Detection of Melanoma Metastases with Thallium-201 Scintigraphy

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Thallium-201 accumulates well in various malignant tumors. The aim of this study was to evaluate the potential of ^{201}Tl imaging in patients with metastatic melanoma. **Methods:** Fifty patients with suspected melanoma metastases were studied after intravenous injection of a mean tracer activity of 100 MBq ^{201}Tl-chloride. We took sequence images up to 5 min (15 sec/image) and immediate whole-body images with a double-headed camera and a high-resolution collimator. **Results:** Of 36 patients with metastatic melanoma confirmed by histopathology, metastases were detected in 28 patients using ^{201}Tl imaging. The tumor-to-background ratio ranged from 2.0 to 4.5 (mean 3.2). There were 8 patients with false-negative findings (sensitivity = 78%). Five false-negative findings were lymph nodes greater than 1.5 cm with tumor-to-background ratios lower than 1.5. Only a few cutaneous metastases smaller than 1 cm could be detected. There was one false-positive finding of an inflamed lymph node. The optimum time for imaging was 2–5 min postinjection. **Conclusion:** These data suggest that ^{201}Tl imaging is an accurate method for the detection of melanoma metastases. The short waiting period after injection, the lack of side effects and the sensitivity of about 80% may qualify this method as a routine investigation in patients with high-risk melanoma.

Key Words: thallium-201; melanoma metastases; malignant tumors

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The incidence of malignant melanoma is 15 per 100,000 people, with a doubling time of 10 yr. The detection of melanoma metastases, especially of involved lymph nodes, and the surgical extirpation in time is highly important for patient survival. To detect melanoma metastases, sonography, CT and MRI are used. Nuclear methods have been of little importance in this area. The first attempts to detect melanoma metastases were made using ^{67}Ga-citrate (*1–3*). In 26 patients, a sensitivity of 84% and a specificity of 98% were reported with ^{67}Ga-citrate.

Jodoquinolin derivatives labeled with ^{125}I or ^{123}I (*4*), isopropyl-*p*-iodoamphetamin (*5*) and thiouracil (*6*) were used to detect melanoma of the retina. In the past several years, more and more monoclonal antibodies and benzamide have been used, but these methods could not be used for routine investigation (*7,8*). The results on ^{201}Tl scintigraphy and malignant melanoma (*9–11*) are poor.

It is well known that ^{201}Tl accumulates in various tumors (*12–14*). In the past several years, there have been reports about malignomas of the thyroid (*15*), breast (*16*) and brain (*17*). The results are promising and show that ^{201}Tl has a high affinity to malignant tissue.

The purpose of this study was to evaluate the diagnostic value of ^{201}Tl imaging in patients with metastatic melanoma and the optimal time for imaging.

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MATERIALS AND METHODS

Fifty patients (22 women, 28 men; aged 28–77 yr) with suspected melanoma metastases entered the study. Most of them had suspicious regional lymph nodes, and five patients had multiple cutaneous metastases on one of the extremities. The main characteristics of the patients are shown in Table 1. After intravenous injection of a mean tracer activity of about 100 MBq ^{201}Tl-chloride, sequence images up to 5 min (15 sec/image) were taken of the suspicious region. Next, simultaneous anterior and posterior whole-body images were taken using an acquisition time of 5 min per image. Therefore, the total acquisition time for whole-body imaging was 30 min. Additionally, anterior-oblique images were obtained to detect possibly affected axillary lymph nodes. Imaging was performed using a large-field-of-view gamma camera (Helix double-headed camera; Elscint, Arlington Heights, OH) equipped with high-resolution collimators for low energy and with two energy peaks of 68 and 166 keV. Tracer uptake at the lesion site was determined using a region of interest technique, and a ratio was calculated using an equal-sized contralateral region. The ratio was defined as the maximum lesion counts divided by the normal tissue counts of the contralateral region or the normal background. The final diagnosis was confirmed by surgical histology, needle aspiration and clinical course.

