Original article

The Accuracy of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in the Evaluation of Bone Lesions of Undetermined Origin

Cuneyt Tamam, Muge Tamam[1], Mehmet Mulazimoglu[1]

Department of Orthopedics and Traumatology, Kasimpasa Military Hospital, [1]Department of Nuclear Medicine, Okmeydani Training and Research Hospital, Istanbul, Turkey

Abstract

The aim of the current study was to determine the diagnostic accuracy of whole-body fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) in detecting carcinoma of unknown primary (CUP) with bone metastases. We evaluated 87 patients who were referred to FDG-PET/CT imaging and reported to have skeletal lesions with suspicion of malignancy. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated. The median survival rate was measured to evaluate the prognostic value of the FDG-PET/CT findings. In the search for a primary, FDG-PET/CT findings correctly diagnosed lesions as the site of the primary true positive (TP) in 64 (73%) cases, 4 (5%) findings diagnosed no site of a primary, and none were subsequently proven to be true negative (TN); 14 (16%) diagnoses were false positive (FP) and 5 (6%) diagnoses were false negative (FN). Life expectancy was between 2 months and 25 months. Whole-body FDG-PET/CT imaging may be a useful method in assessing the bone lesions with suspicion of bone metastases.

Keywords: Bone lesions, carcinoma of unknown primary, 18-fluorodeoxyglucose positron emission tomography/computed tomography, granulomatous disease

Introduction

Carcinoma of unknown primary (CUP) origin is a heterogeneous group of cancers defined by the presence of metastatic disease with no identified primary tumor at initial presentation.[1] CUP accounts for 3–5% of all malignancies in the world and is the fourth most common cause of death from cancer in both males and females. The skeleton, especially its axial and proximal appendicular portion, is a common site for metastasis.[2,3] Among the patients with CUP, 10–15% have skeletal involvement.[4] Clinically, skeletal metastasis of unknown origin is suspected in patients who have symptomatic, osteolytic skeletal lesion with poor margination and who are older than 40 years of age.[3] More than 50% of advanced stage malignant tumors may implicate bones. In general, CUP has an aggressive biological and clinical behavior, with a poor outcome.[2,5] Median survival ranges from only 2 months to 10 months.[3]

Conventional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound provide mainly morphologic information on the primary tumor and potential metastasis. The radiotracer fluorine-18 (18F)-fluorodeoxyglucose (FDG)

Address for correspondence:
Dr. Cuneyt Tamam, Department of Orthopedics and Traumatology, Kasimpasa Military Hospital, Istanbul, Turkey.
E-mail: ctamam@yahoo.com

Access this article online

Quick Response Code:

Website: www.wjnm.org

DOI: 10.4103/1450-1147.176885

How to cite this article: 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;15:124-9.

positron emission tomography (PET) offers functional data on tumor metabolism. Hybrid imaging by FDG-PET/CT enhances the diagnostic capability of detecting the primary tumor by fusing morphologic and functional data.[6,7] FDG-PET/CT has the capacity to detect different tumor types in the whole body with a noninvasive approach and in a single examination.[8]

The purpose of this study was to retrospectively evaluate the accuracy of FDG-PET/CT in detecting the primary tumor in patients with skeletal metastases of unknown origin.

Patients and Methods

Patients

In this retrospective study, we reviewed the medical records and imaging results of 87 patients with skeletal lesions who were referred to FDG-PET/CT imaging between December 2007 and May 2010 for the evaluation of suspicious CUP.

The sample included 55 men (63.3%) and 32 women (36.7%), with a mean age of 60 ± 11 years (range: 32–82 years) who had been followed up for a mean period of 6 months.

The inclusion criteria were having negative results from physical examination, laboratory tests, or conventional imaging modalities which had been conducted for the evaluation of suspicious CUP. None of the patients had a history of cancer and related chemotherapy and/or radiation therapy prior to the FDG-PET/CT imaging. Biopsy was performed for all the patients who received a diagnosis of possible primary lesion in FDG-PET/CT.

The patients with no primary lesion detected on FDG-PET/CT underwent bone biopsy and were clinically followed up for at least 6 months.

