# Differential Accumulation of Iodine-123-Iodobenzamide in Melanotic and Amelanotic Melanoma Metastases In Vivo

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Iodine-123-iodobenzamide (IBZM) is a specific antagonist of dopamine D2 receptors and usually is used to study neuropsychiatric disorders. It also has a substantial affinity for malignant melanomas. This has been attributed to specific dopamine D2 receptor binding on melanoma cells because melanocytes and dopaminergic neurons share the same ectodermal origin and are both able to produce melanin. However, IBZM binding to melanoma metastases occurs predominantly 24 hr after injection, which is much later than maximal specific D2 receptor binding is expected. Furthermore, IBZM binding is not consistent in melanoma patients. This points to another mechanism of IBZM binding to melanoma cells. The aim of this study was to characterize IBZM-binding metastatic melanoma patients clinically and histologically to shed light on the nature of this mechanism. **Methods:** Twenty-one patients with proven or suspected metastases of a malignant melanoma entered this prospective study after surgical removal of the primary tumor. Whole-body scans, planar scintigrams and SPECT scans were performed 2–5 hr and 1 day after intravenous injection of 185 MBq IBZM. **Results:** The suspected diagnosis of metastatic cancer was later confirmed in 17 patients by histology, clinical follow-up, x-ray, CT or other radiologic methods. Four patients were free of tumor tissue at the time of investigation and remained stable for 2 yr thereafter. Twelve of the 17 patients had a melanotic and 5 had an amelanotic subtype of the tumor. Iodine-123-IBZM accumulation occurred in the metastases of 10 of the 12 patients with melanotic melanoma and in 0 of the 5 patients with the amelanotic tumor type ($p < 0.01$; chi-square test). Furthermore, IBZM accumulation occurred in 0 of the 11 amelanotic metastases but in 20 of the 25 melanotic metastases ($p < 0.001$). The sensitivity is, thus, 83% for the detection of melanotic melanoma metastases on a patient basis and 80% on a lesion basis. Iodine-123-IBZM scintigraphy demonstrated one previously unknown metastasis. Six initially suspected lesions were not due to melanoma metastases and were IBZM-negative. No false-positive IBZM accumulations occurred in our patients. **Conclusion:** Iodine-123-IBZM binds to melanotic malignant melanomas with high specificity and moderate sensitivity but not to amelanotic melanomas. Our data suggest that the tracer does not bind to membrane dopamine receptors of the tumor but is built in or closely bound to intracellular melanin.

**Key Words:** melanoma; melanin; dopamine; iodine-123-iodobenzamide; tumor imaging

**J Nucl Med 1998; 39:996–1001**

The importance of malignant melanoma in tumor statistics has increased rapidly in the past two decades: the number of newly reported cases has doubled every 10 yr (*1*). Despite considerable advances in chemotherapy, immunotherapy and radiation therapy, a cure for metastatic melanoma is only possible with accurate surgical removal of the primary cancer and all its metastases. This emphasizes the need for a noninvasive diagnostic test of high accuracy and precision for the detection of melanoma cells.

Recently, dopamine D2 receptor antagonistic benzamides have been proposed as highly specific and sensitive ligands for the detection of melanoma metastases. There are two reasons to assume that these dopaminergic ligands bind to melanoma cells. First, dopaminergic neurons and melanoma cells are both of ectodermal origin. Second, melanocytes and the neurons of the substantia nigra, which are the source of the brain's dopaminergic innervation, produce melanin. Clinical studies have been previously performed with three agents, namely, $^{123}$I-N-(diethylaminoethyl)-4-iodobenzamide (BZA), $^{123}$I-(S)-5-iodo-7-N-[1-ethyl-2-pyrrolidinyl]carboxamino-2,3-dihydrobenzofuran (IBF) and $^{123}$I-iodobenzamide (IBZM) [$^{123}$I-(S)-2-hydroxy-3-iodo-6-methoxy-N-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide]. The sensitivity and specificity of BZA were evaluated in an initial study of five patients (*2*). All known metastases and, additionally, up to the point of investigation, unknown lesions showed a moderate uptake of BZA. The ligand showed a high sensitivity of 81% and a specificity of 100% for the detection of melanoma metastases in a group of 110 patients (*3*). The first use of IBZM as a tracer for imaging of metastatic melanoma has been reported in a case report (*4*). The ligand was evaluated by the same group in a study of 11 patients showing predominantly superficial lesions (*5*), with a reported sensitivity of approximately 80% and a specificity of 100%. The agent IBF showed a much poorer sensitivity of <20% (*6*).

