3′-^{18}F-Fluoro-3′-Deoxy-L-Thymidine: A New Tracer for Staging Metastatic Melanoma?

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In this study, the feasibility of 3′-^{18}F-fluoro-3′-deoxy-L-thymidine PET (^{18}F-FLT PET) for staging patients with clinical stage III melanoma was investigated. **Methods:** Ten patients with melanoma and metastases to the locoregional draining lymph nodes, clinical stage III—based on physical examination, chest radiography, lactate dehydrogenase, and histopathologic confirmation—underwent a whole-body ^{18}F-FLT PET scan 1 h after injection of a median 400-MBq dose (range, 185–430 MBq) of ^{18}F-FLT. All ^{18}F-FLT PET lesions were verified using the American Joint Committee on Cancer Staging System, which includes physical examination, spiral CT, ultrasound, chest radiography, and histopathologic examinations. Size and mitotic rate of metastatic lymph nodes and skin metastases were determined. **Results:** All histopathologic samples and ^{18}F-FLT PET lesions were categorized over anatomic regions and correlated. All locoregional metastases were correctly visualized by ^{18}F-FLT PET. Region-based sensitivity for detection of lymph node metastatic disease was 88%. There were 3 true-negative and 2 false-positive lesions. The detection limit for lymph node metastases appeared to be approximately 6 mm or a mitotic rate of 9 mitoses per 2 mm^2. Two patients were upstaged by ^{18}F-FLT PET, which was confirmed by CT. In 3 patients, ^{18}F-FLT PET detected a total of 3 additional lesions with therapeutic consequences, without influencing staging. These lesions were initially missed by clinical staging. **Conclusion:** ^{18}F-FLT PET seems promising for (re)staging purposes in clinical stage III melanoma. Further research is needed, in which ^{18}F-FLT PET should be compared with ^{18}F-FDG PET.

Key Words: 3′-^{18}F-fluoro-3′-deoxy-L-thymidine; melanoma; staging; PET

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A powerful noninvasive metabolic imaging method for the diagnosis and staging of cancer is PET using ^{18}F-FDG (*1*). The enzyme hexokinase causes intracellular entrapment of ^{18}F-FDG, reflecting glucose metabolism (*2*). ^{18}F-FDG is transported into the cells, which are metabolically active, especially in the case of tumor cells (*3*).

Most melanomas have very high glucose utilization. In vitro experiments demonstrate a high ^{18}F-FDG uptake in melanoma cells (*4*). Therefore, almost parallel with the introduction of sentinel lymph node biopsy (SLNB) in the staging of melanoma patients, ^{18}F-FDG PET emerged as a clinical modality for staging, restaging, and therapy monitoring. Conventional imaging techniques—such as CT, MRI, ultrasound (US), and physical examination—are not as accurate for the detection of metastatic melanoma as SLNB or ^{18}F-FDG PET (*5*). For primary locoregional staging, ^{18}F-FDG PET is surpassed by SLNB (*6–9*). ^{18}F-FDG PET may be of value in stage III or IV melanoma patients or for patients with recurrent melanoma (*5,9–13*).

^{18}F-FDG is not a selective tracer because it is also taken up in macrophages. Macrophages invade tumors and appear in inflammatory lesions, causing false-positive results (*14,15*). Another problem is a decreased uptake in hyperglycemia (*16*). Furthermore, routine whole-body ^{18}F-FDG PET lacks sensitivity for imaging brain metastases because glucose is avidly taken up by the normal brain.

Recently, 3′-^{18}F-fluoro-3′-deoxy-L-fluorothymidine (^{18}F-FLT) has been introduced as a PET tracer by Shields et al., which might not have these drawbacks (*17*). This pyrimidine analog is phosphorylated by the enzyme thymidine kinase 1 (TK_1), which leads to intracellular trapping (*17*). During DNA synthesis, TK_1 activity increases almost 10-fold and is, therefore, an accurate reflection of cellular proliferation (*18*). The aim of this study was to investigate the feasibility of ^{18}F-FLT PET for the staging of regionally metastasized melanoma.

MATERIALS AND METHODS

Patients

This prospective study consisted of 10 consecutive patients with clinical stage III melanoma (locoregional disease). Patients were included from April until November 2002.

