CMJ Original Research September 2018, Volume: 40, Number: 3
Cumhuriyet Medical Journal 238-245
http://dx.doi.org/10.7197/223.vi.412273

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

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

Serdar Savaş Gül

Department of Nuclear Medicine, Gaziosmanpaşa University, Faculty of Medicine, Tokat, Turkey
Corresponding author: Serdar Savaş Gül, MD., Department of Nuclear Medicine, Gaziosmanpaşa University, Faculty of Medicine, Tokat, Turkey
E-mail: gopnukleertip@gmail.com
Received/Accepted: April 03, 2018 / July 31, 2018
Conflict of interest: There is not a conflict of interest.

SUMMARY

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

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

Results: The ^{18}F-FDG PET/CT successfully detected primary tumor in 56 patients with high ^{18}F-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 histopathologicallyand clinically without evidence of a primary tumor but high ^{18}F-FDG uptake involvement (false positive, 6.4%). The ^{18}F-FDG PET/CT scan results were negative for primary site localization in only 2 patients with no ^{18}F-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 ^{18}F-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 (F18-FDG PET/BT) klinik olarak tanıya katkısını değerlendirmektir.

Yöntem: Retrospektif, kesitsel analiz çalışmasında Haziran 2014-Temmuz 2015 tarihleri arasında 124 PBK hastalarının F18-FDG PET/BT incelemesi yapıldı. Artmış 18F-FDG tutulum odağının histopatoloji ile korelasyonu değerlendirildi. F18-FDG PET/BT için tanısal doğruluk, duyarlılık, özgüllük, pozitif öngörü değeri ve negatif öngörü değerleri hesaplandı.

Bulgular: F18-FDG PET/BT, yüksek F18-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 F18-FDG uptake tutulumu olmasına karşın histopatolojik ve klinik olarak primer tümör kanıtı yoktu (yanlış pozitif, % 6.4). Sadece 2 hastada negatif F18-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 investiged and CUPs account for 3 to 5% of all malignancies[1]. CUP accounts for approximately 2% of all new cancer diagnoses, and most registries place it within the top 10 malignancies[2]. The annual age-adjusted incidence per 100,000 population in the United States is 7-12 cases[3]. CUP is a heterogeneous group of malignancies with variable histology[4].

^{18}F-fluorodeoxyglucose (^{18}F-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 CUP[5]. ^{18}F-FDG PET/CT is allowing to determinate the localization of increased metabolic activity in tumor tissue[6].

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

^{18}F-FDG PET/CT Scan Protocol

All patients underwent ^{18}F-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 ^{18}F-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 ^{18}F-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 ^{18}F-FDG PET/CT scan did not turn out to be a primary site by histopathology, these were accepted as "false positive". Unremarkable ^{18}F-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.

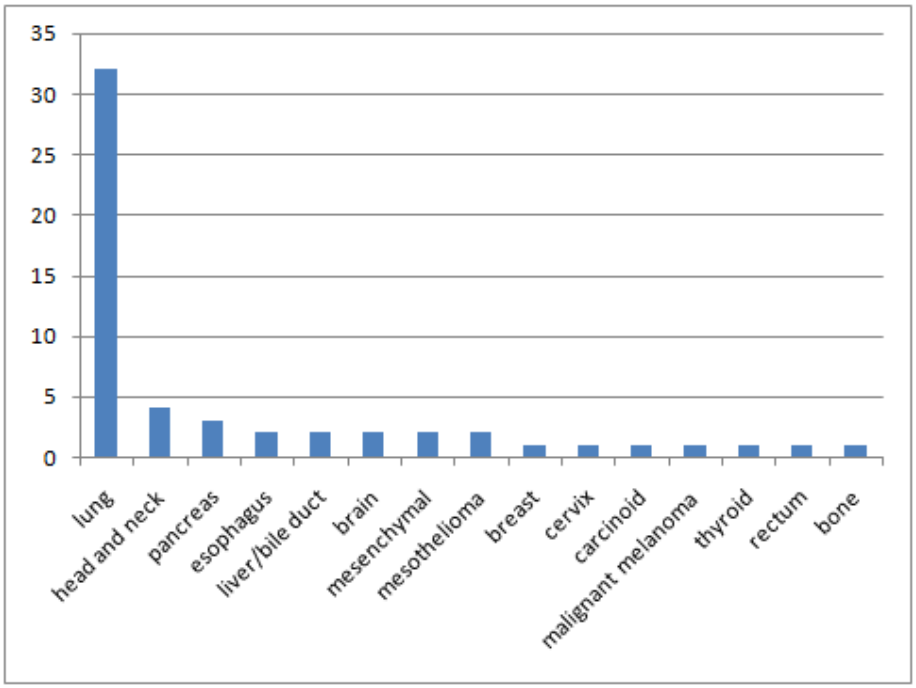
Statistical Analysis

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±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±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±18.4 mg/dl and SUVmax values calculated 10.9±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.