The exact mechanism of the benzamide binding to melanomas remains unclear because there is no evidence from in vitro studies that melanocytes really exhibit dopamine receptors (*7*). Moreover, the time window of IBZM binding to the melanoma cells was different from specific dopamine D2 receptor binding to the striatum known from other in vivo studies (*8,9*): tumor IBZM binding occurs for as long as 24 hr after injection, at a time when specific striate D2 binding is largely diminished (*5*). This leads to the assumption that benzamides such as IBZM do not bind to dopamine D2 receptors on the surface but are incorporated into the cells, possibly by binding to intracellular melanin.

The aim of our study was to examine the mechanisms of IBZM accumulation clinically and histologically. The specific hypothesis was that the accumulation of benzamides in melanomas reflects the existence of intratumoral melanin and not of dopamine D2 receptors.

## MATERIALS AND METHODS

### Patients

Twenty-one patients (11 women, 10 men; mean age ± s.d. = 61 ± 16 yr; age range 32–87 yr) with histologically proven malignant melanoma participated in this prospective study. The main demographic data of this patient group are shown in Table 1.

Received Mar. 11, 1997; revision accepted Aug. 14, 1997.
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**TABLE 1**
Patient and Tumor Characteristics

| Patient no. | Age (yr) | Sex | Clarke's level | Sites of suspected metastases | No. of lesions |
|---|---|---|---|---|---|
| 1 | 32 | F | III | Liver | 2 |
| 2 | 37 | M | IV | Thoracic wall, lung, mediastinum | 3 |
| 3 | 82 | F | III | Lung | 2 |
| 4 | 55 | M | Pleomorphic | Lung | 1 |
| 5 | 71 | M | IV | Brain | 3 |
| 6 | 52 | F | III | Mediastinum | 1 |
| 7 | 70 | F | IV | Lung | 1 |
| 8 | 49 | M | III | Axillary lymph node | 1 |
| 9 | 87 | F | III | Inguinal lymph node | 1 |
| 10 | 63 | M | III | Lung | 1 |
| 11 | 74 | F | III | Retroperitoneal lymph nodes, abdominal wall | 2 |
| 12 | 60 | M | IV | Cervical lymph node, both lungs, liver | 4 |
| 13 | 67 | M | IV | Lung, axillary and inguinal lymph nodes, abdomen, pelvis | 6 |
| 14 | 66 | M | IV | Thoracic wall, liver, lung | 3 |
| 15 | 50 | F | | Vagina, lung | 2 |
| 16 | 77 | F | IV | Right foot | 2 |
| 17 | 70 | F | V | Left foot | 1 |
| 18 | 44 | M | IV | Inguinal lymph nodes, mediastinum, sacral bone | 3 |
| 19 | 32 | M | IV | Back | 1 |
| 20 | 63 | F | III | Thoracic wall | 1 |
| 21 | 78 | F | III | Cervical lymph node | 1 |

The primary tumor was surgically removed in all patients. A total of 42 metastases was suspected based on pathologic chest radiograms, abdominal ultrasounds, CT scans or clinical examination. Histologic analysis of the primary tumor had been completed for all patients at the time of investigation. The presence or absence of intratumoral melanin was examined using a silver impregnation method (Fontana–Masson staining). The study protocol was approved by the Ethical Committee of the University of Düsseldorf.

### Tracer and Scintigraphic Procedures

Iodine-123-iodobenzamide was provided by Cygne (Eindhoven, The Netherlands). The specific activity of IBZM at the time of injection was >100 TBq/mmol. Patients received 185 MBq IBZM intravenously after blockade of thyroid iodine uptake by 1200 mg of perchlorate for 3 days before the examination and for a further 3 days thereafter. All measurements were performed using a double-headed SPECT and whole-body camera (PRISM 2000; Picker, OH) with high-resolution collimation. The energy window of $^{123}I$ was set to 159 ± 16 keV for all examinations. Whole-body scans were performed 3–5 hr after injection in all patients and on the following day in 18 patients, with a scan duration of 1 hr. SPECT scans and planar scintigrams of the known or assumed metastatic locations were performed after the first whole-body scan and also on the following day in eight patients. SPECT was routinely used for imaging the brain immediately and 90 min after injection and, in patients with suspected brain metastases, after 24 hr as well. For most patients, after the first whole-body scan, SPECT was used for imaging the abdomen as well. Chest imaging was only done with SPECT when lesions of unclear location were visible on the planar images. The in-plane resolution (FWHM) of the camera system for SPECT scans was 13 mm, and the axial resolution was 15 mm. For SPECT measurements, 120 projections were obtained within 30 min using a 360° circular rotation of the two detectors. Reconstructed images were filtered using a low-pass filter.

