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# Correlation of $^{18}$F-FDG-PET and histopathology in patients with malignant melanoma

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***Background.*** *Preliminary reports suggest that PET using $^{18}$F-FDG may be a valuable diagnostic tool in patients with advanced malignant melanoma. Therefore, the aim of this study was to correlate PET lesions with histological findings in staging of malignant melanoma.*

***Patients and methods.*** *A total of 82 patients with malignant melanoma underwent 107 PET examinations for primary staging or therapy monitoring. After an intravenous injection of 370 MBq $^{18}$F-FDG whole-body images were acquired on an ECAT EXACT 47 (921) with an axial field-of-view of 16.2 cm (Siemens, CTI). Tumor-suspicious PET findings, results of physical examination, and tumor-suspicious lesions by conventional imaging, i.e. ultrasound, CT, and MRI, were evaluated histologically and correlated with each other on a lesion-by-lesion basis.*

***Results.*** *PET detected 124 lesions with an increased focal tracer uptake. In addition, physical examination and conventional imaging revealed 65 tumor-suspicious lesions. In total, 189 tumor-suspicious lesions were evaluated histologically. $^{18}$F-FDG-PET was true-positive in 115/189 lesions and false-positive in 9/189 lesions. In 21 out of 65 PET-negative lesions, biopsy could not confirm melanoma tissue. In contrast, in 44 out of 65 PET-negative lesions further biopsy revealed malignant melanoma tissue. Sensitivity and specificity of $^{18}$F-FDG-PET for the detection of malignant melanoma tissue were 72% and 70%, respectively. Negative and positive predictive values of $^{18}$F-FDG-PET imaging were 32% and 93%, respectively. With respect to anatomical localization, two thirds of false negative/positive PET lesions were located in the skin or mucosal area.*

***Conclusions.*** *$^{18}$F-FDG-PET is a valuable diagnostic tool in order to prove tumor-suspicious lesions in malignant melanoma. However, for exclusion of skin metastases an accurate physical examination of patients with malignant melanoma by a dermatologist is indispensable. With respect to very aggressive treatment modalities of advanced malignant melanoma $^{18}$F-FDG-PET may help to select the appropriate treatment protocol for each individual patient.*

*Key words: melanoma-diagnosis-pathology; tomography, emission-computed; $^{18}$F-FDG-PET; neoplasm staging; histology; treatment strategy*

## Introduction

Cutaneous malignant melanoma is one of the most common malignancies with a twofold to threefold increasing incidence over the last 40 years.[1] The most important prognostic factor is tumor staging at the time of diagnosis.[2] According to the recommendations of the American Joint Commission on Cancer (AJCC) the clinical stage is divided into four groups. Clinical stages I and II are defined for primary malignant melanomas limited to the site of the origin without any evidence of a tumor spread elsewhere. In case of palpable local lymph node involvement or disseminated disease, the patients are classified as clinical stage III and IV, respectively. At the time of the first presentation, in nearly 80 % of all patients with the clinical stage I or II with, a mean 5-year survival rate of 85 % was noted.[2] However, one third of the latter patients will have clinically undetectable lymph node metastases which, if left untreated, will significantly worsen the survival rate.[3,4] Thus, an accurate tumor staging is a prerequisite for selecting the adequate treatment protocol.

Conventional imaging, *i.e.* computed tomography, magnet resonance imaging, and ultrasound are valuable and well-established diagnostic tools in pretherapeutic staging.[5-8] However, these imaging modalities allow an identification of morphologic changes only, whereas tumor tissue in normal-sized lymph nodes can not be detected by definition.[9] Moreover, morphologically orientated imaging permits a screening of a pre-selected body area only. Since malignant melanomas are known for their aggressive lymphatic and hematogenic spread potency[3,7], one single non-invasive imaging modality with simultaneous imaging of the whole-body would significantly facilitate pre-therapeutic management in these patients. A number of radiotracers have therefore been suggested, *i.e.* $^{67}$Ga-citrate,[10] $^{123}$I-benzamide, $^{123}$I-α-methyltyrosine,[9] and $^{99m}$Tc-labelled antimelanoma-antibodies,[11] though a great number of false-negative findings were reported for all of these radiotracers.[9,12] In contrast, initial experiences demonstrated the clinical potency of positron emission tomography (PET) using 2-[$^{18}$F]-fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) for the detection of both local and systemic spread of metastatic malignant melanoma.[1,13-22] Thus, within its geometric resolution of about 4-6 mm (FWHM), PET is able to detect tumor tissue independent of morphological changes due to an increased rate of glycolysis in malignant transformed cells. Since the early detection of malignant melanoma metastases increases patients' survival rate,[23,24] PET imaging might be a valuable diagnostic tool in detecting melanoma metastases.

