

The diagnostic contribution of (18)F-FDG PET/CT scan in cancer of unknown primary

Primeri bilinmeyen kanserde F(18)-FDG PET/BT tetkikinın tanıya katkısı

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SUMMARY

Objective: The aim of the present study was to evaluate the clinically diagnostic contribution of ¹⁸F-fluorodeoxyglucose positron emission tomography combined with computed tomography (¹⁸F-FDG PET/CT) in patients with cancer of unknown primary (CUP).

Method: The retrospective investigation, cross-sectional analysis of 124 ¹⁸F-FDG PET/CT scans of patients with CUP between June 2014 and July 2015 was performed. The increased ¹⁸F-FDG uptake focus were assessed in correlation with histopathology. The diagnostic accuracy, sensitivity, specificity, positive predictive value and negative predictive values were assessed for ¹⁸F-FDG PET/CT.

Results: The ¹⁸F-FDG PET/CT successfully detected primary tumor in 56 patients with high ¹⁸F-FDG uptake involvement (true positive, 45.2%). 58 patients whose final histopathology and clinically without evidence of a primary tumor (true negative, 46.8%). 8 patients whose final histopathologically and clinically without evidence of a primary tumor but high ¹⁸F-FDG uptake involvement (false positive, 6.4%). The ¹⁸F-FDG PET/CT scan results were negative for primary site localization in only 2 patients with no ¹⁸F-FDG uptake involvement (false negative, 1.6%). Generally, the diagnostic accuracy was found to be 91.9%, sensitivity 96.5%, specificity 87.8%, positive predictive value 87.5%, negative predictive value 96.6%, positive likelihood ratio 7.9% and negative likelihood ratio 0.04%.

Conclusions: It can be said that ¹⁸F-FDG PET/CT may be useful in the diagnosis of patients with CUP.

Keywords: Cancer of unknown primary, (18)F-FDG, PET/CT, sensitivity, specificity

ÖZET

Amaç: Bu çalışmanın amacı, primeri bilinmeyen kanser (PBK) hastalarında ¹⁸F-florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografinin (¹⁸F-FDG PET/BT) klinik olarak tanıya katkısını değerlendirmektir.

Yöntem: Retrospektif, kesitsel analiz çalışmasında Haziran 2014-Temmuz 2015 tarihleri arasında 124 PBK hastalarının ¹⁸F-FDG PET/BT incelemesi yapıldı. Artmış ¹⁸F-FDG tutulum odağının histopatoloji ile korelasyonu değerlendirildi. ¹⁸F-FDG PET/BT için tanısal doğruluk, duyarlılık, özgüllük, pozitif öngörü değeri ve negatif öngörü değerleri hesaplandı.

Bulgular: ¹⁸F-FDG PET/BT, yüksek ¹⁸F-FDG tutulumu olan 56 hastada primer tümör odağını başarıyla saptadı (gerçek pozitif, % 45.2). 58 hastada histopatolojik ve klinik olarak primer tümör bulunamadı (gerçek negatif, % 46.8). 8 hastada yüksek ¹⁸F-FDG uptake tutulumu olmasına karşın histopatolojik ve klinik olarak primer tümör kanıtı yoktu (yanlış pozitif, % 6.4). Sadece 2 hastada negatif ¹⁸F-FDG PET/BT tarama sonuç bulunmasına karşın primer tümör histopatolojik olarak saptandı (yanlış negatif, % 1.6) primer yerleşim lokalizasyonu için negatif idi. Genel olarak tanısal

doğruluk % 91.9, duyarlılık % 96.5, özgüllük % 87.8, pozitif öngörü değeri % 87.5, negatif öngörü değeri % 96.6, pozitif olabilirlik oranı % 7.9 ve negatif olabilirlik oranı % 0.04 olarak bulundu.

Sonuç: PBK hastalarının tanısında F18-FDG PET/BT'nin yararlı olabileceği düşünülebilir.

Anahtar sözcükler: Primeri bilinmeyen kanser, F18-FDG PET/BT, duyarlılık, özgüllük

INTRODUCTION

Cancer of unknown primary (CUP) is defined as the detection of metastatic cancer where the site of primary origin remains obscured even after diagnostic investigated and CUPs account for 3 to 5% of all malignancies¹. CUP accounts for approximately 2% of all new cancer diagnoses, and most registries place it within the top 10 malignancies². The annual age-adjusted incidence per 100,000 population in the United States is 7-12 cases³. CUP is a heterogeneous group of malignancies with variable histology⁴.

¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography combined with computed tomography (PET/CT) is a non-invasive diagnostic nuclear medicine imaging method which the existence of a proven tumor metastasis without evidence of a primary origin, and the management of the patients with CUP⁵. ¹⁸F-FDG PET/CT is allowing to determinate the localization of increased metabolic activity in tumor tissue⁶.

Also there are several research results about the performance of ¹⁸F-FDG PET/CT in patients with CUP in the literature. This study was to evaluate the clinically diagnostic performance, and utility of ¹⁸F-FDG PET/CT in patients with CUP.

MATERIAL AND METHODS

Study Design

This is a retrospective, cross-sectional study of patients with CUP who were referred to ¹⁸F-FDG PET/CT scan during the period of June 2014 to July 2015 and 124 patients (female: 44, male: 80; average age: 59.7 years, standard deviation: 13.3 and age range: 20-86 years) with metastases from an unknown primary tumor were included in this study. The patients' files with initial diagnosis of CUP were retrieved from the archive. 46 of 124 patients had histopathologically proven metastatic disease with unknown primary site. 78 out of 126 patients were enrolled with a clinical suspicion of malignancy due to history of profound weight loss or progressive weakness with elevated tumor markers or suspicious lesions on cross-sectional

radiological imaging where biopsy was not possible. When all available investigations could not detect primary, these patients were treated as confirmed CUP cases and were followed-up for a minimum of 12 months.

¹⁸F-FDG PET/CT Scan Protocol

All patients underwent ¹⁸F-FDG PET/CT scan according to the standard protocol. Patients had fasted for at least 6 h and their blood glucose levels were checked before ¹⁸F-FDG injection using a finger-stick blood glucose meter. The blood glucose level <160 mg/dl was ensured. A dose of 0.10 mCi/kg of body weight of ¹⁸F-FDG was injected intravenously to each patient under proper glycemic control. Each patient was obliged to drink at least 1 L of water. At 60 minutes, whole body PET/CT scan acquisition was performed by a dedicated PET scanner (Siemens Biograph 2, USA) with 3 min acquisition for each 8-9 bed positions (patient supine, arms on patient's side, vertex to thigh position). Spatial resolution for the PET scanner was 5 mm. Contrast enhanced CT scan was acquired over 1 min with a low dose of 70-120 kVp and tube current 10-90 mAs. No intravenous contrast material was used for the CT scans. The CT data were used for attenuation correction of PET images. Increased ¹⁸F-FDG uptake were evaluated by visual and semiquantitative analysis. For the semiquantitative evaluation of PET data, the metabolic activities of lesions were analyzed using standart uptake value (SUV). The SUV was calculated by normalizing the radioactivity concentration in a three-dimensional region of interest placed over the lesion, for patient weight and injected radioactivity. All image datasets were visually evaluated and quantitatively analyzed by a single nuclear medicine physician.

Data Analysis and Interpretation

In the investigation of a primary tumor, detection of the primary malignancy site was considered to be positive (true positive) only when confirmed by histopathology. If findings on ¹⁸F-FDG PET/CT scan did not turn out to be a primary site by histopathology, these were accepted as "false positive". Unremarkable ¹⁸F-FDG PET/CT scans were considered as true negative, while false

negative results indicated ^{18}F -FDG PET/CT scans where the primary site remained obscured.

