The Journal of International Medical Research
2007; 35: 547 – 553

Detection of Metastases in Patients with Cutaneous Melanoma Using FDG-PET/CT

C Akcali[1], S Zincirkeser[2], Z Erbagcý[1], A Akcali[3], M Halac[4], G Durak[2], S Sager[4] and E Sahin[2]

[1]Department of Dermatology, [2]Nuclear Medicine and PET Centre, and [3]Department of Neurology, Medical School, Gaziantep University, Gaziantep, Turkey; [4]Nuclear Medicine and PET Centre, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey

This study aimed to detect metastases in patients with stage III or IV cutaneous melanoma by ^{18}F-fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG-PET/CT). Thirty-nine patients with clinically evident stage III or IV melanoma underwent whole-body FDG-PET/CT scans for metastatic disease and these results were compared with those of biopsy. Scans for 38 of the patients were evaluated; one patient's scan could not be evaluated. There were 11 true-positive, two false-positive, 24 true-negative and one false-negative scans for the detection of melanoma metastases, with sensitivity 91%, specificity 92%, accuracy 92%, and positive and negative predictive values 84% and 96%, respectively. False-positive FDG-PET/CT scans were due to sarcoidosis in the lung and infected cyst in the liver. It is concluded that FDG-PET/CT scanning has high sensitivity and specificity for detecting stage III or IV metastatic melanoma.

KEY WORDS: Melanoma; Metastases; Fluorodeoxyglucose (FDG); Positron emission tomography (PET); Computed tomography (CT)

Introduction

The frequency of newly diagnosed cutaneous melanomas has been steadily increasing for several decades by 3 – 8% each year,[1,2] with 80% of malignant melanomas thought to be related to excessive exposure to sunlight, particularly in childhood. Melanoma is a widely metastasizing neoplastic disease and has a particularly unpredictable pattern of spread. Haematogenous factors may be the cause of extranodal metastases early in the course of disease and should be considered.[3 – 5] Local lesions and lesions that are distant from the primary site may be found in patients with no regional lymph node disease.[6] Imaging has an important role in the identification and location of metastases and, therefore, in the management and prognosis of melanoma.[7] Conventional imaging techniques, such as chest radiography, ultrasonography, computed tomography (CT) and magnetic resonance imaging, are of limited value in identifying melanoma metastases.[8] On the other hand, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) has been shown to be superior to conventional imaging techniques in the non-invasive diagnosis of melanoma metastases.[9 – 11] The recent introduction of combined PET/CT procedures

may significantly improve the diagnostic accuracy of metabolic imaging in the evaluation of patients with melanoma, reducing the rate of false-positives and increasing the rate of true-positives. Combined PET/CT aids surgical planning compared with PET alone. In today's clinical practice, PET/CT scanners allow the simultaneous assessment of both the metabolic and the anatomical characteristics of the primary tumour and its potential local, regional and distant extension.[12,13]

The aim of this clinical study was to evaluate FDG-PET/CT for the detection of metastatic disease in patients with stage III or IV melanoma.

Patients and methods

PATIENTS

The patients included in this study were recruited from the Department of Nuclear Medicine and PET Centre at the Medical School of Gaziantep University and from the Department of Nuclear Medicine and PET Centre at the Cerrahpasa Medical School of Istanbul University. All patients fasted for at least 4 h before imaging and, in order to be entered into the study, their fasting blood sugar level was required to be within the normal range. Oral and written informed consents were obtained from the subjects.

IMAGING

Whole-body FDG-PET/CT imaging with a Siemens Biograph® 2 PET-CT system (Siemens, Knoxville, TN, USA) was performed 1 h after intravenous administration of ^{18}F-FDG and images were obtained from the vertex to the upper thigh region. High-quality images were acquired and semiquantitative measurements of glucose metabolism obtained. Images were evaluated by two nuclear medicine physicians. Use was made of coronal–sagittal images and correlation with CT results whenever the exact location of a lesion was uncertain. Regions of interest were drawn on the images and the semiquantitative standardized uptake value (SUV) was determined, defined as the amount of local tissue radioactivity normalized for the injected dose and the patient's body weight.