Therefore, the aim of this study was to determine the clinical value of $^{18}$F-FDG-PET in patients with malignant melanoma by comparing PET to findings of both clinical examination and morphological imaging, and to correlate these findings with histological results on a lesion-to-lesion basis.

## Patients and methods

### *Patients*

A total of 82 patients (37 female, 45 male) aged from 28 to 80 years with histologically proven malignant melanoma were investigated. The primary tumors were located in the skin area of the head and neck region in 17 patients, in the upper extremities in 6, in the lower extremities in 18, on the chest wall in 3, on the back in 29, and on the abdominal wall

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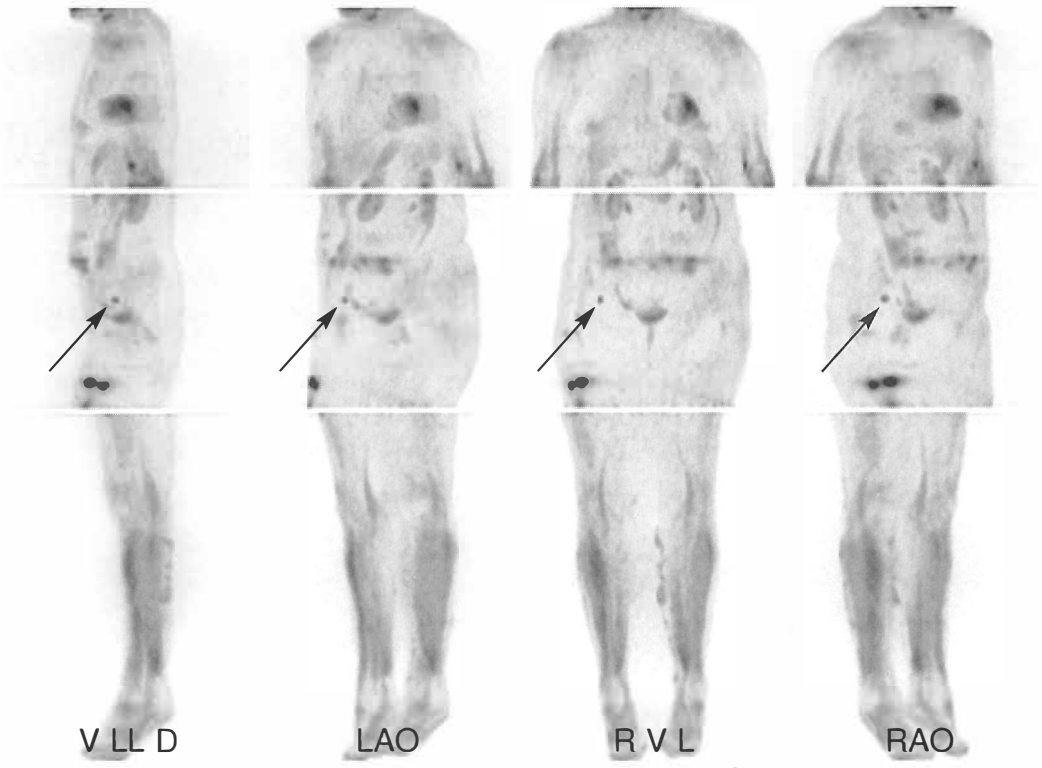