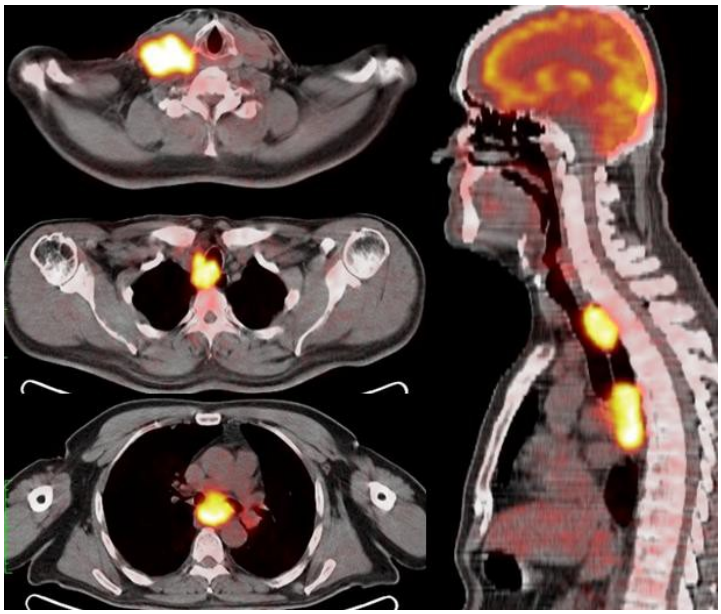
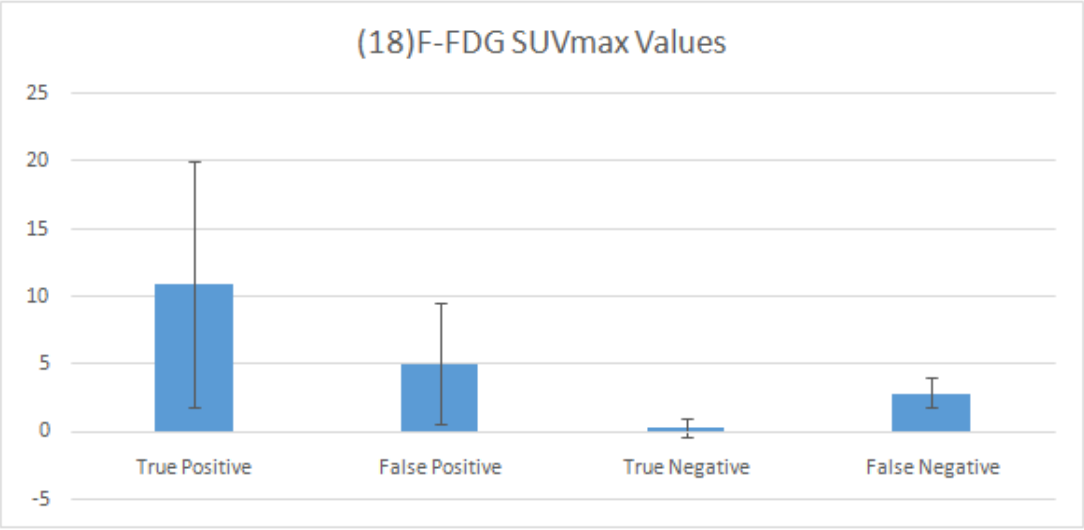