The FDG-PET/CT images were studied qualitatively (glucose uptake) and quantitatively (SUV) for the presence of distant metastases. Glucose uptake above the level of the surrounding tissue and an SUV > 2.5 indicated malignancy. The SUV serves as a normalized target-to-background measure and it takes into account the differences between normalizing for body weight, for lean body mass and for body surface area. In our study we used the most prevalent SUV calculation, as follows: SUV = (mCi/ml [decay-corrected] in tissue)/(mCi of tracer injected/body weight [g]).

Distant metastases were determined on an organ-to-organ basis. Results of the FDG-PET/CT scans were compared with biopsy results and the sensitivity, specificity, accuracy, positive and negative predictive values for detection of metastases by FDG-PET/CT were calculated.

Results

Whole-body FDG-PET/CT was carried out in 39 patients (21 [54%] male; 18 [46%] female; age 23 – 79 years, mean ± SD 53.8 ± 33.2 years) with clinically evident stage III or IV melanoma in order to diagnose metastatic disease. One patient's PET scan could not be evaluated, leaving 38 scans for evaluation. There were 11 true-positive, two false-positive, 24 true-negative and one false-negative (Fig. 1) FDG-PET/CT scans for the detection of melanoma metastases, and

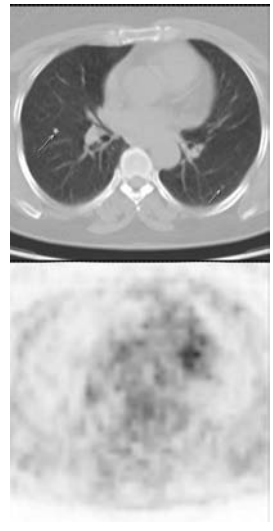


FIGURE 1: PET-negative, CT-positive metastases of malignant melanoma in a 44-year-old-woman with a history of malignant melanoma. The CT component of PET/CT showed nodular opacities in both lungs (arrows in upper panel), which showed metastases of malignant melanoma on biopsy. A transaxial ^{18}F-FDG PET scan (lower panel) showed normal ^{18}F-FDG uptake in both lungs, probably because the lesions were smaller than the resolution limit

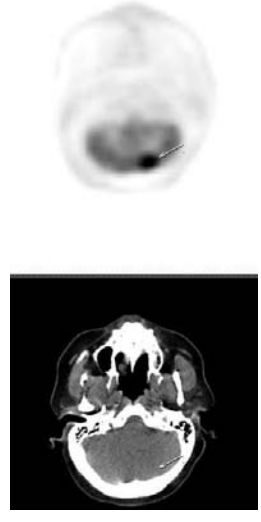


FIGURE 2: PET-positive, CT-negative metastases of malignant melanoma in a 53-year-old-woman with a history of malignant melanoma. A transaxial ^{18}F-FDG PET image showed increased ^{18}F-FDG uptake in the left cerebellum (arrow in upper panel), which was consistent with a metastasis. The CT component of PET/CT did not show any abnormality in the same area (arrow in lower panel)

sensitivity of 91%, specificity of 92%, accuracy of 92%, and positive and negative predictive values of 84% and 96%, respectively. Sites of melanoma with true scans were the cerebellum (one) (Fig. 2), the lungs (six) (Fig. 3), the liver (five), bone (two), regional nodes (nine), mediastinal nodes (five), pelvic nodes (two), the skin and subcutaneous tissues (three), the spleen (one) and the bowel (one). The false-positive scan results were due to sarcoidosis in the lung and infected cysts in the liver. The false-negative scan was probably due to the lesion being below the resolution limit.