RESULTS

Evaluation of the Optimum Time for Imaging

For five patients, a time-activity curve of the metastases was evaluated during the first 25 min. In all metastases the maximal uptake was reached 1 min after injection. A representative time-activity curve of a lymph node metastasis in the groin is shown in Figure 1. The highest tumor-to-background (T/B) ratios ranged from 1 to 5 min after injection, and there was a slow decrease in the following 20 min.

Patient Analysis

Of 36 patients with metastatic melanoma confirmed by histology, 28 patients had high uptake in the lesion with a T/B ratio of 2.0–4.5 (mean 3.2). A representative example of a positive ^{201}Tl scan is shown in Figure 2. For 16 patients with one suspicious lesion in sonography, ^{201}Tl imaging could detect additional metastases that, so far, had not been confirmed by other methods. Also, all these metastases could be eliminated by surgery. These 6 patients (of 50) benefited most from ^{201}Tl scintigraphy in this study.

There were eight patients with false-negative findings. Three of them had axillary metastases (25, 30 and 80 mm), but tracer uptake was not sufficiently high (T/B ratio lower than 1.5). In three patients, the lesions were smaller than 1.5 cm (two patients with axillary and one with an inguinal lymph node metastasis). The remaining two patients had a metastasis infraclavicularly and popliteally, with a tumor size of 1.5 cm. One patient with multiple lung metastases (size ranging from 1 to 3 cm) had diffuse increased uptake in the lung, but the

TABLE 1
Patient Characteristics

Patient no.	Sex	Age (yr)	Site of lesion	No. of lesions	Size (mm)	^{201}Tl uptake	Histology
1	M	66	Infraclavicular	1	15	−	MM
2	M	65	Inguinal	2	35	+	MM
					40	+	MM
3	M	69	Inguinal	2	20	+	MM
			Popliteal	1	20	+	MM
4	F	76	Leg	Multiple	10–30	+	MM
5	F	77	Leg	Multiple	10–30	+	MM
			Lung	Multiple	10–30	−	MM
6	F	49	na	0	na	−	na
7	F	72	Orbita	1	20	+	MM
8	M	45	na	0	na	−	na
9	M	43	na	0	na	−	na
10	M	28	Axilla	1	80	−	MM
11	M	33	Supraclavicular	2	20	+	MM
12	M	44	na	0	na	−	na
13	F	68	Inguinal	1	30	+	MM
14	F	55	Leg	Multiple	10–30	+	MM
15	M	58	Axilla	1	50	+	MM
16	F	39	Inguinal	2	30	+	MM
					20	+	MM
17	F	62	Lower leg	2	25	+	MM
					15	+	MM
18	F	43	Thigh	Multiple	3–20	+	MM
19	F	47	Soft-tissue trunk	10	10–50	+	MM
20	M	48	Axilla	1	40	+	MM
			Inguinal	1	30	+	MM
21	M	66	na	0	na	−	na
22	F	59	Thigh	1	45	+	Inflammation
23	F	65	na	0	na	−	na
24	F	56	Inguinal	1	40	+	MM
25	M	75	Inguinal	1	10	+	MM
				1	20	+	MM
26	F	54	Foot	1	10	+	MM
				1	20	+	MM
				1	30	+	MM
27	F	68	na	0	na	−	na
28	F	68	Axilla	1	30	−	MM
29	F	74	Axilla	1	6	−	MM
30	M	66	Axilla	1	15	+	MM
				1	20	+	MM
31	M	49	Axilla	1	25	+	MM
32	F	55	Popliteal	1	15	−	MM
33	M	62	Inguinal	1	10	−	Negative
34	M	52	Iliacal	3	30–50	+	MM
35	M	56	na	0	na	−	na
36	M	48	na	0	na	−	na
37	M	62	na	0	na	−	na
38	F	44	Lower leg	1	40	+	MM
39	M	62	Pectoralis	3	20–30	+	MM
40	M	50	Thigh	Multiple	3–10	−	MM
			Inguinal	1	10	−	MM
41	M	58	Axilla	3	4–7	−	MM
42	M	70	Axilla	1	12	−	Negative
43	F	48	Inguinal	1	50	+	MM
44	M	63	Axilla	1	25	−	MM
45	M	61	Axilla	1	35	+	MM
46	M	57	Axilla	3	25–30	+	MM
47	M	75	Inguinal	1	30	+	MM
48	F	42	Iliacal	2	20,3	+	MM
49	F	50	Lower leg	2	15,25	+	MM
			Inguinal	1	10	+	MM
50	M	62	na	0	na	−	na