The exclusion criteria were having insufficient clinical data in medical files, absence of any histopathologic diagnosis for primary tumor, and having no clinical and radiologic follow-up of at least 6 months. The histopatological verification and/or follow-up data were accepted as a gold standard in the present study.

Patient preparations

The patients had fasted for at least 6 h and their blood glucose levels were controlled before FDG injection. All of the patients had blood glucose levels lower than 200 mg/dL. No intravenous (IV) contrast material was used for the CT scans. Water soluble iodinated contrast material diluted in 1,000 mL of water was given to each patient orally prior to the investigation. CT scans with oral contrast were performed to get a detailed image of the stomach and intestines.

Scanning procedure

18-fluorodeoxyglucose positron emission tomography/computed tomography imaging

Whole-body PET/CT imaging was performed on a biograph (Siemens Biograph 6, Chicago, IL, USA) using a full-ring high resolution (HI-REZ) LSO PET and a six-slice CT scanner (Siemens Biograph 6, Chicago, IL, USA). The data were acquired 50 min after the administration of FDG (296–555 MBq FDG according to body weight). The CT scan was performed first with the following parameters: 50 mAs, 140 kV, and 5-mm section thickness.

18F-FDG uptake was analyzed semiquantitatively by recording the maximum standardized uptake value (SUVmax) and qualitatively by visual interpretation of the images. The criterion for malignancy was FDG hypermetabolism at the site of most prominent lesion in bone visible on at least 2 contiguous PET slices-showing a higher maximum standardized uptake value (SUVmax) than background bone activity and corresponding to CT abnormalities not attributable to benign bone pathologies. Multiple myeloma (MM) was considered in hypermetabolic focal areas that was correlative to CT abnormalities such as lytic lesions, minor lytic changes, osteopenic areas. FDG-PET/CT images were analyzed in three planes––axial, coronal, and sagittal––in the gray scale color table for PET.

Statistical analysis

In calculating sensitivity and specificity, true positive (TP) was considered when FDGPET/CT suggested the location of the primary tumor and it was subsequently confirmed, whereas false positive (FP) was considered when this location was not confirmed. The sites suggested by FDG-PET/CT were confirmed by histopathological analysis of tissue obtained by biopsy or surgery that was considered as the gold standard; however, imaging procedures or clinical follow-ups were accepted if no histopathological proof could be obtained. Even if other lesions were detected, when FDG-PET/CT did not suggest the location of the primary tumor, it was considered to be true negative (TN) if the primary tumor remained unknown in the follow-up. It was considered false negative (FN) if the primary tumor was identified subsequent to negative FDG-PET/CT.

Statistical analyses were executed using the Statistical Package for the Social Sciences version 10.0 software (SPSS Inc., Chicago, IL, USA). The sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and relative risk were calculated. The Kaplan-Meier test was used for survival analysis. *P* values of less than 0.05 were considered to be statistically significant with

95% confidence interval. The following criteria were accepted as a standard of reference: (a) Histopathological findings; (b) obvious clinical findings such as fungating carcinoma; (c) the combination of negative clinical findings, negative findings of other imaging studies, or negative follow-up findings; (d) resolution of apparent abnormalities at subsequent PET studies without intervening therapy together with negative clinical follow-up findings; and (e) the combination of positive clinical findings at the time of PET/CT and resolution of the tumor after chemotherapy or radiation therapy.

The local ethics committee of Okmeydani Training and Research Hospital, located in Istanbul, Turkey approved the study (IRB 07.07.2010/852) and informed consent was obtained from all patients participating in this study.

Results

Out of 87 patients referred to our clinic with bone metastases of unknown primary, 55 were males (63.3%) and 32 were females (36.7%). Seventeen out of 87 patients underwent bone biopsy before FDG-PET/CT. The diagnoses were squamous cell cancer metastases in 10 patients and adenocarcinoma metastasis in 7 patients. In 4 patients, primary site could not be found on PET/CT and the true negativity (TN) was confirmed with bone biopsy. Among 87 patients, we detected multiple lesions in 79 (90%) patients, a solitary lesion in 4 (5%) patients, and did not find any malignant lesion in 4 (5%) patients on FDG-PET/CT.