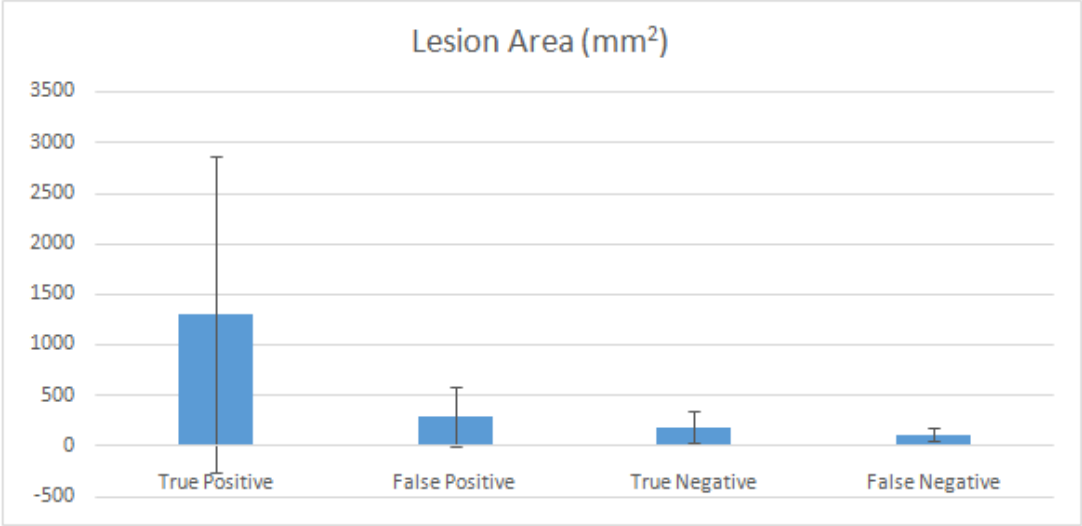
Figure 1. ^{18}F-FDG PET/CT in a 58-year-old man who presented with a pathologically proven metastatic squamous cell cancer of unknown primary in enlarged right cervical lymph node. ^{18}F-FDG PET/CT in the axial and sagittal plane shows intense ^{18}F-FDG uptake in the right cervical lymph node, mediastinum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

False positive ^{18}F-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 ^{18}F-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 mm^2 vs false positive lesion size: 293.3±296.3 mm^2, $p = 0.005$, Graphic 3). The images of patient with false positive ^{18}F-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.

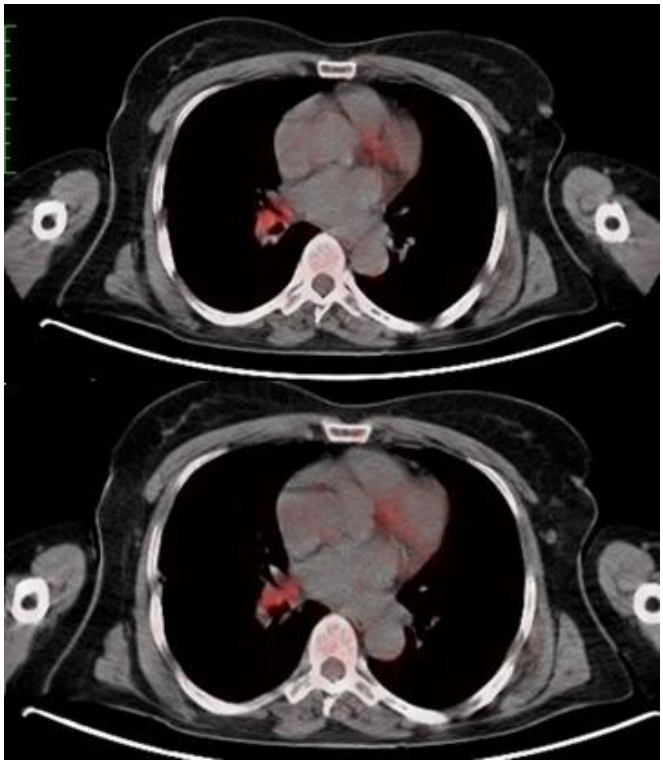


Figure 2. A 62-year-old-female patient with false positive ^{18}F-FDG PET/CT scan. Axial ^{18}F-FDG PET/CT scan show hypermetabolic foci in mediastinum soft tissue mass (SUVmax: 5.6). Biopsy of the mediastinum mass revealed post-infection granulomatous reaction.

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 prognosis[9]. If there was still no evidence of primary tumor, PET/CT examination was considered. In CUP, diagnostic ^{18}F-FDG PET/CT is a useful tool for the delineation of a primary focus as it provides functional and morphological detail[10-13]. The behavior of the tumor is significantly dependent on the location of the primary disease[14].