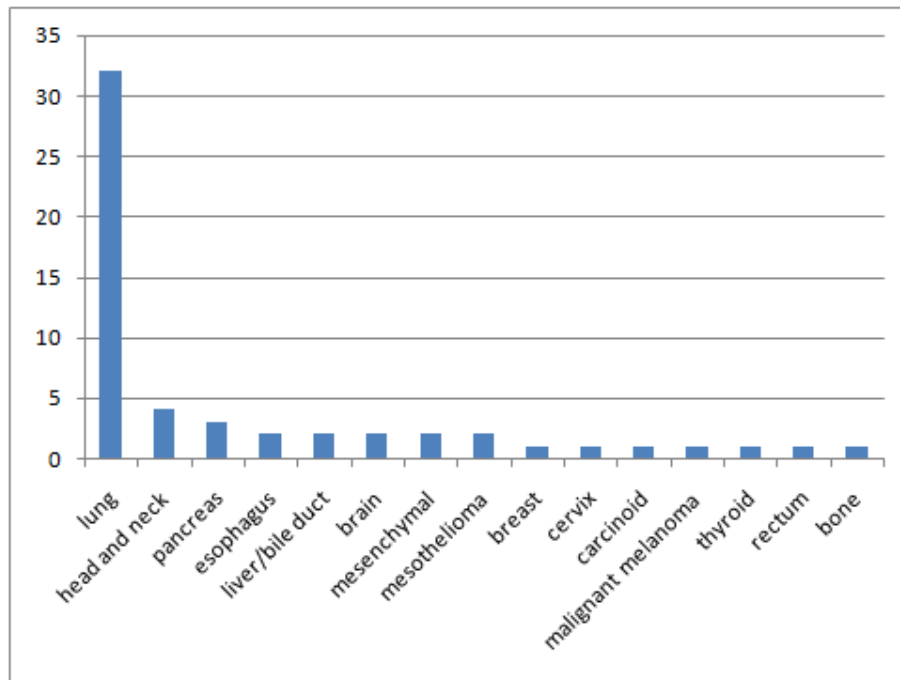
Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences version 15 (Chicago, IL, USA). Means of metric variables were compared using two-sample t-test. Levene's test was used to test the equality of variance of the variables. Correlation was tested using Spearman's correlation test. Quantitative variables (e.g. age) were presented as mean \pm SD. Qualitative variables (e.g. gender, identified unknown primary tumors on PET/CT) were expressed as frequency and percentages. The sensitivity, specificity, accuracy, positive predictive values, negative predictive values, positive likelihood ratio and negative likelihood ratio were calculated for ^{18}F -FDG PET/CT scans. Statistical significance was considered with a $p < 0.05$.

RESULTS

True positive ^{18}F -FDG PET/CT scans

^{18}F -FDG PET/CT correctly detected primary tumor in 56 (45.2%) of 124 patients (female: 16, male: 40; average age: 60.4 \pm 12.6 years). All of these patients primary sites were subsequently proven by histopathology. The most common site of primary tumor detected by ^{18}F -FDG PET/CT was lung (n = 32), which was followed by head and neck (n = 4), pancreas (n = 3), esophagus (n = 2), liver/bile ducts (n = 2), brain (n = 2), mesenchymal (n = 2), mesothelioma (n = 2) and other (n = 7; breast, cervix, carcinoid, malignant melanoma, thyroid, rectum and bone) (Graphic 1). Fasting blood glucose levels were 120.3 \pm 18.4 mg/dl and SUVmax values calculated 10.9 \pm 9.1. The images of patient with true positive ^{18}F -FDG PET/CT scan were shown in Figure 1.



Graphic 1. Primary tumors indicated by ^{18}F -FDG PET/CT scan as true positive.

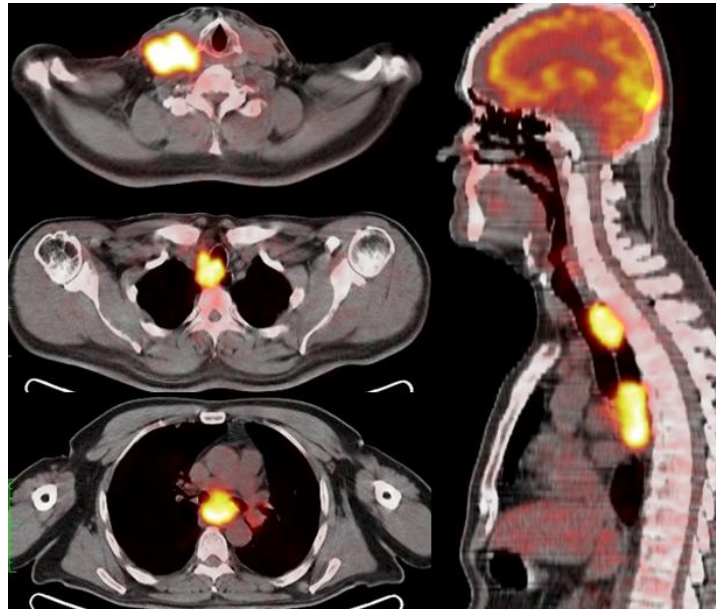
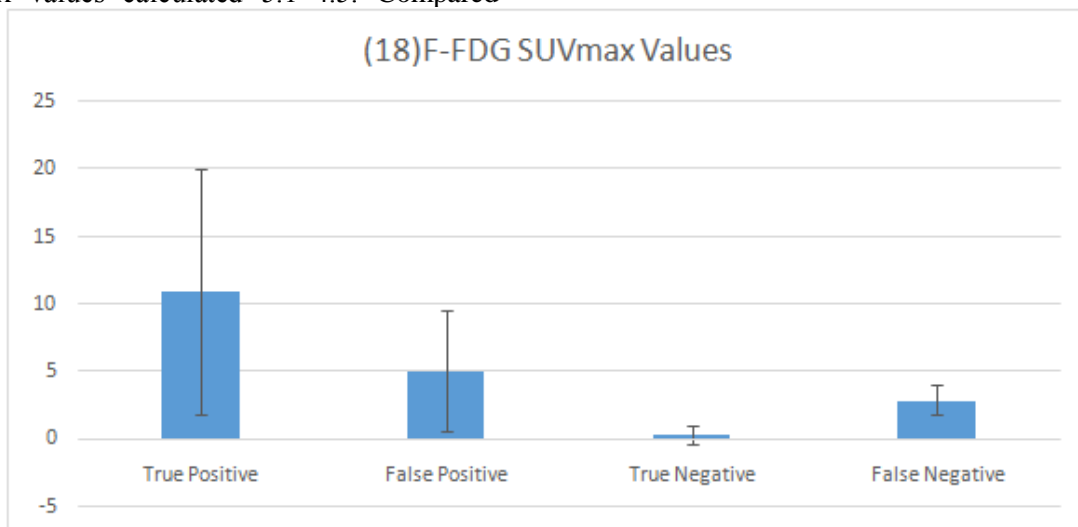