The localization of primary tumors detected with FDG-PET/CT were: 45 lung (43 TP, 2 FN), 21 bone (10 FN, 4 FP, 7TP), 4 breast (4 TP), 1 gastric (1 TP), 2 kidney (2 TP), 1 nasopharynx (1 TP), 2 rectum (1 TP, 1 FN), 2 prostate (1 TP, 1 FN), 1 sarcoma (1 TP), 1 testis (1 TP), 1 thyroid (1 TP), 1 aplastic anemia (1 TP). In five patients, FDG-PET/CT was negative. One patient had diaphragmatic and multiple bone metastases and died in 3 months (1FN). The primary of the other four patients was not found and they are still alive (4 TN).

Among TP patients, 24 had squamous cell cancer (lung), 20 adenocarcinoma (lung cancer: 16, gastric cancer: 1, kidney cancer: 2, prostate cancer: 1), 7 multiple myeloma, 4 invasive ductal carcinoma (breast), 4 low-grade differentiated cancer (lung: 3, rectum cancer: 1), 1 aplastic anemia, 1 thyroid follicular cancer, 1 testis germ cell tumor, 1 sarcoma, and 1 undifferentiated cancer (nasopharynx cancer). The diagnoses of five FP patients were as follows: Four were diagnosed with bone inflammatory-granulomatous disease (tuberculosis) and one with brucellosis. The following diagnoses were made in 14 FN patients: Multiple myeloma in four patients, adenocarcinoma (prostate cancer) in two patients, bronchoalveolar cancer in two patients, diffuse B cell lymphoma in two patients, mucinous (appendix cancer) in one patient, signet ring cell (gastric cancer) in two patients, and one patient had diaphragmatic and multiple bone metastases with undetected primary focus. The primary focus of these patients could not be detected due to low FDG affinity in these tumors. In the search for a primary site, FDG-PET/CT findings correctly diagnosed lesions as the site of primary TP in 64 (73%) cases, 4 (5%) findings diagnosed no site of a primary, and none were subsequently proven to be TN. Fourteen (16%) diagnoses were FP and 5 (6%) were FN.

The sensitivity of FDG-PET/CT is 82% and the specificity is 44%. Positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (ACC) were 93, 28 and 73%, respectively. In our study, there were seven TP and four FN results for multiple myeloma. The sensitivity was 63. 6%. Thirty one out of 87 patients died (1–21 months), whereas 56 patients are still alive. According to our findings, the mean survival time was 17 ± 1 months for our all patients. The life expectancy was between 2 months and 25 months.

Discussion

It is widely accepted that CUP is a heterogeneous group of metastatic malignancies, in which primary tumor has not been found and clinical signs of the disease are not significant at the time of evaluation.[2] The early identification of primary tumor may enable a more specific and effective treatment, thus leading to a longer mean survival time for CUP patients.[6,9] The results of our study indicated that FDG-PET/CT was able to detect 75% of primary tumors in patients with CUP and the diagnostic accuracy (73%), sensitivity (82%), and specificity (44%) of FDG-PET/CT. The detection rates reported in the literature showed a significant variation that ranged from 22% to 73%, with an overall detection rate of 37%.[2,7,8,10,11] The meta-analyses on FDG-PET/CT reported primary tumor detection rates ranging between 24.5% and 43%, sensitivities ranging between 87% and 91.9%, and specificities ranging between 71% and 81.9%.[2,12,13]

In their study, Fencyl *et al*. stated that the sensitivity and specificity in the search for CUP were similar in patients with histologically proven metastatic disease and patients with clinical suspicion of the presence of a malignancy.[5] Contrary to their findings, our study revealed a lower rate of specificity due to the higher rate of false positive results, which could be explained by higher granulomatous disease incidence in this sample. In the current study, all results were based on "biopsy-proven malignancy from unidentified anatomical origin following conventional diagnostic evaluation,"[14] which makes our study a unique one. In

the current study, the most prevalent location of primary tumors detected by FDG-PET/CT was the lung, which was consistent with the literature.[2] Benign processes such as infection (i.e., hepatitis, abscess), inflammation (peritoneal inflammation), and granulomatous diseases (i.e., sarcoidosis, tuberculosis, and amyloidosis) are known to cause FP results and thereby reduce specificity. The most common site for FP FDG-PET/CT results was vertebral bone tuberculosis. This may have been due to increased glucose utilization and FDG uptake caused by increased cellular metabolism in inflammatory lesions.[13,15,16]