Two patients had a unknown primary and 2 patients had a primary melanoma, which was too small to assess the Clark level. All patients gave written informed consent. For inclusion, the liver and kidney functions and hematologic parameters (hemoglobin,

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hematocrit, erythrocytes, thrombocytes, leukocytes, and white cell count) had to be within normal limits. Pregnant patients and patients with psychiatric disorders were excluded. All screened patients could be included in the study. The Medical Ethics Committee of Groningen University Hospital approved the study protocol.

PET Studies

Synthesis of FLT was performed according to the method of Machulla et al. (*19*) ^{18}F-FLT was produced by ^{18}F-fluorination of the 4,4′-dimethoxytrityl–protected anhydrothymidine, followed by a deprotection step. After purification by reversed-phase high-performance liquid chromatography, the product was made isotonic and passed through a 0.22-μm filter. ^{18}F-FLT was produced with a radiochemical purity of >95% and specific activity of >10 TBq/mmol. The radiochemical yield was 6.7% ± 3.7% (decay corrected).

Eight studies were performed using an ECAT EXACT HR+ (Siemens/CTI, Inc.) and 2 studies were performed on an ECAT 951/31 (Siemens/CTI, Inc.). Before PET imaging, patients were instructed to fast for at least 6 h to keep the study comparable with studies performed with ^{18}F-FDG (*20*). They were also instructed to drink 1 L of water before imaging to stimulate ^{18}F-FLT excretion from the renal calyces and stimulate subsequent voiding. Surgery followed ^{18}F-FLT PET after a median period of 26 d (range, 7–45 d).

Sixty minutes after injection, a nonattenuation–corrected whole-body scan was acquired from crown to femur with 8 min per bed position. Because detection or exclusion of malignant lesions, rather than the quantitative determination of uptake, is the main goal of this feasibility study, only nonattenuation–corrected PET images were obtained. If the primary tumor was located under the level of the femur, the patient was scanned from crown to foot. PET images were iteratively reconstructed (ordered-subset expectation maximization) (*21*).

Pathologic Evaluation and Staging

The histology of all primary lesions and metastasis were evaluated according to the latest version of the American Joint Committee on Cancer (AJCC) (*22*). The emphasis of this classification is on tumor thickness, ulceration, and number of positive lymph nodes. Breslow thickness and Clark level of the primary lesion were evaluated. In all metastatic lesions (in-transit and lymph node metastases), tumor size and mitotic rate were measured. Tumor size was expressed in millimeters or as micrometastasis if <2 mm. Mitotic rate was expressed in number of mitoses per 2 mm^2 at ×400 magnification.

The staging took place according to the last version of the AJCC (*22*). All patients were first staged clinically, by physical examination, lactate dehydrogenase, chest radiography, and histopathologic confirmation of the locoregional lymph node(s). Next, the patients were staged on the basis of the ^{18}F-FLT PET images only and finally were staged pathologically after surgery. The included patients with stage III melanoma had locoregional metastases in the lymph nodes of the groin or axilla.

Data Analysis

^{18}F-FLT PET images were analyzed for uptake in malignant lesions and normal anatomic structures. Two experienced PET physicians evaluated the images independently and were aware of the original location of the primary lesion but unaware of other clinical information. They subsequently reached consensus on a lesion-by-lesion basis. The pathologist was unaware of the results of the PET images.

Because it was impossible to exactly match individual lesions on PET with the exact same lymph nodes as analyzed after resection or cytologic aspiration, it was decided to categorize all histopathologic and PET findings into relevant anatomic regions. The regions were defined as follows: superficial or deep groin, parailiac, obturator, popliteal, supraclavicular, axillary, mediastinal, skeleton, back, neck, arm, calf, and heel. PET and histologic data from these areas were correlated and sensitivity and specificity were calculated. Therefore, only regions with histopathologic confirmation were analyzed for accuracy.

Per anatomic region, all positive lymph nodes were measured in millimeters and the mitotic rate of the lymph node with the highest proliferation was calculated to estimate the detection level of ^{18}F-FLT PET.

The results of clinical staging (before surgery), staging with ^{18}F-FLT PET (before surgery), and pathologic staging (after surgery) were compared.