**Figure 1.** Maximum intensity projections (MIPs) from the left lateral (V LL D), anterior (R V L), right anterior oblique (RAO), and left anterior oblique (LAO) views of a patient (58/f) with a primary malignant melanoma of the right lower extremity. The patient was clinically suspected for inguinal lymph node metastases. Note increased $^{18}$F-FDG uptake of both the primary tumor and the lymph node metastasis (arrow). Since no distant metastases were detected by $^{18}$F-FDG-PET the patient was classified stage IIIB.

in 2 patients. Unusual sites of the primary malignant melanoma were the vulva and the retina in one and two patients, respectively. The anatomic site of the primary tumor was unknown in the remaining 4 patients.

A description of the Clark level[25] was available for 57 patients with the following distribution: level I, no patient; level II, 2 patients; level III, 13 patients; level IV, 34 patients; level V, 2 patients. Two patients were classified Clark level II/III, level III/IV and level IV/V, respectively.

Moreover, the classification results of the primary lesion thickness according to the Breslow scheme[26] were available for 59 patients. There were 10 patients with thin lesions (0,75 mm or less), 38 with intermediate lesions (0,76-3,99 mm), and 11 patients with thick lesions of 4 mm or greater.

*PET scanning*

The patients fasted for at least 12 hours prior to PET-scanning in order to minimize blood insulin levels and glucose utilization of normal tissue.27 Whole-body emission images were acquired without attenuation correction 60 min after i.v. injection of 370 MBq $^{18}$F-FDG using an ECAT EXACT 47 (921) scanner (Siemens/CTI) with an axial field-of-view of 16.2 cm.

The patients were placed in the PET gantry feet first with both arms folded over the

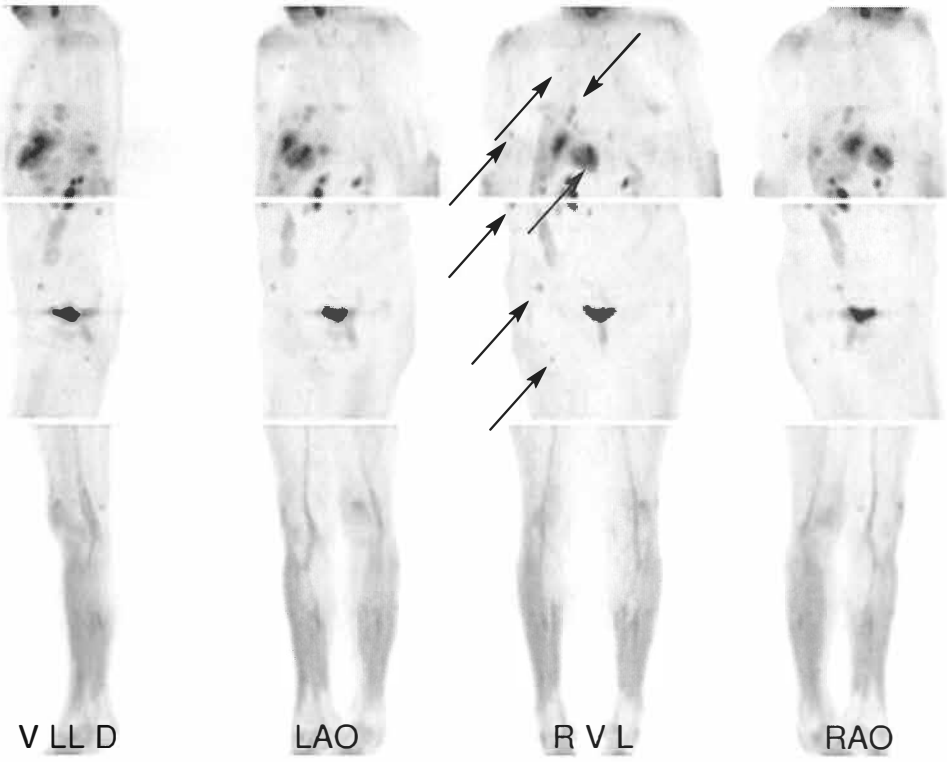


**Figure 2.** MIPs in same views as in figure 1 of a patient (69/f) after surgical treatment of a malignant melanoma located at the right leg. Note multiple metastases in [18]F-FDG-PET (arrows). However, a total of six metastases located within the skin area could not be identified by [18]F-FDG-PET imaging but by an accurate clinical examination.