In a tuberculosis-endemic country, FDG PET/CT positive lesions should be cautiously interpreted in terms of granulomatous diseases because FP results may lead to mismanagement. Thus, a histopathological examination of FDG-PET/CT positive lesions should be performed.

The FN FDG-PET/CT sites and results were as follows: Two patients had bronchoalveolar cancer in the lung, one had mucinous cancer in the appendix, two had signet ring cell cancer in the gastric region (signet ring cell cancer), two had diffuse large B cell cancer in the lymphoma, two had adeno cancer in the prostate, four had skeletal involvement (multiple myeloma), and one had diaphragmatic and multiple bone metastases with undetected primary focus.

The FN FDG-PET/CT results may be explained by the facts that: (a) The biological features of the primary tumor may be different from those of the tumor cells in the nodal regions (metastases may uptake higher levels of FDG than in the primary; in low-grade epithelial tumors FDG uptake can be low or absent); (b) the size of primary lesion may be smaller than the resolution power of FDG-PET/CT (especially within the abdomen, pelvis, and head and neck, which are anatomically complicated areas);[5,17] (c) the primary tumor may disappear after seeding the metastases because its angiogenic incompetence leads to marked apoptosis and cellular turnover[13,18] or because it may have regressed spontaneously.[2,7,13,17,18]

Multiple myeloma is another reason for FN FDG-PET/CT result. FDG-PET/CT is an increasingly used modality used to confirm the staging of multiple myeloma.[19] The advantage of FDG PET/CT over other imaging techniques lies in its ability to detect medullary and extramedullary lesions and the possibility to discriminate disease from necrotic tissue and radiation changes. It is a better modality than 99mTc-MIBI and magnetic resonance imaging (MRI) in the detection of focal lesions of multiple myeloma. However, MRI is superior to FDG-PET/CT in detecting multiple myeloma lesions in the spine because of its infiltrative pattern.[19,20] Bredella *et al*. stated that the sensitivity and specificity of FDG PET/CT in detecting myelomatous involvement was 85% and 92%, respectively.[21] On the other hand, FDG-PET/CT fails to differentiate multiple myeloma lesions from multiple lytic bone lesions unless the patient is referred to our department with clinical suspicion of multiple myeloma. In our study, there were