RESULTS

^{18}F-FLT Distribution in Patients

Ten patients were included. Patient and primary melanoma characteristics are shown in Table 1. Patients received a median 400-MBq dose (range, 185–430 MBq) of ^{18}F-FLT. Intense ^{18}F-FLT uptake was observed in the skeleton, with a distribution pattern that is typical for bone marrow uptake (Fig. 1). The liver also showed avid uptake. Minor uptake is observed in intestinal structures. All other organs and tissues showed low-grade and homogeneous uptake. No activity was present in the brain.

In all patients, ≥1 abnormal lesions were found using ^{18}F-FLT PET. Patient-based sensitivity therefore was 100%.

Region-Based Analysis

Twenty-two true-positive, 3 true-negative, 3 false-negative, and 2 false-positive regions were observed, resulting in a pathologically proven sensitivity of 88% (Table 2). There were 3 true-negative and 2 false-positive lesions.

TABLE 1
Patient Characteristics

Patient no.	Age (y)	Sex	Clark level	Breslow thickness (mm)	Locoregional disease
1	48	F	*	*	Groin
2	39	F	IV	1.8	Groin
3	42	M	IV	4.1	Axilla
4	73	M	IV	4.4	Groin
5	78	M	IV	1	Groin
6	34	M	†	6	Axillae
7	40	M	IV	1.35	Axilla
8	29	M	*	*	Groin
9	40	F	III	0.7	Axilla
10	54	M	†	>4	Groin

*Unknown primary.
†Primary melanoma too small to assess Clark level.

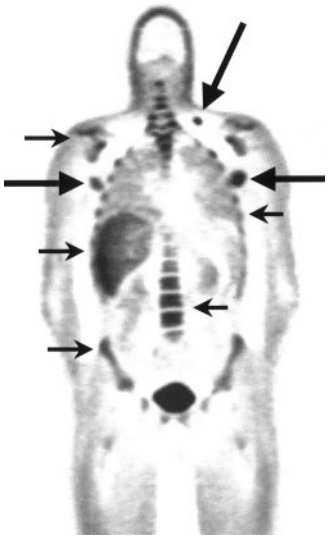

FIGURE 1. ^{18}F-FLT PET of 34-y-old man (patient 6) 2 mo after resection of primary melanoma on back. Metastases (large arrows) are observed in left and right axillae and left supraclavicular area. Physiologic uptake (small arrows) is observed in liver and 1 marrow—for example, in pelvis, vertebrae, ribs, and bony structures of shoulder; less intense, uniform tracer uptake is present in lungs. Uptake of tracer in brain is negligible, and no uptake is observed in mediastinum and myocardium.

Two of the 3 false-negative results were caused by multiple cutaneous and subcutaneous malignant lesions (satellite or primary lesions) located on the back of 2 patients, with diameters ranging from 1 to 10 mm and mitotic rate ranging from 5 to 16 mitoses per 2 mm^2 (Table 3). The other false-negative result was caused by a micrometastasis in a lymph node in the groin.

One of the 2 false-positive lesions was located in the groin, but no positive lymph nodes were found after resection of the groin area. The other false-positive lesion was located in the heel. This was the location of the primary melanoma, which was resected in total 4 y earlier and is still clinically negative.

The 3 true-negative regions, which displayed very little or no ^{18}F-FLT uptake, were 1 region with negative lymph nodes after resection and 2 resected benign skin lesions, 1 located on the calf and 1 on the arm.

At the lesion level, analysis of tumor size and mitotic rate of metastatic lymph nodes revealed that the smallest detected lesion consisted of 3 closely adjacent lymph nodes, with a micrometastasis (<2 mm) in each lymph node. The detected lesion, with the lowest mitotic activity that was still detected, had a mitotic rate of 9 mitoses per 2 mm^2.

In 2 of the above-mentioned true-positive lesions, ^{18}F-FLT PET detected malignancy, which was initially missed with conventional staging techniques. In both patients, this had therapeutic consequences because either dissection or radiation therapy was now indicated, but this had no influence on staging. These lesions were found in patients 1 and 2. In patient 1, a lesion in the fossa poplitea was indicated as malignant by ^{18}F-FLT PET and was confirmed on US-guided aspiration cytology. The patient underwent a groin dissection and a resection of the popliteal lesion. In the supraclavicular region of patient 2, an additional lesion was detected, which was confirmed by US-guided aspiration cytology. This patient received radiation therapy for locoregional control.