abdomen. Images were acquired for 4 min per bed position covering the feet up to the middle of the femurs. Then, the patients were repositioned in the gantry head first, and the second set of images was acquired from the brain down to the waist. Prior to the third acquisition set from the waist down to the lower extremities, the patients were asked to empty the bladder in order to decrease urine activity. Emission data were reconstructed by filtered back projection using a Hanning filter with a cut-off frequency of 0.4 of Nyquist frequency. Thus, transaxial spatial resolution was approximately 12 mm. PET-images were printed on transparency film (Helios 810, Sterling) using a linear gray scale with highest activity displayed in black. Images were displayed with an upper threshold of five times of the mean activity in the lung. Standardized documentation included both 20 transversal and 20 coronal slices with a slice thickness of 13.5 mm each, and maximum-intensity-projections (MIPs) in the anterior, left lateral, right-anterior-oblique, and left-anterior-oblique view as published previously.[28]

*Evaluation*

Two independent nuclear medicine physicians interpreted PET images visually. All tumor-suspicious findings were evaluated histologically. Moreover, all patients underwent physical examinations as well as morphological imaging, i.e. chest X-ray, CT scans of the chest, brain and abdomen or MRI. Additional tumor-suspicious lesions of conventional

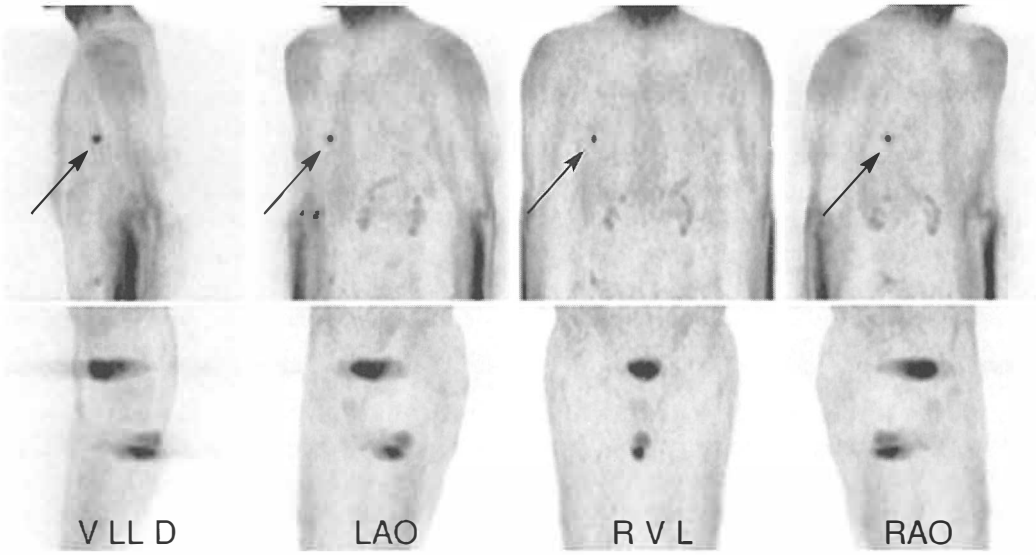


**Figure 3.** MIPs in same views as in figure 1 of a patient (56/m) after the excision of a malignant melanoma of the right leg. Patient showed up with a tumor-suspicious lesion in the right lung in postsurgical X-ray of the chest. $^{18}$F-FDG-PET revealed an increased glucose metabolism within the lesion, and histology confirmed malignant melanoma metastasis. Thus, the patient was classified as stage IV.

imaging or physical examination were evaluated histologically, too. The results of histology and tumor-suspicious lesions were correlated on a lesion-by-lesion basis with special respect to anatomical localization.

