	7%
Tongue Sq.C.C	1	3.5%
Thyroid	1	3.5%
Testicular	1	3.5%
Bladder	1	3.5%
Prostate	1	3.5%
Gastric	1	3.5%
Pancreatic	1	3.5%
Peritoneal Mesothelioma	1	3.5%
Total proved tumor pathology	29	100%

Table R6: Interpretation of the PETCT findings among 30 patients of study group.

PET/CT findings	No of patient	Percentage %
True positive	25	83. 4 %
False positive	1	3.3 %
True negative	1	3.3 %
False negative	3	10 %

Table R7: Sensitivity, Specificity, Accuracy, PPV and NPV of FDG-PET-CT for detection of primary tumor in cases of CUP according to our study.

Sensitivity	Specificity	Accuracy	PPV	NPP
89.3 %	50 %	86.6 %	96 %	25 %

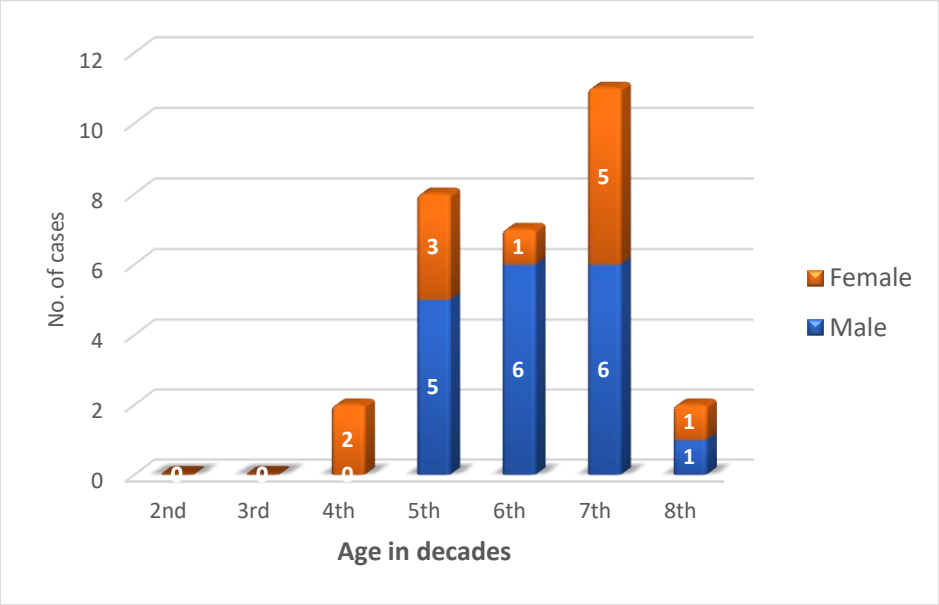

Fig. R1: Age Distribution

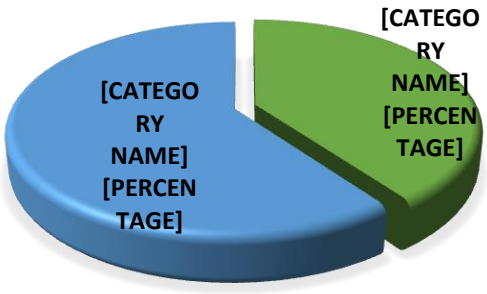

Fig. R2: Sex Distribution

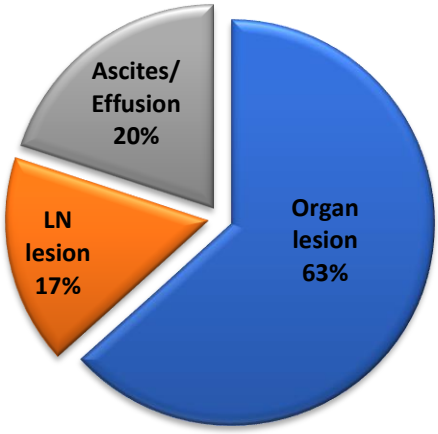

Fig. R3: Lesions on presentation

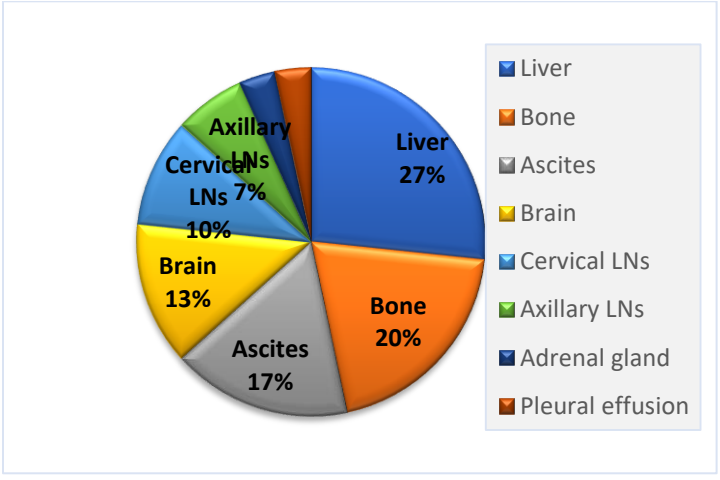

Fig. R4: Anatomical Site of Lesions on Presentation

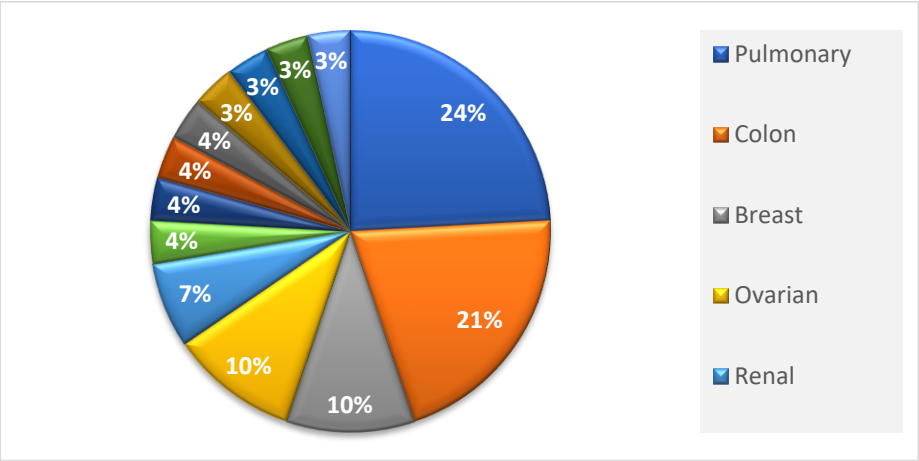

Fig. R5: 1[ry] Tumors

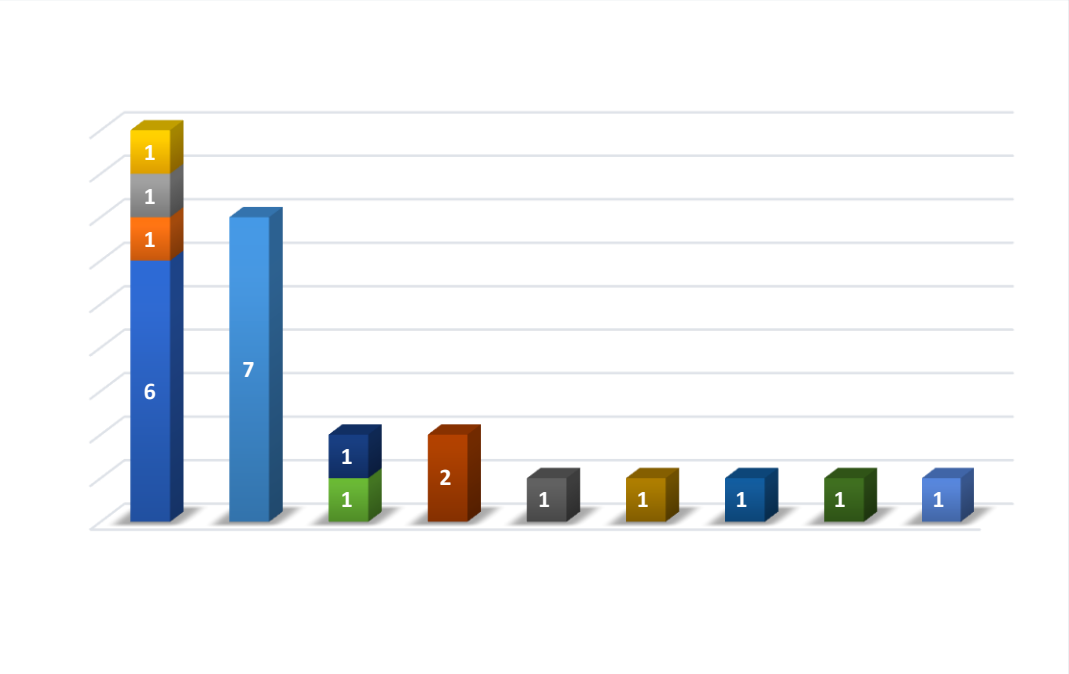

Fig. R6: Distribution of True +ve Cases

Discussion

The most frequent sites of primary tumors detected by 18F-FDG-PET/CT in this work were GIT & lungs in agreement with the literature ***(7).***

A study done by **(8)**, reported a sensitivity of 87% with a specificity of 83%. This study showed a detection rate of 83.4% in a group of 30 cases with CUP with 89.3%, 50% sensitivity and specificity respectively. In another study on a group of 136 patients, detection rate reached 49%; with sensitivity of 71% & specificity of 57.6%. Most of the included patients in that study presented with two or more metastatic sites **(9)**.