MM = malignant melanoma; na = not applicable; + = positive; − = negative.

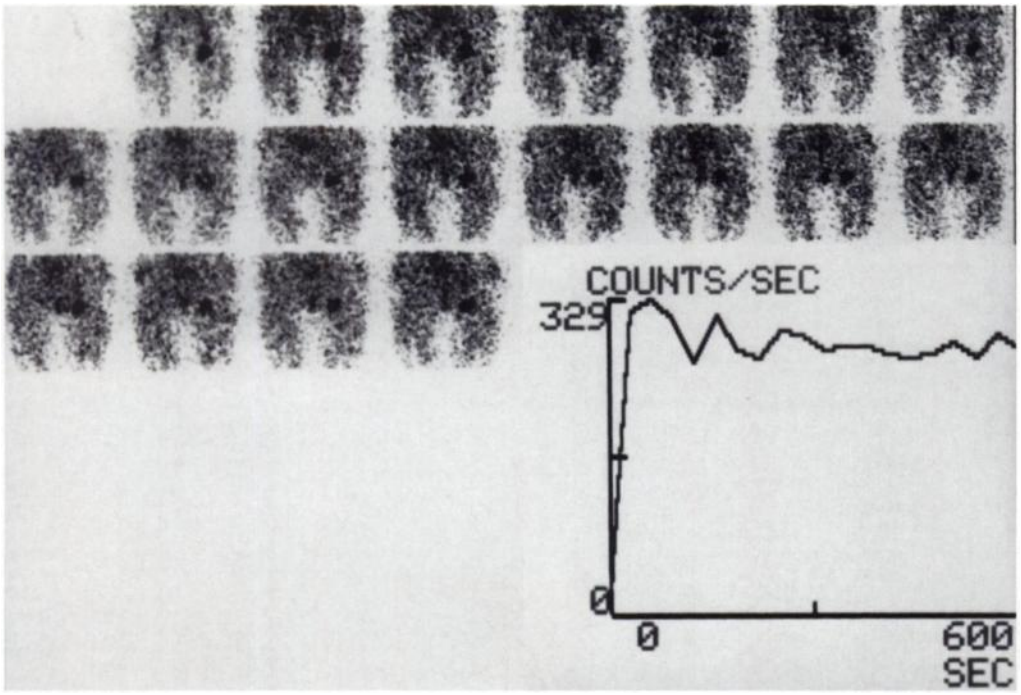

FIGURE 1. Time-activity curve of a lymph node metastasis during the first 10 min postinjection.

metastases could not be visualized in detail (Patient 5). They were not confirmed by histopathology, so we excluded this patient from the lesion analysis. One false-positive finding was caused by lymphadenitis and was located in the proximal thigh. The size of the lesion was 45 mm in diameter (Patient 22).

Thallium-201 imaging was true-negative for 14 patients. One patient with a palpable tumor in the groin and another patient with an axillary lymph node had true-negative findings, as proved histopathologically. The remaining 12 patients underwent follow-up for 6 mo by physical examination and sonography, and no metastases were found.

There were five patients with multiple cutaneous and subcutaneous metastases and high ^{201}Tl uptake in the majority of lesions (Fig. 3). However, only a few metastases smaller than 1 cm could be distinguished from the background. Thallium-201 imaging did not detect multiple cutaneous metastases in one patient with cutaneous metastases on the lower leg in which the lesions were all smaller than 1 cm.