^{18}F-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. ^{18}F-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 failed[15]. The diagnostic accuracy of ^{18}F-FDG PET/CT imaging in patient with CUP group is influenced by a number of factors, including the tumor biological behavior, size, and anatomical location[16]. In respect of determining primary localization, ^{18}F-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 ^{18}F-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 origin[18]. 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 ^{18}F-FDG PET/CT PET alone and combined ^{18}F-FDG PET/CT detected a primary tumor in 10 patients (26%) and 11 patients (28%), respectively[19]. Wang et al. have shown that the accuracy, sensitivity and specificity of ^{18}F-FDG PET/CT scan 93.7%, 95.7% and 91.7% respectively[20]. Generally, the ^{18}F-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 CUP[21]. High ^{18}F-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 ^{18}F-FDG uptake lesions by ^{18}F-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 malignancy[22]. In our study, the average SUVmax value was reported to be 10.9 ±9.1 in patient with true ^{18}F-FDG positive PET/CT scan.

In 85% of patients with neck lymph nodes metastasis the primary tumor is localized in the head and neck region[23]. Pathologically isolated nodal metastases can be divided into squamous cell cancers, adenocarcinomas and undifferentiated tumors[24].

The ^{18}F-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 results[25]. Further studies showed that the cells involved in the infection and inflammation, especially neutrophils and monocytes/macrophages, have demonstrated levels of ^{18}F-FDG uptake[26]. Literature on the exact causes of false positive ^{18}F-FDG PET/CT results is benign inflammatory lesions and pulmonary infarction have been reported etiologies[27-29]. Our study showed 8 false positive ^{18}F-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 ^{18}F-FDG uptake that may be wrongly interpreted as negative[30]. Similar to that in the breast, false-negative ^{18}F-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 present[5]. 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.

REFERENCES

1- Fizazi K, Greco FA, Pavlidis N. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011;22 Suppl 6:vi64-68.

2- Elboga U, Kervancioğlu S, Sahin E, Basibuyuk M, Celen YZ, Aktolun C. Utility of F-18 fluorodeoxyglucose posıtron emıssıon tomography/computed ın carcınoma of unknown primary. Int J Clin Exp Pathol 2014;7(12):8941-6.

3- Pavlidis N, Fizazi K. Carcinoma of unknown primary (CUP). Crit Rev Oncol Hematol 2009;69:271-8.

4- Klein CA. Parallel progression of primary tumors and metastases. Nat Rev Cancer 2009;9:302-12.

5- Kwee TC, Basu S, Alavi A. PET and PET/CT for unknown primary tumors. Methods Mol Biol 2011;727:317-33.

6- Hasbek Z, Doğan ÖT, Sarı İ, Yücel B, Şeker MM, Turgut B, Berk S, Siliğ Y. The Diagnostic Value of the Correlation between Serum Anti-p53 Antibody and Positron Emission Tomography Parameters in Lung Cancer. Mol Imaging Radionucl Ther 2016;25(3):107-13.

7- Kwee TC, Kwee RM. Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis. Eur Radiol 2009;19(3):731-44.

8- Bochtler T, Löffler H, Kramer A. Diagnosis and management of metastatic neoplasms with unknown primary. Semin Diagn Pathol 2017. pii: S0740-2570(17)30147-8.

9- Riaz S, Nawaz MK, Faruqui ZS, Kazmi SA, Loya A, Bashir H. Diagnostic Accuracy of 18F-Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography in the Evaluation of Carcinoma of Unknown Primary. Mol Imaging Radionucl Ther 2016;25(1):11-8.

10- Talavera-Rubio MP, Garcia-Vicente AM, Palomar-Munoz AM, Pilkington-Woll JP, Poblete-Garcia VM, Soriano-Castrejon A. Usefulness of (18) F-fluorodeoxyglucose-positron emission tomography computerized tomography in the identification of the primary tumor in patients with cancer of unknown origin. Med Clin (Barc) 2013;140:14-9.

11- Burglin SA, Hess S, Hoilund-Carlsen PF, Gerke O. 18F-FDG PET/CT for detection of the primary tumor in adults with extracervical metastases from cancer of unknown primary: A systematic review and meta-analysis. Medicine (Baltimore) 2017;96(16):e6713.

12- Börksüz MF, Erselcan T, Hasbek Z, Yücel B, Turgut B. Morphologic and Metabolic Comparison of Treatment Responsiveness with 18Fludeoxyglucose-Positron Emission Tomography/Computed Tomography According to Lung Cancer Type. Mol Imaging Radionucl Ther 2016;25(2):63-9.