When an IBZM-accumulating tumor was visible, regions of interest were drawn in all whole-body and planar images over the lesion and over the corresponding contralateral regions, the latter representing background activity. A tumor-to-background ratio was calculated this way.

## RESULTS

The most important histologic data and lesion sites are given in Table 2. Although all of the 21 patients were initially suspected of having a total of 42 metastases, clinical follow-up showed that 4 of them had no residual tumor at the time of investigation. The remaining 17 patients had a total of 36 lesions. Six initially suspicious lesions were not due to melanoma metastases, as shown by clinical follow-up or histology. Iodine-123-IBZM binding was positive in 10 of the 17 patients and in 20 of the 36 melanoma metastases. One lesion was unknown before the IBZM examination. No false-positive IBZM binding was observed. This accounts for an overall sensitivity of 56% on a lesion basis or 59% on a patient basis and a specificity of 100%. The accuracies were 62% and 67%, respectively.

Melanin was initially present in the primary tumor of 12 patients with 25 lesions. Five patients with a total of 11 lesions suffered from an amelanotic melanoma. The mean diameter of the melanotic metastases was 20 mm (range 3–30 mm), whereas the mean diameter of the amelanotic metastases was 28 mm (range 20–50 mm). No IBZM binding was observed in the lesions of the above-mentioned five patients with amelanotic melanomas, although they all exhibited active tumor tissue (Table 3). Iodine-123-IBZM binding was positive in 20 of the 25 lesions and in 10 of the 12 patients suffering from melanotic melanoma. The differences in IBZM binding between the two patient groups (melanotic and amelanotic tumor) are significant, with $p < 0.01$ on a patient basis and $p < 0.001$ on a lesion basis (chi-square test; Table 3). The data account for a sensitivity of 80% on a lesion basis and 83% on a patient basis for the detection of melanotic melanoma metastases. Table 4 shows the sensitivity of the method for melanotic metastases in different organs.

Figure 1 shows the scintigrams of a patient with three brain metastases proven by a CT scan. We performed SPECT scans of the brain immediately after injection, after 90 min and on the following day. The duration of each scan was 30 min. The first scan shows IBZM delivery to the brain tissue, which is highly dependent on regional cerebral blood flow. The largest metastasis is only visible as a cold lesion within the cortex. The second scan shows specific dopamine D2 receptor binding of IBZM to the striatum after 90 min, when unspecific cortical binding has largely diminished. Again, the metastasis is only seen as a cold lesion. It is only after 24 hr that IBZM accumulation in two metastases exceeds the binding to the surrounding brain tissue, including the dopamine D2 receptor-rich striatum and the sigma-1 receptor-rich hippocampus and thalamus (Fig. 2).

Fifteen lesions were examined twice, 4 and 24 hr after injection (Table 2). The tumor-to-background ratio increased significantly in these metastases between the first and the second examination ($p < 0.05$, Student's t-test). This effect was most pronounced in the liver and brain lesions, which were hardly seen on the early images but were usually very prominent on the late images because the surrounding cortical or hepatic IBZM had cleared. An example is given in Figure 3, which shows a patient with two liver metastases. The scans were taken 4 and 24 hr after injection. The liver excretion of IBZM and its metabolites is high at 4 hr; three focal accumu-