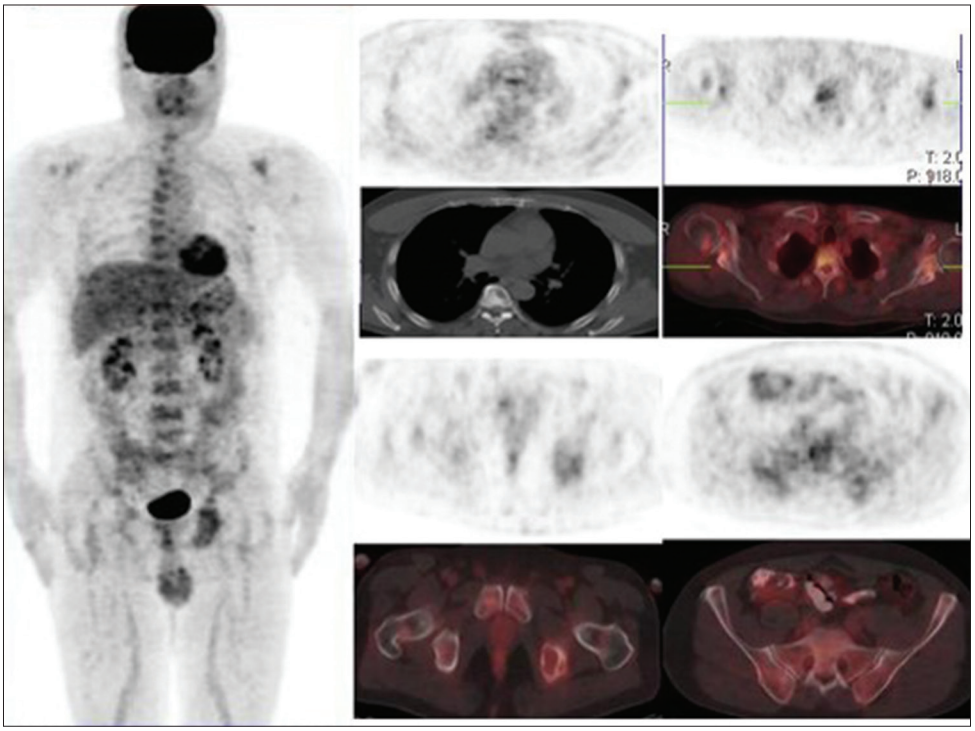

Figure 1: A 48-year-old male patient with hip pain. MRI detected multiple lytic lesions on the pelvis. PET/CT shows an increased uptake of FDG at the sternum, bilateral scapula, vertebral column, and pelvis. Histopathologic verification revealed multiple myeloma

seven TP [Figure 1] and four FN results for multiple myeloma. The sensitivity was 63.6%. In the current study, the number of both FN and FP cases was 13, which was inconsistent with the literature. In addition to the facts explained above for FN results, FN and FP FDG-PET/CT results may have been due to: (a) A second primary tumor,[6,22] (b) inflammation-inflammatory disease, (c) FDG uptake in some cancers mimicking benign lesions, and (d) moderate FDG uptake[13,23,24] The prognosis of patients with CUP syndrome is generally poor and the median survival is approximately between 4 months and 12 months.[3,7,25,26] According to our findings, the mean survival time was 9 months for all of our patients and the life expectancy was between 5 months and 25 months.

Conclusion

Whole-body FDG-PET/CT imaging is proven to be a useful method in the search of the primary focus and metastasis in patients with CUP. In the current study, the rate of specificity of whole-body FDG-PET/CT was lower than the literature, indicating a higher rate of FP results, which may be explained by higher granulomatous disease incidence. Although the histopathological verification is the gold standard, by recognizing the technical limitations of FDG-PET/CT, FP and FN results may be decreased and the diagnostic performance in assessing CUP can be improved.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of intrest.