Figure 1. ¹⁸F-FDG PET/CT in a 58-year-old man who presented with a pathologically proven metastatic squamous cell cancer of unknown primary in enlarged right cervical lymph node. ¹⁸F-FDG PET/CT in the axial and sagittal plane shows intense ¹⁸F-FDG uptake in the right cervical lymph node, mediastinum and distal esophagus (SUVmax: 21,3). Histopathological examination of a directed biopsy was revealed in squamous cell carcinoma of the distal esophagus.

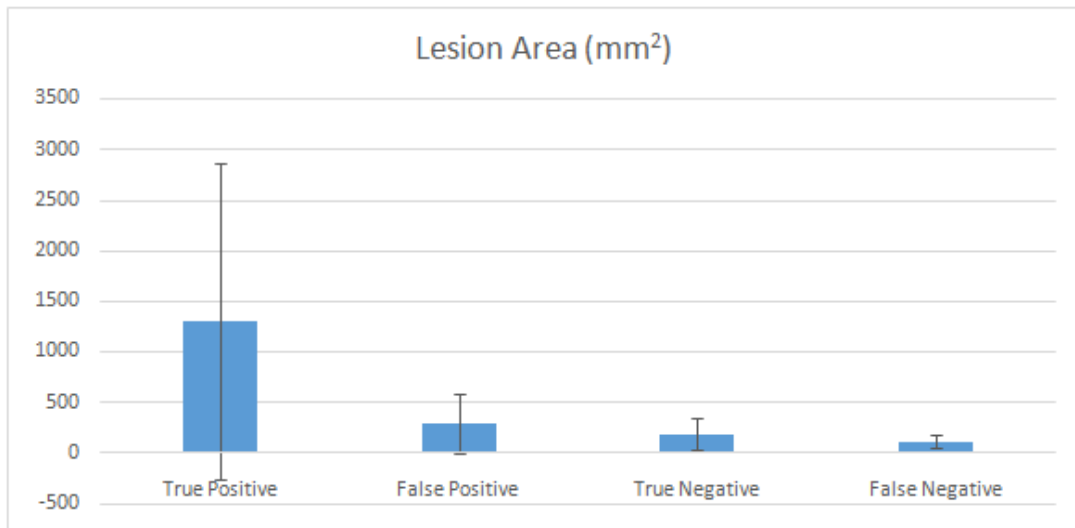
False positive ¹⁸F-FDG PET/CT scans

In 8 (6.4%) patients (female: 6, male: 2; average age: 63.7±12.2 years), the hypermetabolic lesions that were identified on ¹⁸F-FDG PET/CT scans did not turn out to be malignant/primary on subsequent biopsy. Lymph node biopsy was reported as a post-infection reaction. Fasting blood glucose levels were 119.2±21.1 mg/dl and SUVmax values calculated 5.1±4.5. Compared

with true positive results, there was a significantly low SUVmax value in false positive patients (p = 0.028, Graphic 2). Compared with true positive results, there was a significantly low lesion area in false positive patients (true positive lesion size: 1302.5±1568.6 mm² vs false positive lesion size: 293.3±296.3 mm², p = 0.005, Graphic 3). The images of patient with false positive ¹⁸F-FDG PET/CT scan were shown in Figure 2.