**TABLE 2**
Histologic, Clinical and Scintigraphic Data of All Lesions and Patients

| Patient no. | Lesion no. | Site of lesion | Tumor confirmed | IBZM | Melanin | Size of lesion (mm) | T/B early | T/B late |
|---|---|---|---|---|---|---|---|---|
| 1 | 1, 2 | Liver | + | + | + | 20–30 | 1.4 | 2.3 |
| 2 | 3 | Thoracic wall | + | − | − | 50 | — | — |
| | 4 | Mediastinum | + | − | − | 30 | — | — |
| | 5 | Lung | + | − | − | 30 | — | — |
| 3 | 6 | Mediastinum | − | − | | — | — | — |
| | 7 | Abdomen | − | − | | — | — | — |
| 4 | 8 | Lung | + | − | − | 25 | — | — |
| 5 | 9–11 | Brain | + | 2+ | + | 10–30 | 0.5 | 2.1 |
| 6 | 12 | Mediastinum | − | − | | — | | |
| 7 | 13 | Lung | + | + | + | 20 | 1.1 | 1.2 |
| 8 | 14 | Axilla | + | + | + | 20 | 1.2 | 1.3 |
| 9 | 15 | Inguinal | − | − | | — | — | — |
| 10 | 16 | Lung | + | + | + | 20 | 1.1 | 1.2 |
| 11 | 17 | Abdominal wall | + | − | + | 40 | — | — |
| | 18 | Abdomen | + | + | + | 40 | 2.3 | — |
| 12 | 19 | Cervical | + | − | − | 20 | — | — |
| | 20 | Lung | + | − | − | 20 | — | — |
| | 21 | Lung | + | − | − | 20 | — | — |
| | 22 | Liver | + | − | − | 20 | — | — |
| 13 | 23 | Lung | + | + | + | 20 | 1.3 | 1.5 |
| | 24 | Abdomen | + | + | + | 20 | 2.4 | 2.9 |
| | 25 | Axilla | + | + | + | 20 | 1.4 | 1.7 |
| | 26 | Inguinal | + | + | + | 20 | 1.6 | 1.5 |
| | 27 | Abdomen | + | + | + | 20 | 2.4 | 2.9 |
| | 28 | Abdomen | + | + | + | 20 | 2.4 | 2.9 |
| 14 | 29 | Thoracic wall | + | + | + | 25 | 1.8 | 2.1 |
| | 30 | Lung | + | + | + | 15 | 1.3 | 1.6 |
| | 31 | Liver | + | + | + | 15 | 1.0 | 1.8 |
| 15 | 32 | Lung | + | − | + | 15 | — | — |
| | 33 | Pelvis | + | − | + | 20 | — | — |
| 16 | 34, 35 | Foot | + | + | + | 5 | 1.9 | — |
| 17 | 36 | Leg | + | − | + | 3 | — | — |
| 18 | 37 | Inguinal | + | − | − | 30 | — | — |
| | 38 | Sacral bone | − | − | − | — | — | — |
| | 39 | Mediastinum | + | − | − | 40 | — | — |
| 19 | 40 | Back | − | − | | — | — | — |
| 20 | 41 | Thoracic wall | + | + | + | 15 | 1.3 | 2.4 |
| 21 | 42 | Cervical | + | − | − | 20 | — | — |

T/B = tumor-to-background ratio.

lations are visible. After 24 hr, the gallbladder has emptied and can now clearly be differentiated from the metastases. SPECT scans are mandatory in suspected abdominal metastases: the comparison of early and late scans with the CT scan shows, in most cases, whether "hot" IBZM-accumulating regions are due to tumor or intestinal activity.

**TABLE 3**
Dependence of IBZM Binding on the Melanin Content of the Tumor*

| | No. of patients | | No. of lesions | |
|---|---|---|---|---|
| | Amelanotic | Melanotic | Amelanotic | Melanotic |
| IBZM+ | 0/5 | 10/12 | 0/11 | 20/25 |
| IBZM− | 5/5 | 2/12 | 11/11 | 5/25 |
| p value | <0.01 | | <0.001 | |

*The second and third columns from the left show the numbers of IBZM positive vs. negative patients, respectively, bearing melanotic and amelanotic tumors. The right two columns show these results on a lesion basis.