Additional Lesions

Eleven previously unknown lesions were present on ^{18}F-FLT PET (Table 3). These were not histopathologically confirmed but were analyzed with conventional staging techniques. Five lesions were true-positive when compared with CT or physical examination. Two mediastinal and 2 paraaortal lesions were confirmed as metastases (>1 cm); 1 lesion in the supraclavicular lesion was confirmed on physical examination.

Four of these 11 unknown lesions were true-negative based on a completely normal CT scan or clinical follow-up. One mediastinal lesion and 1 paraaortal lesion were negative on CT (<1 cm). Two lesions in the head and neck area were confirmed to be clinically negative as well during clinical follow-up.

Finally, 2 lesions detected by ^{18}F-FLT PET and interpreted as malignant could not be evaluated. The lesion in patient 2, which was interpreted as benign, was located in a lumbar vertebra, which was below the level of the CT scan. The bone scan, which was performed 2.5 mo later, showed multiple lesions in the spine. It can be assumed that these lesions were already present at the time of the ^{18}F-FLT PET. The remaining lesion in patient 5 was located in the area of popliteal lymph nodes of the involved leg next to a vascular prosthesis. However, recently this patient developed brain metastases, for which he was palliatively treated. During a follow-up of period of 3 mo, this lesion remained clinically negative. Although the above-mentioned 2 lesions were not confirmed by histopathology, it can be assumed that these 2 lesions were malignant because these patients developed disseminated disease within 12 wk.

There were 4 lesions, which were missed on ^{18}F-FLT PET, without histopathologic evaluation (Table 3). These 4 lesions were false-negative on ^{18}F-FLT PET when compared with CT. Three of these lesions were interpreted as mediastinal lymph node metastases (>1 cm) on CT and 1 was interpreted as a bone metastasis in a thoracic vertebra on CT.

TABLE 2
Cross Table of FLT PET Regions Compared with Histopathologic Regions

Comparison	FLT +	FLT −
Histopathology +	22	3
Histopathology −	2	3

Sensitivity = 88%; specificity = 60%.

TABLE 3
False-Negative, False-Positive, and Additional FLT PET Findings

Location	No. of lesions	PA	Result	Diagnostics
Deep groin	1	Pos	FN	Aspiration cytology
Dermal or subcutaneous metastases on back	9	Pos	FN	Histopathology
Back (primary tumor)	1	Pos	FN	Histopathology
Deep groin	1	Neg	FP	Histopathology
Leg (heel)	1	Neg	FP	Reresection in 1998 negative and clinically negative, follow-up of 5 y
Mediastinal	3	NP	FN	CT
Thoracic vertebra	1	NP	FN	CT
Lumbar vertebra	1	NP	NA	Bone scan with multiple bone metastases (also spinal) 2.5 mo after PET
Fossa poplitea	1	NP	NA	Clinically negative, follow-up of 4 mo
Mediastinal	1	NP	TN	CT
Paraaortal	1	NP	TN	CT
Head and neck	2	NP	TN	Clinically negative, follow-up of 3 mo
Mediastinal	2	NP	TP	CT
Paraaortal	2	NP	TP	CT
Supraclavicular	1	NP	TP	Physical examination

PA = pathologic examination.
Pos = positive; FN = false-negative; Neg = negative; FP = false-positive; NP = not performed; NA = not assessable; TN = true-negative; TP = true-positive.

Effect of ^{18}F-FLT PET on Staging

^{18}F-FLT PET detected the extent of the locoregional disease correctly in all patients (Table 4). The clinical (before surgery), ^{18}F-FLT PET, and pathologic (after surgery) staging were compared. All patients were clinical stage III. However, 1 patient was upstaged to stage IV both by CT and by ^{18}F-FLT PET, as both modalities detected mediastinal metastases. Another patient was upstaged by ^{18}F-FLT PET as compared with the clinical presurgical staging, which was confirmed by CT. The detected metastases, which caused the upstaging in the second patient, were located in paraaortal (lymphatic) region.

DISCUSSION

This study shows the feasibility of ^{18}F-FLT PET in the visualization of locoregional metastasized melanoma as well as metastatic disease.