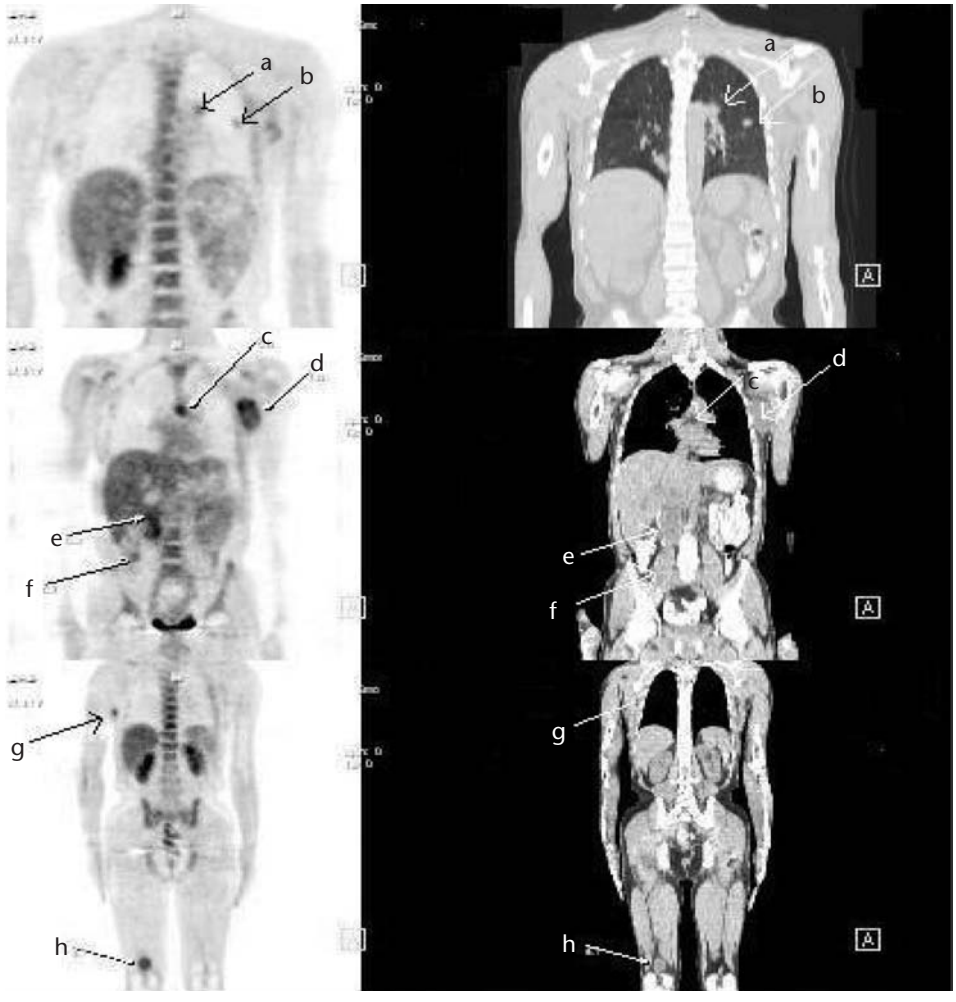


FIGURE 3: PET- and CT-positive metastases of malignant melanoma. A 41-year-old-man with malignant melanoma was referred to a PET/CT centre for staging. Coronal FDG-PET images (right-hand images) showed increased ^{18}F-FDG uptake in the (a) left hilar lymph node, (b) left lung, (c) left paratracheal lymph node, (d) left axillar lymph node, (e) right pararenal area, (f) caecal area, (g) right axillar lymph node, and (h) the distal part of the right femur. The CT component of PET/CT showed lesions at the same places (left-hand images or label 'A')

Discussion

In recent decades the number of new melanomas diagnosed is increasing.[2] The technique of FDG-PET imaging has been found to be efficient in detecting melanoma metastases, with a high overall specificity (56 – 100%) and sensitivity (67 – 100%).[14 – 16] In a prospective study of 106 patients with stage III disease, unsuspected metastases were detected in 15% of patients; the overall sensitivity and specificity for lesion detection were 92% and 90%, respectively, and the FDG-PET result influenced overall management in 22% of the patients.[17] In another study of 84 patients with recurrent melanoma, FDG-PET impacted therapy in 26%, upstaging one-third and downstaging two-thirds of cases.[18] However, FDG-PET can miss small-volume disease and micrometastatic disease.