## Results

In a total of 82 patients PET detected 124 lesions with an increased focal tracer uptake. Following physical examination and conventional imaging, 65 additional lesions were recorded to be suspicious for malignant melanoma metastases. Thus, a total of 189 lesions were evaluated histologically.

PET was true-positive in 115/124 lesions (Figure 1) and false-positive in 9/124 lesions. In 21/65 PET-negative lesions, biopsy did not confirm melanoma tissue, whereas histology was positive for melanoma metastases in the remaining 44 lesions (Figure 2). Thus, for the detection of malignant melanoma tissue PET had an overall sensitivity of 72% and an overall specificity of 70%. The negative predictive value of $^{18}$F-FDG PET was 32%. In contrast, the positive predictive value was 93%.

PET findings were either false-positive or false-negative in a total of 53 lesions. With regard to anatomical localization, 33 out of these lesions were located in the skin or within mucosal areas. Two lesions were situated in the lungs and three in the mesenterium. Five lesions were located in the axillary lymph nodes. The remaining 10 lesions were located in different regions of the body, *e.g.* the lung, the mediastinum. Thus, with respect to anatomical localization, almost two thirds of either false-positive or false-negative PET findings were located in the skin or within mucosal areas. If false-positive or false-negative skin or mucosal lesions were not taken into account, PET remained false-negative in 11 lesions with histologically proven melanoma tissue. Thus, in this subgroup, the sensitivity of PET scanning in melanoma patients increased to 91%.

## Discussion

Initial studies assessed the clinical utility of $^{18}$F-FDG-PET for the detection of metastatic malignant melanoma. Gritters and coworkers[3] studied 12 patients with a total of 52 biopsy- or CT-diagnosed melanoma lesions. All patients underwent additional $^{18}$F-FDG-PET. Their initial data demonstrated the potential role of $^{18}$F-FDG-PET for the detection of metastatic malignant melanoma, especially in untreated extrathoracic lesions. Steinert and coworkers[22] examined 33 patients with primary diagnosis or known relapse of malignant melanoma. In their patients, $^{18}$F-FDG-PET showed a sensitivity of 92% for the detection of malignant melanoma lesions. Moreover, the specificity was 77% without further clinical information and 100% with clinical information. Corresponding findings were demonstrated by Holder and coworkers[16] who recommended $^{18}$F-FDG-PET as a primary strategy imaging modality in the staging of melanoma patients.

In this study, a total of 82 patients with malignant melanoma underwent 107 $^{18}$F-FDG-PET examinations. In 115 out of 124 lesions with pathological focal increased $^{18}$F-FDG uptake, PET was true-positive. Moreover, in 9 PET-positive lesions, histology could not confirm malignant melanoma tissue. In contrast, in 44 out of 65 lesions detected by clinical examination or morphological imaging, only histological evaluation revealed malignant melanoma tissue. However, 21 out of 65 PET-negative lesions were true-negative. In accordance with the findings of other investigations the results of this study show that whole-body $^{18}$F-FDG-PET is an accurate imaging modality in patients with malignant melanoma in order to screen the whole-body for the presence of metastases.