A meta-analysis on FDG-PET/CT reported sensitivities for primary tumor detection ranging between 87% and 91.9% which agrees with our study. However, detection rates ranging between 24.5% and 43%, and specificities ranging between 71% and 81.9% ***(10)*** which is against our result this may be rendered to the number of studied cases.

Another study, showing an agreement with our study, showing sensitivity of FDG-PET/CT in primary tumor detection in patients with cancer of unknown primary of 82% and specificity of 44%. Diagnostic accuracy (ACC), Positive predictive value (PPV) and negative predictive value (NPV) were 73%, 93% and 28%, respectively. The specificity rate of FDG-PET/CT was less than the literature, indicating a higher rate of false positive results, which might be reasoned by higher frequency of granulomatous diseases ***(11)***.

A study done by **(12)** found that A careful history review and patient clinical examination are extremely important to increase FDG-PET/CT specificity, because inflammatory lesions are found to be among the most common non oncological causes of FDG uptake with 37% of benign lesions being inflammatory in nature. Also, **(13*)*** stated that the high false positive results rates can be attributed to FDG uptake caused by increased cellular metabolism in inflammatory lesions. Unfortunately, FDG is not a cancer-specific tracer and its uptake has been described in a number of inflammatory lesions like tuberculosis, sarcoidosis, fungal infections, and cerebral abscesses ***(13).***

However, false negatives can be explained by facts that tumor cells in the metastatic

lesions may differ in biological features from those of the primary tumor, metastases may uptake higher FDG levels than the primary, FDG uptake can be small or absent, in low grade epithelial tumors ***(14).*** Also, the primary tumor size may be smaller than the resolution power of FDG-PET/CT especially in anatomically complicated areas as in abdomen and pelvis and in breast cancer with low18F-FDG uptake ***(15).