The development of combined PET/CT scanners has dramatically changed the approach to PET imaging; the integration of anatomical (CT) and metabolic (PET) images allows more accurate determination of abnormal sites and their clinical relevance.[19,20] The superiority of PET/CT compared with PET in the assessment of metastatic melanoma has already been reported[13] Use of FDG-PET/CT has a significant impact on the interpretation of suspected metastatic lesions (Fig. 1) and gives fewer false-negative and false-positive results (Figs 2 and 3).[21] In a recent study that included 250 patients with melanoma (AJCC [American Joint Committee on Cancer] stages I – IV), PET/CT was found to be significantly more accurate than PET and CT alone for the staging of visceral and non-visceral metastases.[22] The CT component of PET/CT was found to be particularly helpful in the detection of lung metastases, which were often missed by PET alone. These data also showed an incremental treatment effect of PET/CT in the restaging and therapy control of patients with melanoma.[22] Being able precisely to locate sites of abnormal ^{18}F-FDG uptake helps in identifying those patients suitable for surgery as well as in locating isolated metastases.[23,24] Use of PET/CT is also helpful in detecting metastases at unusual sites of primary melanoma, such as ocular melanoma.[25 – 27] In addition, PET/CT has been found capable of identifying incidental metastatic melanoma in patients with other malignancies, although this is an unusual finding.

Further assessment of this technology, including the ability to integrate PET/CT data with therapy planning, will be important for the management of melanoma in the future, particularly in helping to identify patients suitable for surgery. Surgery can be curative for stage III disease and is the only therapy that influences survival in patients with stage IV disease.[28,29] The sensitivity (91%), specificity (92%) and accuracy (92%) of FDG-PET/CT in our study was high and comparable with the best results in the literature.[13, 30 – 33] Previous studies have suggested that FDG-PET may be insensitive in the detection of metastases in the cerebral cortex.[34] An assessment of the sensitivity FDG-PET in detecting cerebral metastases was not possible as most patients did not have a focused FDG-PET scan of the brain.[34] The cerebral areas are not included in many studies,[35 – 37] images generally being obtained from the base of the skull to the upper thigh region. In our study, however, whole-body acquisitions were obtained from the vertex to the upper thigh region, so we were able to observe cerebral metastases.

The present study had several shortcomings. Its retrospective nature may have introduced bias into the data. Furthermore, our standard reference

material included patient follow-up data obtained from clinical and/or laboratory reports, and images obtained with other techniques. Reading earlier CT and MRI reports before the PET analysis could have reduced the clinical relevance of our results, in other words, being aware of the results of the patients previous CT and MRI results may have influenced our interpretation of the PET/CT results.

In conclusion, PET/CT scanning has high sensitivity and specificity for detecting stage III and IV metastatic melanoma. The CT component of PET/CT helps to establish the correct anatomical location of the lesions and to differentiate between physiological and non-physiological ^{18}F-FDG uptake, thus facilitating appropriate interpretation of the PET scan and decreasing the numbers of false-positive and false-negative results.

Conflicts of interest

No conflicts of interest were declared in relation to this article.