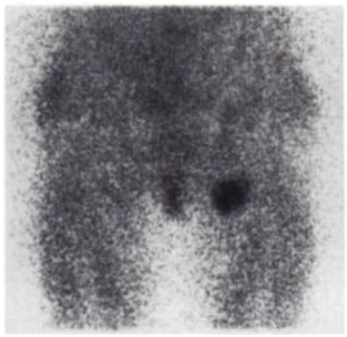

FIGURE 2. Anterior view of the pelvis and thighs. Scintigraphy was performed 10 min after tracer administration. Pathological uptake of radiotracer in a lymph node of the left groin with a T/B ratio of 3:2.

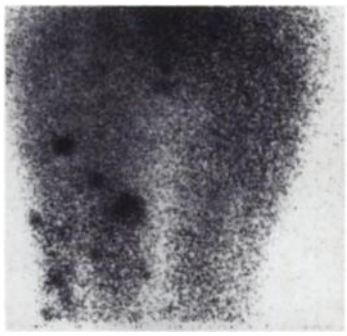

FIGURE 3. A 76-yr-old woman had an excision of a primary malignant melanoma on the right lower leg 3 yr ago. In the past 4 mo, multiple cutaneous metastases appeared on the right thigh. Planar imaging of the legs 10 min after administration of 100 MBq ^{201}Tl clearly showed multiple metastases.

Lesion Analysis

Of 63 lymph node metastases confirmed by histopathology, 53 were detected with ^{201}Tl imaging. Information on the number of lesions according to the localization is given in Table 2. In this analysis, five patients with multiple cutaneous metastases had to be excluded because of uncountable lesions. The majority of the detected cutaneous metastases were smaller than 2 cm, with a few being smaller than 1 cm.

Ten metastases (seven patients with one lesion and one patient with three lesions) that were confirmed by histology showed no significant uptake in ^{201}Tl scintigraphy. Of these 10 metastases, 3 were larger than 1.5 cm, 2 were 1.5 cm and 3 were smaller than 1.5 cm.

Statistical Patient Analysis

The sensitivity of ^{201}Tl imaging for detecting melanoma metastases was 78% (28 true-positive, 8 false-negative), the specificity was 93% (13 true-negative, 1 false-positive) and the accuracy was 82% (Table 3).

TABLE 2
Results of Thallium-201 Scintigraphy According to Localization of Metastases and Overall Lesion Sensitivity

Localization	No. of lesions	True-positive	False-negative	Sensitivity (%)
Axillary	16	7	7	
Inguinal	15	14	1	
Local lesions	5	5		
Iliacal	5	5		
Orbita	1	1		
Lung	*			
Other	12	10	2	
Trunk, soft tissue	10	10		
Total	63	53	10	84%

*Multiple lesions, but not confirmed by histopathology, with diffuse uptake in the lung.

TABLE 3
Results of Thallium-201 Scintigraphy: Patient Analysis

No. of patients	Disease positive		Disease negative	
	True-positive	False-negative	True-negative	False-positive
50	28	8	13	1

Sensitivity = 78%; specificity = 93%; accuracy = 82%.

Statistical Lesion Analysis

The overall lesion sensitivity was 84% (53 true-positive, 10 false-negative).