However, in this study, $^{18}$F-FDG-PET had a sensitivity of 72% and a specificity of 70% only. It is remarkable that 53 lesions were either false-negative or false-positive in $^{18}$F-FDG-PET. Two thirds of these lesions were located within the skin or mucosal areas. Thus, the skin and mucosal areas might be problematic regions for the detection of malignant melanoma metastases with $^{18}$F-FDG-PET. One possible cause of false-positive results is the fact that $^{18}$F-FDG is excreted via the urine. Thus, the contaminations of the skin, predominantly at the lower extremities might be interpreted as tumor-suspicious lesions of the skin. Moreover, it is known that patients treated with interferon alpha and interleukin-2 exhibit cutaneous inflammatory infiltrations at the injection site,[24] which may cause false-positive results in $^{18}$F-FDG-PET. However, the majority of false PET findings were false-negative. The limited impact of $^{18}$F-FDG-PET for the detection of skin and mucosal metastases might be due to physiological and technological reasons. First, tumor lesions located within the regions of high physiological $^{18}$F-FDG uptake, *i.e.* the brain or the kidneys, might not be identified by $^{18}$F-FDG-PET imaging. Second, the detection of small skin/mucosal lesions with diameters of less than 5 mm might be limited by geometrical resolution of $^{18}$F-FDG-PET. Moreover, PET-images in this study were reconstructed by filtered back-projection. As a consequence, melanoma metastases in borderline areas, *i.e.* the skin, can hardly be differentiated from non-malignant transformed tissue. This problem might be solved by time-consuming iterative reconstruction algorithms. Moreover, the high number of false-negative PET lesions located within the skin and mucosal area underlines the necessity of an accurate and careful physical examination of the patient in daily clinical patient management. With these limitations in mind, whole-body $^{18}$F-FDG-PET is a suitable imaging modality in order to prove tumor-suspicious lesions in malignant melanoma. However, for exclusion of skin metastases an accurate physical examination by a dermatologist is still indispensable.

Any diagnostic test should, in principle, not only be judged with respect to its statistic data, e.g. sensitivity, specificity, negative and positive predictive value, and accuracy, but rather in the light of its effect on treatment strategy. The therapeutic approach in malignant melanoma mainly depends on the extent of the disease. In clinical stages I (pT1/T2 N0 M0) and II (pT3/T4 N0 M0), excision of the primary malignancy is the golden standard. In the last few years elective lymphadenectomy was abandoned since its additional value for the patients' survival rate was demonstrated in retrospective patient studies only,[29,30] but not in randomized prospective patient studies.[30] If patients show up with regional lymph node metastases or in-transit-metastases but no distant metastases (stage IIIb), the therapeutic approach includes therapeutic lymphadenectomy. However, 10-year survival-rate decreases from 97% in patients staged pT1N0M0 to 19% in patients staged N1 or N2 and MO melanoma.[31] The primary treatment goal in patients with M1 malignant melanoma (clinical stage IV) is the reduction of tumoral masses in order to prolong patients' life expectancy as well as to improve the quality of life.[32] In principle, there are three therapeutic options: surgery, external radiotherapy, and chemotherapy. In case of isolated metastases, an operative treatment has proved to be helpful in the prolongation of patients' life expectancy. Most studies demonstrated life prolongation in case of total resection of all tumoral masses only.[33] Thus, 10-year survival-rate was expected to be as low as 3% in these patients with advanced malignant melanoma.[31] However, there is no well-established, standardized systemic treatment protocol for patients with distant metastases. Thus, the treatment strategy itself is still under clinical investigation and is the focus of several patient studies. There is now evidence that patients with stage IV malignant melanoma benefit from an aggressive chemotherapy with interleukin-2 and interferon alpha. These authors report of 5-year survival-rate of up to 10%.[24,34]

Thus, in addition to sensitivity and specificity of high-resolution ultrasonography of 70% and 90%,[35] respectively, even patients with advanced malignant melanoma may benefit from the detection of metastases by $^{18}$F-FDG-PET due to several reasons. First, patients' survival rate decreases with an increasing number of involved lymph node regions.[36] Second, prognosis of patients is better with an early detection of metastases and with small tumor masses at the time of detection.[36] Third, $^{18}$F-FDG-PET has been proved superior in the detection of lung metastases (Figure 3) as compared to conventional, well-established computed tomography.[37,38] Last, 18F-FDG-PET offers the advantage to image the whole body in one single procedure which is especially important because in malignant melanoma often unexpected, aberrant metastatic spread is found. Thus, $^{18}$F-FDG-PET has already been suggested for the staging of malignant melanoma.[22]

## Conclusions

$^{18}$F-FDG-PET is a valuable diagnostic tool in order to prove tumor-suspicious lesions in malignant melanoma. However, for exclusion of metastases physical examination by dermatologist and conventional imaging are indispensable. With respect to very aggressive treatment modalities of advanced malignant melanoma $^{18}$F-FDG-PET may help to select the appropriate treatment protocol for the individual patient.

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