In 10 patients, ^{18}F-FLT PET was compared with the histopathologic results of the locoregional lymph nodes. All available resected tissue samples and lesions on ^{18}F-FLT PET were categorized in anatomic regions and were compared. The sensitivity was 88% and the specificity was 60%, based on 3 true-negative and 2 false-positive lesions. Due to the low number of false-positive and true-negative lesions, the specificity is less reliable. ^{18}F-FLT PET detected all

TABLE 4
Staging

	Clinical staging			PET staging			Pathologic staging			
Patient no.	T	N	Stage	N	M	Stage	T	N*	M	Stage
1	†	+	III	+	0	III	†	p2b	0	IIIB
2	2a	+	III	+	1	IV	2a	p3	1c	IV
3	4b	+	III	+	0	III	4b	p3	0	IIIC
4	4b	+	III	+	1	IV	4b	p3	1c	IV
5	1a	+	III	+	0	III	1a	p3	0	IIIC
6	4b	+	III	+	0	III	4b	p3	0	IIIC
7	2a	+	III	+	0	III	2a	p1b	0	IIIB
8	†	+	III	+	0	III	†	p3	0	IIIC
9	1a	+	III	+	0	III	1a	p1b	0	IIIB
10	4b	+	III	+	0	III	4b	p3	0	IIIC

*All patients had locoregional lesions visualized by FLT PET.
†Unknown primary.
+ = positive lymph nodes on physical or cytologic examination.

locoregional metastases. Analyzing the effect of ^{18}F-FLT on tumor stage, 2 patients (20%) could be upstaged. However, CT also generated this upstaging.

The detection limit for lymph node metastases was lower than for the in-transit metastases. All in-transit metastases were below the detection limit of lymph node metastases of approximately 6 mm (3 lesions with micrometastases of <2 mm) and below the detection limit of ^{18}F-FLT PET of a mitotic rate of 9 mitoses per 2 mm^2. All in-transit metastases had a diameter of 1–10 mm and a mitotic rate of 5–10 mitoses per 2 mm^2. Taking the detection limit into account, the sensitivity of ^{18}F-FLT PET increased to 90% when compared with histopathologically examined samples only. Comparing ^{18}F-FLT with ^{18}F-FDG, the detection limit of ^{18}F-FDG PET for lymph nodes with melanoma metastases also depends on tumor volume and imaging equipment and technique (*9*,*11–13*,*23–27*). A tumor volume of >78 mm^3 is needed for a sensitivity of $>90\%$ or a diameter of at least 6 mm for a sensitivity of $>83\%$ (*11*,*27*). These ^{18}F-FDG data are in the same range as our ^{18}F-FLT findings.

The role of ^{18}F-FDG PET for detecting melanoma has been evaluated extensively over the last decade. For staging patients with stage I and II melanoma, the SLNB will remain the method of choice (*5*,*24*). ^{18}F-FDG PET can be of value in stages III and IV or for patients with recurrent melanoma (*10*,*28*). In the literature, there is a large variation in the sensitivity and specificity of ^{18}F-FDG PET for the detection of melanoma metastases. A recent review by Mijnhout et al. showed a sensitivity and specificity of ^{18}F-FDG PET for the detection of melanoma metastases of 79% (95% confidence interval [CI], 66%–93%) and 86% (95% CI, 78%–95%), respectively (*13*). Recent reports show comparable results (*10*,*22*,*28*,*29*). ^{18}F-FDG PET displays false-negative findings caused by small skin metastases or primary small skin lesions of melanoma (*28*,*29*). The cutaneous and subcutaneous lesions that were missed by ^{18}F-FDG PET had a diameter between 1 and 10 mm (*29*). When comparing these figures with the performance of ^{18}F-FLT PET, ^{18}F-FLT PET appears to be as accurate as ^{18}F-FDG PET and has the same detection limit (*28*).

In this study, no patient had brain or liver metastases. The detection of liver metastases by ^{18}F-FLT PET could be disturbed by the physiologic uptake in the liver. However, brain metastases could be detected because there is no physiologic uptake of ^{18}F-FLT in the brain and ^{18}F-FLT PET has been able to detect brain tumors (*17*,*30*,*31*).

CONCLUSION

The results of our study indicate that ^{18}F-FLT PET could be a new method for staging melanoma patients with stage III disease and probably also for investigating the extent of stage IV disease. The question of whether ^{18}F-FLT PET or ^{18}F-FDG PET performs best in staging melanoma patients with stage III disease remains to be answered.

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