• Received for publication 7 March 2007 • Accepted subject to revision 15 March 2007
• Revised accepted 6 June 2007
Copyright © 2007 Field House Publishing LLP

References

1 Langley RGB, Barnhill RL, Mihm MC, *et al*: Neoplasms: cutaneous melanoma. In: *Fitzpatrick's Dermatology in General Medicine* (Freedberg IM, Eisen AZ, Wolff K, *et al*, eds) 6th edn. New York: McGraw-Hill, 2003; pp 917 – 947.
2 Hall HI, Miller DR, Rogers JD, *et al*: Update on the incidence and mortality from melanoma in the United States. *J Am Acad Dermatol* 1999; **40**: 35 – 42.
3 Reintgen D, Cruse CW, Wells K, *et al*: The orderly progression of melanoma nodal metastases. *Ann Surg* 1994; **220**: 759 – 767.
4 Meier F, Will S, Ellwanger U, *et al*: Metastatic pathways and time courses in the orderly progression of cutaneous melanoma. *Br J Dermatol* 2002; **147**: 62 – 70.
5 Skobe M, Hamberg LM, Hawighorst T, *et al*: Concurrent induction of lymphangiogenesis, angiogenesis, and macrophage recruitment by vascular endothelial growth factor-C in melanoma. *Am J Pathol* 2001; **159**: 893 – 903.
6 Leiter U, Meier F, Schittek B, *et al*: The natural course of cutaneous melanoma. *J Surg Oncol* 2004; **86**: 172 – 178.
7 King DM: Imaging of metastatic melanoma. *Cancer Imaging* 2006; **6**: 204 – 208.
8 Miranda EP, Gertner M, Wall J, *et al*: Routine imaging of asymptomatic melanoma patients with metastases to sentinel lymph nodes rarely identifies systemic disease. *Arch Surg* 2004; **139**: 831 – 837.
9 Swetter S, Carroll L, Johnson D, *et al*: Positron emission tomography (PET) is superior to computerized tomography (CT) for metastatic staging in melanoma patients. *Clin Positron Imaging* 2000; **3**: 154.
10 Gulec SA, Faries MB, Lee CC, *et al*: The role of fluorine-18 deoxyglucose positron emission tomography in the management of patients with metastatic melanoma: impact on surgical decision. *Clin Nucl Med* 2003: **28**: 961 – 965.
11 Jadvar H, Johnson DL, Segall GM: The effect of fluorine-18 fluorodeoxyglucose positron emission tomography on the management of cutaneous malignant melanoma. *Clin Nucl Med* 2000; **25**: 48 – 51.
12 Schwimmer J, Essner R, Patel A, *et al*: A review of the literature for wholebody FDG PET in the management of patients with melanoma. *Q J Nucl Med* 2000; **44**: 153 – 167.
13 Schöder H, Larson SM, Yeung HW: PET/CT in oncology: integration into clinical management of lymphoma, melanoma, and gastrointestinal malignancies. *J Nucl Med* 2004; **45**(Suppl 1): 72S – 81S.
14 Prichard RS, Hill AD, Skehan SJ, *et al*: Positron emission tomography for staging and management of malignant melanoma. *Br J Surg* 2002; **89**: 389 – 396.
15 Holder WD Jr, White RL Jr, Zuger JH, *et al*: Effectiveness of positron emission tomography for detection of melanoma metastases. *Ann Surg* 1998; **225**: 764 – 771.
16 Rinne D, Baum RP, Hor G, *et al*: Primary staging and follow-up of high risk melanoma patients with whole-body ^{18}F-fluorodeoxyglucose positron emission tomography. *Cancer* 1998; **82**: 1664 – 1671.
17 Tyler DS, Onaitis M, Kherani A, *et al*: Positron emission tomography screening in malignant melanoma. *Cancer* 2000; **89:** 1019 – 1025.
18 Stas M, Stroobants S, Dupont P, *et al*: 18-FDG PET scan in the staging of recurrent melanoma: additional value and therapeutic impact.