References

1. Abbruzzese JL, Lenzi R, Raber MN, Pathak S, Frost P. The biology of unknown primary tumors. Semin Oncol 1993;20:238-43.
2. Kwee TC, Kwee RM. Combined FDG-PET/CT for the detection of unknown primary tumors: Systematic review and meta-analysis. Eur Radiol 2009;19:731-44.
3. Pavlidis N, Fizazi K. Carcinoma of unknown primary (CUP). Crit Rev Oncol Hematol 2009;69:271-8.
4. Rougraff BT, Kneisl JS, Simon MA. Skeletal metastases of unknown origin. A prospective study of a diagnostic strategy. J Bone Joint Surg Am 1993;75:1276-81.
5. Fencl P, Belohlavek O, Skopalova M, Jaruskova M, Kantorova I, Simonova K. Prognostic and diagnostic accuracy of [18F] FDG-PET/CT in 190 patients with carcinoma of unknown primary. Eur J Nucl Med Mol Imaging 2007;34:1783-92.
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;31:59-66.
7. 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.
8. Kole AC, Nieweg OE, Pruim J, Hoekstra HJ, Koops HS, Roodenburg JL, *et al*. Detection of unknown occult primary tumors using positron emission tomography. Cancer 1998;82:1160-6.
9. Sève P, Billotey C, Broussolle C, Dumontet C, Mackey JR. The role of 2-deoxy-2-[F-18]fluoro-D-glucose positron emission tomography in disseminated carcinoma of unknown primary site. Cancer 2007;109:292-9.
10. Alberini JL, Belhocine T, Hustinx R, Daenen F, Rigo P. Whole-body positron emission tomography using fluorodeoxyglucose in patients with metastases of unknown primary tumours (CUP syndrome). Nucl Med Commun 2003;24;1081-6.
11. Antoch G, Vogt FM, Freudenberg LS, Nazaradeh F, Goehde SC, Barkhausen J, *et al*. Whole-body dual-modality PET/CT and whole-body MRI for tumor staging in oncology. JAMA 2003;290:3199-206.
12. Delgado-Bolton RC, Fernández-Pérez C, González-Maté A, Carreras JL. Meta-analysis of the performance of 18F-FDG PET in primary tumor detection in unknown primary tumors. J Nucl Med 2003;44:1301-14.
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;29:791-802.
14. Pelosi E, Pennone M, Deandreis D, Douroukas A, Mancini M, Bisi G. Role of whole body positron emission tomography/computed tomography scan with 18F-fluorodeoxyglucose in patients with biopsy proven tumor metastases from unknown primary site. Q J Nucl Med Mol Imaging 2006;50:15-22.
15. Yen RF, Chen KC, Lee JM, Chang YC, Wang J, Cheng MF, *et al*. 18F-FDG PET for the lymph node staging of non-small cell lung cancer in a tuberculosis-endemic country: Is dual time point imaging worth the effort? Eur J Nucl Med Mol Imaging 2008;35:1305-15.
16. Lee JW, Kim BS, Lee DS, Chung JK, Lee MC, Kim S, *et al*. 18F-FDG PET/CT in mediastinal lymph node staging of non-small-cell lung cancer in a tuberculosis-endemic country: Consideration of lymph node calcification and distribution pattern to improve specificity. Eur J Nucl Med Mol Imaging 2009;36:1794-802.
17. Abbruzzese JL, Abbruzzese MC, Lenzi R, Hess KR, Raber MN. Analysis of a diagnostic strategy for patients with suspected tumors of unknown origin. J Clin Oncol 1995;13:2094-103.
18. Naresh KN. Do metastatic tumours from an unknown primary reflect angiogenic incompetence of the tumour at the primary site?--A hypothesis. Med Hypotheses 2002;59:357-60.
19. Lütje S, de Rooy JW, Croockewit S, Koedam E, Oyen WJ, Raymakers RA. Role of radiography, MRI and FDG-PET/CT in diagnosing, staging and therapeutical evaluation of patients with multiple myeloma. Ann Hematol 2009;88:1161-8.
20. Fonti R, Salvatore B, Quarantelli M, Sirignano C, Segrato S, Petruzziello F, *et al*. 18FFDG PET/CT, 99mTc-MIBI, and MRI in evaluation of patients with multiple myeloma. J Nucl Med 2008;49:195-200.
21. Bredella MA, Steinbach L, Caputo G, Segall G, Hawkins R. Value of FDG PET in the assessment of patients with multiple myeloma. AJR Am J Roentgenol 2005;184:1199-204.
22. Xu H, Zhang M, Zhai G, Li B. The clinical significance of 18F-FDG-PET/CT in early detection of second primary malignancy in cancer patients. J Cancer Res Clin Oncol 2010;136:1125-34.

23. Schmid DT, Kneifel S, Stoeckli SJ, Padberg BC, Merrill G, Goerres GW. Increased 18F-FDG uptake mimicking thyroid cancer in a patient with Hashimoto's thyroiditis. Eur Radiol 2003;13:2119-21.
24. Chen YK, Ding HJ, Chen KT, Chen YL, Liao AC, Shen YY, *et al*. Prevalence and risk of cancer of focal thyroid incidentaloma identified by 18F-fluorodeoxyglucose positron emission tomography for cancer screening in healthy subjects. Anticancer Res 2005;25:1421-6.
25. Kwee TC, Basu S, Cheng G, Alavi A. FDG PET/CT in carcinoma of unknown primary. Eur J Nucl Med Mol Imaging 2010;37:635-44.
26. Fernandez-Cotarelo MJ, Guerra-Vales JM, Colina F, de la Cruz J. Prognostic factors in cancer of unknown primary site. Tumori 2010;96:111-6.