13- Hasbek Z, Yucel B, Salk I, Turgut B, Erselcan T, Babacan NA, Kacan T. Potential impact of atelectasis and primary tumor glycolysis on F-18 FDG PET/CT on survival in lung cancer patients. Asian Pac J Cancer Prev 2014;15(9):4085-9.

14- Santhanam P, Chandramahanti S, Kroiss A, Yu R, Ruszniewski P, Kumar R, et al. Nuclear imaging of neuroendocrine tumors with unknown primary: why, when and how? Eur J Nucl Med Mol Imaging 2015;42(7):1144-55.

15- Özman Ö, Arslan N. The Role of PET/CT in Head and Neck Cancer. Turkiye Klinikleri J E.N.T.-Special Topics 2010;3(4):72-81.

16- Su YY, Chen SS, Hsieh CH, Liao CT, Lin CY, Kang CJ, et al. Defining risk groups of patients with cancer of unknown primary site and cervical nodal metastases

by F-18 fluorodeoxyglucose positron emission tomography and computed tomography imaging. Kaohsiung J Med Sci 2016;32(8):407-13.
17- İnan İE, Kılıç C, Tunçel Ü. The correlation of positron emission tomography-computed tomography assessment with histopathological results in the diagnosis of head and neck cancer of unknown primary. Kulak Burun Bogaz Ihtis Derg 2012;22(6):319-23.
18- 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;45:218-24.
19- Nassenstein K, Veit-Haibach P, Stergar H, Gutzeit A, Freudenberg L, Kuehl H, et al. Cervical lymph node metastases of unknown origin: primary tumor detection with whole-body positron emission tomography/computed tomography. Acta Radiol 2007;48:1101-8.
20- Wang G, Wu Y, Zhang W, Li J, Wu P, Xie C. Clinical value of whole-body F-18 fluorodeoxyglucose positron emission tomography/computed tomography in patients with carcinoma of unknown primary. J Med Imaging Radiat Oncol 2013;57:65-71.
21- Algin E, Ozet A, Gumusay O, Cetin B, Akdemir UO, Benekli M, et al. Association between survival and maximum standardized uptake value of liver metastases detected by 18-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography in patients with adenocarcinoma of unknown primary origin. Ann Nucl Med 2014;28(9):891-6.
22- Ouyang L, Shi ZY, Lin ZG. 18F-FDG PET-CT makes a significant contribution to diagnosis of malignancy in patients with cervical lymphadenopathy: a study using optimal scale regression tests. Chin Med J (Engl) 2013;126:659-67.
23- Chorost MI, Lee MC, Yeoh CB, Molina M, Ghosh BC. Unknown primary. J Surg Oncol 2004;87(4):191-203.
24- Regelink G, Brouwer J, de Bree R. Detection of unknown primary tumours and distant metastases in patients with cervical metastases: value of FDG-PET versus conventional modalities. Eur J Nucl Med Mol Imaging 2002;29(8):1024-30.
25- Stokkel MP, Bongers V, Hordijk GJ, van Rijk PP. FDG positron emission tomography in head and neck cancer: pitfall or pathology? Clin Nucl Med. 1999;24:950-4.
26- Çakır T, Atasever T. F-18 Flourodeoxy Glucose Positron Emission Tomography/ Computed Tomography Imaging in Infection and Inflammation. Nucl Med Semin 2016;2:79-89.
27- Nassenstein K, Veit-Haibach P, Stergar H, Gutzeit A, Freudenberg L, Kuehl H, et al. Cervical lymph node metastases of unknown origin: primary tumor detection with whole-body positron emission tomography/computed tomography. Acta Radiol 2007;48:1101-8.
28- Gutzeit A, Antoch G, Kühl H, Egelhof T, Fischer M, Hauth E, et al. Unknown primary tumors: detection with dual-modality PET/CT-initial experience. Radiology 2005;234:227-34.
29- Kaya AO, Coskun U, Unlu M, Akdemir UO, Ozdemir NY, Zengin N, et al. Whole body 18F-FDG PET/CT imaging in the detection of primary tumours in patients with a metastatic carcinoma of unknown origin. Asian Pac J Cancer Prev 2008;9:683-6.
30- Kole AC, Nieweg OE, Pruim J. Detection of unknown occult primary tumors using positron emission tomography. Cancer 1998;82:1160-6.