Melanoma Res 2002; **12**: 479 – 490.
19 Beyer T, Townsend DW, Brun T, *et al*: A combined PET/CT scanner for clinical oncology. *J Nucl Med* 2000; **41**: 1369 – 1379.
20 Townsend DW, Carney JP, Yap JT, *et al*: PET/CT today and tomorrow. *J Nucl Med* 2004; **45**(Suppl 1): 4 – 14.
21 Kumar R, Mavi A, Bural G, *et al*: Fluorodeoxyglucose-PET in the management of malignant melanoma. *Radiol Clin North Am* 2005; **43**: 23 – 33.
22 Reinhardt MJ, Joe AY, Jaeger U, *et al*: Diagnostic performance of whole body dual modality ^{18}F-FDG PET/CT imaging for N- and M-staging of malignant melanoma: experience with 250 consecutive patients. *J Clin Oncol* 2006; **24**: 1178 – 1187.
23 Mijnhout GS, Hoekstra OS, van Tulder MW, *et al*: Systematic review of the diagnostic accuracy of ^{18}F-FDG PET in melanoma patients. *Cancer* 2001; **91**: 1530 – 1542.
24 Macapinlac HA: FDG PET and PET/CT imaging in lymphoma and melanoma. *Cancer J* 2004; **10**: 262 – 270.
25 Freudenberg LS, Schueler AO, Beyer T, *et al*: Whole-body fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) in staging of advanced uveal melanoma. *Surv Ophthalmol* 2004; **49**: 537 – 540.
26 Finger PT, Kurli M, Reddy S, *et al*: Whole-body PET/CT for initial staging of choroidal melanoma. *Br J Ophthalmol* 2005; **89**: 1270 – 1274.
27 Kamel EM, Thumshirn M, Truninger K, *et al*: Significance of incidental ^{18}FFDG accumulations in the gastrointestinal tract in PET/CT: correlation with endoscopic and histopathologic results. *J Nucl Med* 2004; **45**: 1804 – 1810.
28 Brand CU, Ellwanger U, Stroebel W, *et al*: Prolonged survival of 2 years or longer for patients with disseminated melanoma: an analysis of related prognostic factors. *Cancer* 1997; **70**: 2345 – 2353.
29 Meyer T, Merkel S, Goehl J, *et al*: Surgical therapy for distant metastases of malignant melanoma. *Cancer* 2000; **89**: 1983 – 1991.
30 Stas M, Stroobants S, Dupont P, *et al*: 18-FDG PET scan in the staging of recurrent melanoma: additional value and therapeutic impact. *Melanoma Res* 2002; **12**: 479 – 490.
31 Swetter SM, Carroll LA, Johnson DL, *et al*: Positron emission tomography is superior to computed tomography for metastatic detection in melanoma patients. *Ann Surg Oncol* 2002; **9**: 646 – 653.
32 Wong C, Silverman DH, Seltzer M, *et al*: The impact of 2-deoxy-2[^{18}F]fluoro-D-glucose whole body positron emission tomography for managing patients with melanoma: the referring physician's perspective. *Mol Imaging Biol* 2002; **4**: 185 – 190.
33 Jadvar H, Johnson DL, Segall GM: The effect of fluorine-18 fluorodeoxyglucose positron emission tomography on the management of cutaneous malignant melanoma. *Clin Nucl Med* 2000; **25**: 48 – 51.
34 Larcos G, Maisey MN: FDG-PET screening for cerebral metastases in patients with suspected malignancy. *Nucl Med Commun* 1996; **17**: 197 – 198.
35 Patz EF Jr, Lowe VJ, Hoffman JM, *et al*: Focal pulmonary abnormalities: evaluation with F-18 fluorodeoxyglucose PET scanning. *Radiology* 1993; **188**: 487 – 490.
36 Avril N, Dose J, Janicke F, *et al*: Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. *J Clin Oncol* 1996; **14**: 1848 – 1857.
37 Lowe VJ, Fletcher JW, Gobar L, *et al*: Prospective investigation of positron emission tomography in lung nodules. *J Clin Oncol* 1998; **16**: 1075 – 1084.

Address for correspondence
Assistant Prof. Dr C Akcali
Universite Bul. 23 Nisan Mah. No. 285/7, 27310 Gaziantep, Turkey.
E-mail: cenkakcali @ yahoo.com