Graphic 2. Comparisons of all patient with CUP characteristics according to SUVmax values.



Graphic 3. Comparisons of all patient with CUP characteristics according to lesion size.

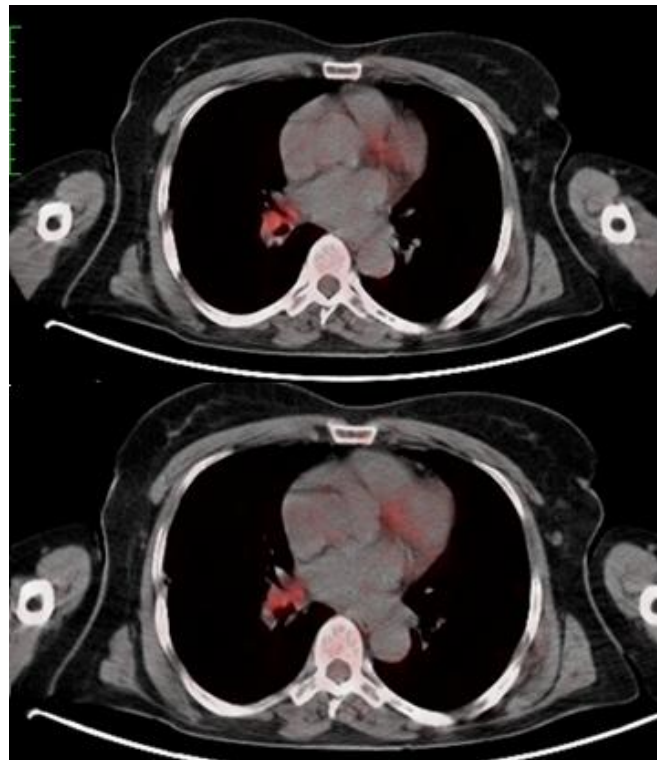


Figure 2. A 62-year-old-female patient with false positive ^{18}F -FDG PET/CT scan. Axial ^{18}F -FDG PET/CT scan show hypermetabolic foci in mediastinum soft tissue mass (SUVmax: 5.6). Biopsy of the mediastinum mass revealed post-infection granulomatous reaction.

True negative ^{18}F -FDG PET/CT scans

58 (46.8%) of 124 patients (female: 21, male: 37; average age: 58.1 ± 14.2 years) analyzed in our study remained without clinically evidence of a primary tumor. ^{18}F -FDG PET/CT scans performed in this study subgroup did not reveal any suspicious area likely to be a primary neoplasm.

Fasting blood glucose levels were 117.4 ± 15.8 mg/dl and SUVmax values calculated 0.3 ± 0.7 .

False negative ^{18}F -FDG PET/CT scans

The remaining 2 (1.6%) patients (female: 1, male: 1; average age: 70 ± 1.4 years) were false negative studies, in which the known sites of metastasis or additional sites of metastasis not showed ^{18}F -FDG

PET/CT scans while primary site could be identified by histopathology. The cancer diagnoses of these patients were head and neck and bladder. Fasting blood glucose levels were 123.5 ± 9.1 mg/dl and SUVmax values calculated 2.9 ± 1.1 .

DISCUSSION

The CUP, a heterogeneous group of epithelial cancers, is defined as a biopsy-proven malignancy whose anatomical origin remains unidentified after a thorough diagnostic evaluation^{7,8}. Investigating a primary tumor in CUP has always been a diagnostic problem. Early detection of primary tumor site by specific therapy improves prognosis⁹. If there was still no evidence of primary tumor, PET/CT examination was considered. In CUP, diagnostic ¹⁸F-FDG PET/CT is a useful tool for the delineation of a primary focus as it provides functional and morphological detail¹⁰⁻¹³. The behavior of the tumor is significantly dependent on the location of the primary disease¹⁴.