DISCUSSION

Although the affinity of ^{201}Tl to malignant tissues has been known for a long time, the mechanism of uptake is still not completely defined. The size of Tl+ (crystal radius 1.44 A) is between that of K+ (1.33 A) and Rb+ (1.48 A), and, accordingly, it should be expected that Tl+ would behave the same as these alkali cations. Thallium-201 has the greatest influx in the muscle cell of these three (*18*). An active uptake by potassium-sodium adenosine triphosphatase is highly likely (*19–24*). A Tl-Na-2 Cl cotransport and a calcium-dependent ion channel has been discussed (*19*). The maximal uptake of ^{201}Tl with bronchus and breast cancer and with lymphoma ranges from 8 to 15 min and is consistent with the time of maximal uptake in the myocardium (*20*). Another researcher (*16*) found the maximal uptake in breast cancer to be between 2 and 14 min postinjection. The uptake of ^{201}Tl in tumors is a flow-dependent process, but blood flow is only one important factor, and other factors such as viability of tumor cells, metabolic activity and areas of tumor necrosis also play a considerable role (*20–22*). Similar mechanisms, like in muscle cells, are of high probability. In our patients, we found the highest T/B ratio between 2 and 5 min postinjection and the maximal tumor uptake 1 min postinjection. This finding is consistent with the results of breast cancer studies, which showed an optimum tumor visualization on the images performed 2–14 min postinjection (*16*). Therefore, we think that delayed images do not increase the diagnostic outcome. The mean reason for the early uptake in tumor tissue may be the high perfusion of the melanoma metastases and the high affinity to melanoma tissue. The intensity of thallium uptake in the metastases is comparable to the results using benzamides (*25*) and monoclonal antibodies (*7,26*).

Cutaneous malignant melanoma preferably first spreads to regional lymph nodes; however, distant metastases with or without micrometastases in the regional lymph node also are not rare. The probability of distant metastases is higher in primary tumors with an increasing Breslow thickness. The early and accurate diagnosis of regional nodes or distant metastases is crucial for planning the extent and type of therapy. The extent of staging depends on the thickness of the primary lesion. The standard staging and follow-up procedures in high-risk melanoma (Breslow thickness greater than 1.5 cm) include physical examination, sonography of the regional lymph nodes and liver, chest radiography and, in some cases, CT. However, these methods are less sensitive in detecting tumor involvement, especially in normal-sized or slightly enlarged lymph nodes.

Using whole-body ^{201}Tl scintigraphy, we could detect 53 of 63 malignant lesions. There were 10 false-negative lesions and 1 false-positive lesion. The overall sensitivity of lesion detection was 84%. The highest T/B ratios were found in the metastases of the extremities because there is low absorption by overlying tissue. We cannot extrapolate our results to patients with central lesions (e.g., para-aortic and mediastinal lymph nodes and liver metastases, respectively) because there were no such patients in this study. We think ^{201}Tl imaging is of limited value in the abdomen because of physiological uptake in liver, kidneys and gastrointestinal tract.

The sensitivity of ^{201}Tl imaging depends greatly on the size and localization of the lesion. Metastases smaller than 2 cm could be detected provided that it was possible to get the detector sufficiently close to the lesion and that the detection was not disturbed by overlying physiological uptake such as liver, bowel, heart and salivary glands. This was of special concern in the extremities, axillae, inguinal regions, the brain and the neck. Nevertheless, involved lymph nodes smaller than 1 cm were less detectable. Size appears to be the main factor associated with a false-negative result in scintigraphy. On the other hand, we cannot explain why three lesions larger than 1.5 cm were not detected. Histology showed no necrotic tissue, possibly because the low uptake is connected to a special histological type.

Lymphatic mapping with regional lymphoscintigraphy using colloids recently has become more important in the detection of the first metastases in the sentinel lymph node. Lymphatic mapping and gamma-probe-guided extirpation of the sentinel lymph node can detect lymph node metastases when the size of the metastases is smaller than 1 cm and cannot be detected by conventional methods (*27*). One patient (Patient 41) with a high-risk cutaneous malignant melanoma on the trunk was investigated with whole-body ^{201}Tl imaging and lymphatic mapping. Two sentinel axillary lymph nodes and one other lymph node, eliminated by gamma-probe guided surgery, were negative on ^{201}Tl imaging but positive at histopathology. The size of these metastases was only 4–7 mm.

The most important use of ^{201}Tl imaging is to detect lymph node and distant metastases in patients with high-risk melanoma, especially those with positive sentinel lymph nodes, for whom the possibility of further metastases is high. We could not answer the question of whether ^{201}Tl imaging can detect sentinel lymph node metastases when other methods cannot. Furthermore, the results of this study show that ^{201}Tl imaging can detect metastases that are clinically relevant and not detectable by routine physical examination or sonography. The sensitivity may be comparable to scintigraphy with radiolabeled benzamides and radioimmunoscintigraphy, but both are more expensive. The advantages of ^{201}Tl imaging are the good overview of the whole body, the short amount of time needed for the test (about 25 min) and the lack of side effects.