*** Another explanation by ***(16)*** that the primary tumor may vanish after sending the metastasis because its angiogenic incompetence and apoptosis or because it may have spontaneously regressed. Also, false negative FDG PET/CT results may be caused by a high background signal, which results from the presence of physiological FDG uptake especially in the neck and gastrointestinal tract; this may hide the primary lesion ***(11).***

To reduce the number of false positive and false negative results, applying dual-time-point FDG PET/CT imaging might help to differentiate between malignant and non-malignant lesions ***(12).***

True negative results might favor the hypothesis of biological features in CUP angiogenetic incompetence of the tumor at primary site, which leads to severe apoptosis and cell turnover, reflecting its clinical disappearance ***(11).*** Also, may be due to wrong clinical suspicious of malignancy by the clinicians. The high reliability of true negative result on PET/CT image can help avoid unnecessary surgical or invasive interventions for further identifications ***(17).***

Conclusion and Recommendations

- FDG-PET/CT information improves the accuracy of diagnostic imaging in patients with CUP with sensitivity of 89.3%, accuracy of 86.6 % and specificity of 50%.
- Even in false negative cases, FDG PET/CT could detect further unknown metastatic lesions that modifying the disease stage with positive impact on patient's management.
- FDG PET/CT is a single modality with several practical advantages in primary tumor site early detection in CUP patients compared to multiple investigations, thus facilitating early selection of proper treatment protocols and improving patient's prognosis.