¹⁸F-FDG PET/CT is widely used in routine clinical practice in the management of various types of cancers. Its accuracy in initial staging is better than CT but may be similar to magnetic resonance imaging. ¹⁸F-FDG PET/CT scan is important in the detection of the primary site in patients with CUP with a success rate of 27%, after all other conventional imaging modalities have failed¹⁵. The diagnostic accuracy of ¹⁸F-FDG PET/CT imaging in patient with CUP group is influenced by a number of factors, including the tumor biological behavior, size, and anatomical location¹⁶. In respect of determining primary localization, ¹⁸F-FDG PET/CT's sensitivity was determined as 66.6%, its specificity as 33.3%, its positive predictive value as 80%, and its negative predictive value as 20%¹⁷. Roh et al. have shown that sensitivity of ¹⁸F-FDG PET/CT (87.5%) was significantly higher ($p = 0.016$) than that of CT alone (43.7%) in detecting primary tumors in 44 patients presenting with cervical metastases from unknown origin¹⁸. Similarly, in the study by Nassenstein et al. who investigated 39 patients with cervical metastases of unknown origin CT alone revealed the primary tumor in only 5 patients (13%), while ¹⁸F-FDG PET/CT PET alone and combined ¹⁸F-FDG PET/CT detected a primary tumor in 10 patients (26%) and 11 patients (28%), respectively¹⁹. Wang et al. have shown that the accuracy, sensitivity and specificity of ¹⁸F-FDG PET/CT scan 93.7%, 95.7% and 91.7% respectively²⁰. Generally, the

¹⁸F-FDG PET/CT's diagnostic accuracy was determined as 91.9%, its sensitivity as 96.5%, its specificity as 87.8%, its positive predictive value as 87.5%, its negative predictive value as 96.6%, its positive likelihood ratio as 7.9%, and its negative likelihood ratio as 0.04%.

diagnostic accuracy was found to be 91.9%, sensitivity 96.5%, specificity 87.8%, positive predictive value 87.5%, negative predictive value 96.6%, positive likelihood ratio 7.9% and negative likelihood ratio 0.04% in this study.

The SUVmax is a prognostic factor influencing survival of patients with CUP²¹. High ¹⁸F-FDG uptake pattern on PET/CT scan were found to be important predictors in localizing the primary site of malignancy. The SUV-based quantitative analysis of the high ¹⁸F-FDG uptake lesions by ¹⁸F-FDG PET/CT is the most important diagnostic criteria to distinguish benign from malignant tumors. Currently, a maximum SUV of 2.5 is a widely accepted standard threshold in the diagnosis of malignancy²². In our study, the average SUVmax value was reported to be 10.9 ± 9.1 in patient with true positive ¹⁸F-FDG PET/CT scan.

In 85% of patients with neck lymph nodes metastasis the primary tumor is localized in the head and neck region²³. Pathologically isolated nodal metastases can be divided into squamous cell cancers, adenocarcinomas and undifferentiated tumors²⁴.

The ¹⁸F-FDG is not a cancer-specific agent and an optimal tracer for every anatomical region, especially with concomitant inflammatory process, may conceal or even simulate the neoplasm, which produces false negative or false positive results²⁵. Further studies showed that the cells involved in the infection and inflammation, especially neutrophils and monocytes/macrophages, have demonstrated levels of ¹⁸F-FDG uptake²⁶. Literature on the exact causes of false positive ¹⁸F-FDG PET/CT results is benign inflammatory lesions and pulmonary infarction have been reported etiologies²⁷⁻²⁹. Our study showed 8 false positive ¹⁸F-FDG PET/CT scans, that indicated the post-infection reaction.

This relates to small tumors size (not more than 15 mm) that is on the borderline of PET scan resolution. Moreover, well-differentiated squamous cell carcinoma is characterized by a lower ¹⁸F-FDG uptake that may be wrongly interpreted as negative³⁰. Similar to that in the breast, false-negative ¹⁸F-FDG PET/CT results in

other locations are most likely attributable to small lesion size and low or no ^{18}F -FDG uptake. The small CUP with a size around or below the spatial resolution of a PET system may not be reliably detected unless high FDG uptake is present⁵. In this study, ^{18}F -FDG PET/CT results displayed false negative in two patients with head and neck and bladder cancer. The tumor size of the patient with head and neck cancer was 12x10 mm.

CONCLUSION

In conclusion, our study confirmed a high effectiveness of ^{18}F -FDG PET/CT in the diagnosis process of patients with CUP to sensitivity, specificity, and accurately. FDG-PET/CT is a potentially useful imaging modality in the setting of CUP from lesion size and SUVmax values aspects.

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