CONCLUSION

Thallium-201 has high affinity for the tissue of malignant melanomas. The good T/B ratio, the short time needed for examination, the sensitivity of about 80% and the lack of side effects qualify this method as a useful tool for detecting high-risk melanomas.

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Technetium-99m-Tetrofosmin Uptake in Brain Tumors by SPECT: Comparison with Thallium-201 Imaging

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Thallium-201 is clinically used for the assessment of primary and recurrent brain tumors. The biologic properties of ^{201}Tl that allow it to accumulate within the tumor cells render ^{201}Tl useful in evaluating tumor malignancy, but its physical characteristics and nonroutine availability limits its use in some institutions, as compared to ^{99m}Tc-labeled compounds. The aim of this study was to assess the feasibility of using ^{99m}Tc-tetrofosmin for imaging brain tumors and to compare its uptake with that of ^{201}Tl. **Methods:** Twenty-six patients with 27 intracranial masses were studied with SPECT. In the first group of seven patients (Group A), the timing for optimal acquisition of the ^{99m}Tc-tetrofosmin scan was assessed. In the second group of 19 patients (Group B), two sequential ^{201}Tl (74–148 MBq intravenous) and ^{99m}Tc-tetrofosmin (740–925 MBq intravenous) studies were performed 20 min after tracer injection and compared. **Results:** In Group A, no significant difference in the tumor-to-background (T/B) ratio among the 20-, 40- and 120-min postinjection studies was observed. In Group B, the quality of reconstructed images with ^{99m}Tc-tetrofosmin, judged visually, was superior to that of ^{201}Tl in 47% of all studies and was comparable in the remaining 53%. A significant relationship between ^{201}Tl and ^{99m}Tc-tetrofosmin T/B ratio ($r = 0.75$, $p < 0.01$) was found. The T/B ratio of ^{99m}Tc-tetrofosmin was significantly higher than that of ^{201}Tl (23.3 ± 21.5 compared to 6.1 ± 2.9, $p < 0.005$). **Conclusion:** Technetium-99m-tetrofosmin is a suitable radiotracer for the imaging of intracranial lesions with SPECT. Moreover, a better definition of tumor margins and a higher contrast between neoplastic and normal brain tissue can be achieved.

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Thallium-201 SPECT has been used successfully in the assessment of the biologic activity of primary and recurrent intracranial neoplasms due to its ability to accumulate within tumor cells (*1,2*). The metabolic state and growth rate of tumor cells are the most important factors determining ^{201}Tl uptake in vitro (*3,4*). In vivo, regional blood flow, blood-brain barrier (BBB) permeability and tissue viability are the main factors contributing to the uptake of the tracer (*5*). The increase in BBB permeability alone is not necessarily responsible for the uptake because some lesions, such as resolving hematomas and areas of radiation necrosis, show a low ^{201}Tl uptake (*6*). Tumor viability, on the other hand, is the most relevant factor responsible for ^{201}Tl uptake; in fact, a strict correlation of ^{201}Tl index, i.e., the tumor-to-background (T/B) ratio, with histologic grade, proliferative activity and overall prognosis of intracranial tumors has been demonstrated (*7*). Despite these considerable biologic advantages, ^{201}Tl has some limitations from the clinical standpoint. First, the long half-life and biologic distribution limit the amount of activity administered to the patient. Second, ^{201}Tl may be less available than ^{99m}Tc-labeled compounds in some institutions. Third, the low-energy photon flux of the radionuclide affects the quality of the image, particularly in brain tumors with diameters smaller than 1.5 cm, with a thin rim of ring enhancement during postcontrast magnetic resonance imaging (MRI) studies (*8*). However, optimal image quality with good definition of tumor size and margins is required for