References

1. Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet. 2012 Apr 14;379(9824):1428-35.

2. Pavlidis N, Fizazi K. Carcinoma of unknown primary (CUP). Crit Rev Oncol Hematol. 2009 Mar;69(3):271-8.
3. Varadhachary GR, Raber MN. Cancer of unknown primary site. N Engl J Med. 2014 Aug 21;371(8):757-65.
4. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al; European Association of Nuclear Medicine (EANM). FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015 Feb;42(2):328-54.
5. Roh JL, Kim JS, Lee JH, Cho KJ, Choi SH, Nam SY, et al. Utility of combined (18)F-fluorodeoxyglucose-positron emission tomography and computed tomography in patients with cervical metastases from unknown primary tumors. Oral Oncol. 2009 Mar;45(3):218-24.
6. Yapar Z, Kibar M, Yapar AF, Paydas S, Reyhan M, Kara O, et al. The value of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in carcinoma of an unknown primary: diagnosis and follow-up. Nucl Med Commun. 2010 Jan;31(1):59-66.
7. Yaylali O, Kiraç FS, Yüksel D. The role of 18F-FDG PET-CT in the detection of unknown primary malignancy: a retrospective study. Turk J Med Sci. 2016 Feb 17;46(2):474-82.
8. Karapolat I, Kumanlıoğlu K. Impact of FDG-PET/CT for the Detection of Unknown Primary Tumours in Patients with Cervical Lymph Node Metastases. Mol Imaging Radionucl Ther. 2012 Aug;21(2):63-8.
9. Møller AK, Loft A, Berthelsen AK, Pedersen KD, Graff J, Christensen CB, et al. A prospective comparison of 18F-FDG PET/CT and CT as diagnostic tools to identify the primary tumor site in patients with extracervical carcinoma of unknown primary site. Oncologist. 2012;17(9):1146-54.
10. Thapa P, Kalshetty A, Basu S. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in carcinoma of unknown primary: A subgroup-specific analysis based on clinical presentation. World J Nucl Med. 2018 Oct-Dec;17(4):219-222.
11. Tamam C, Tamam M, Mulazimoglu M. The Accuracy of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in the Evaluation of Bone Lesions of Undetermined Origin. World J Nucl Med. 2016 May-Aug;15(2):124-9.
12. Parghane RV, Basu S. Dual-time point ^{18}F-FDG-PET and PET/CT for Differentiating Benign From Malignant Musculoskeletal Lesions: Opportunities and Limitations. Semin Nucl Med. 2017 Jul;47(4):373-391.
13. Dong MJ, Zhao K, Lin XT, Zhao J, Ruan LX, Liu ZF. Role of fluorodeoxyglucose-PET versus fluorodeoxyglucose-PET/computed tomography in detection of unknown primary tumor: a meta-analysis of the literature. Nucl Med Commun. 2008 Sep;29(9):791-802.
14. Kwee TC, Basu S, Saboury B, Ambrosini V, Torigian DA, Alavi A. A new dimension of FDG-PET interpretation: assessment of tumor biology. Eur J Nucl Med Mol Imaging. 2011 Jun;38(6):1158-70.

15. Fencl P, Belohlavek O, Skopalova M, Jaruskova M, Kantorova I, Simonova K.
16. carcinoma of unknown primary. Eur J Nucl Med Mol Imaging. 2007 Nov;34(11):1783-92.
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.
Prognostic and diagnostic accuracy of [18F]FDG-PET/CT in 190 patients with
18. Vercellino L, Montravers F, de Parades V, Huchet V, Kerrou K, Bauer P, et al. Impact of FDG PET/CT in the staging and the follow-up of anal carcinoma. Int J Colorectal Dis. 2011 Feb;26(2):201-10.

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