## DISCUSSION

This study examines tumor binding of IBZM in 21 patients with malignant melanoma. The main finding was that IBZM binding was not observed in amelanotic metastatic lesions but was

**TABLE 4**
Sensitivity of Iodine-123-Iodobenzamide Scintigraphy for the Detection of Melanotic Melanoma Metastases in Various Organs*

| Organ | No. of suspected lesions | No. confirmed | No. melanin-positive | No. IBZM-positive |
|---|---|---|---|---|
| Lung | 9 | 9 | 5 | 4 |
| Skin | 8 | 7 | 6 | 4 |
| Lymph nodes | 7 | 6 | 3 | 3 |
| Abdomen/pelvis | 6 | 5 | 5 | 4 |
| Liver | 4 | 4 | 3 | 3 |
| Mediastinum | 4 | 2 | 0 | 0 |
| Brain | 3 | 3 | 3 | 2 |
| Bone | 1 | 0 | 0 | 0 |
| Total | 42 | 36 | 25 | 20 |

*IBZM binding was never positive in melanin-negative tumors or in nonconfirmed lesions.

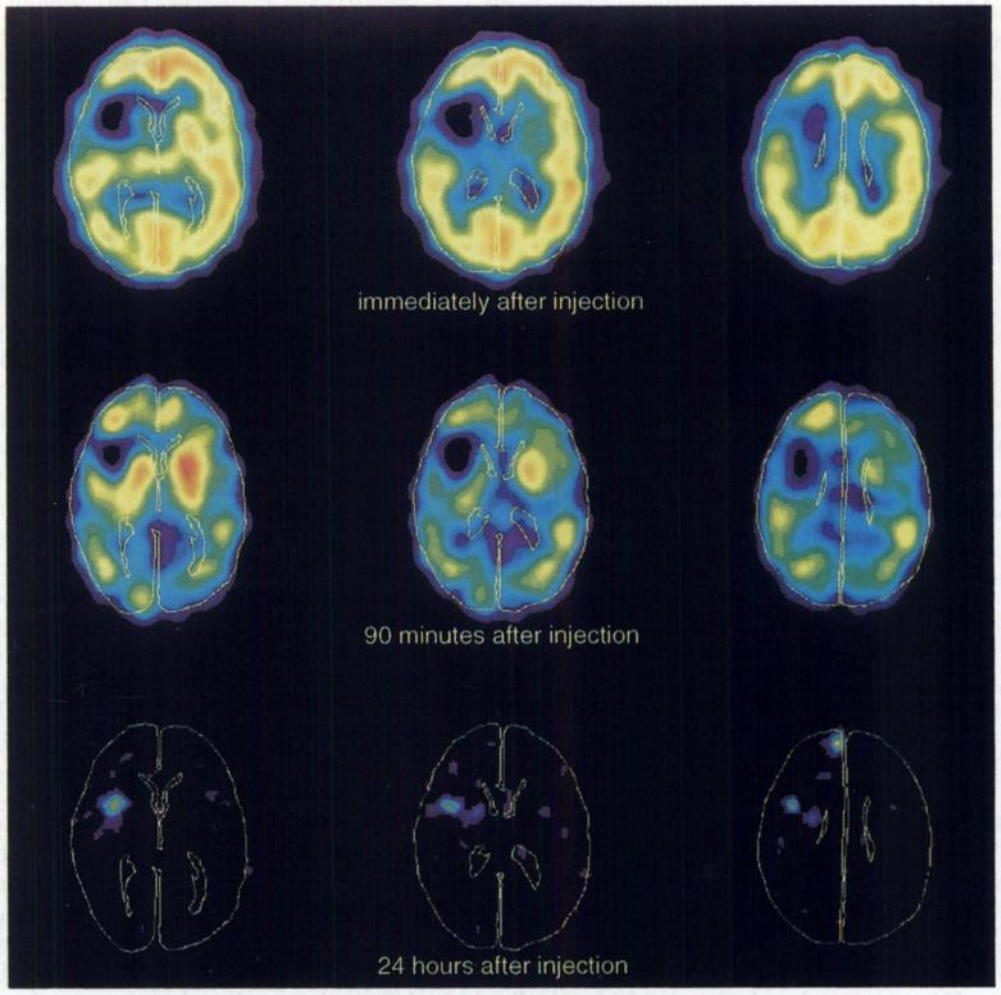


**FIGURE 1.** Brain metastases of a malignant melanoma immediately, 90 min and 24 hr after injection of IBZM. Shown are transversal SPECT slices with a 9-mm thickness.

observed in 80% of melanotic metastases. The difference between melanotic and amelanotic metastases regarding their IBZM-binding properties was significant, with $p < 0.001$. This seems to imply that IBZM is built in or is closely bound to melanin. This could further imply that the amount of IBZM binding is a measure of intratumoral melanin turnover or content.

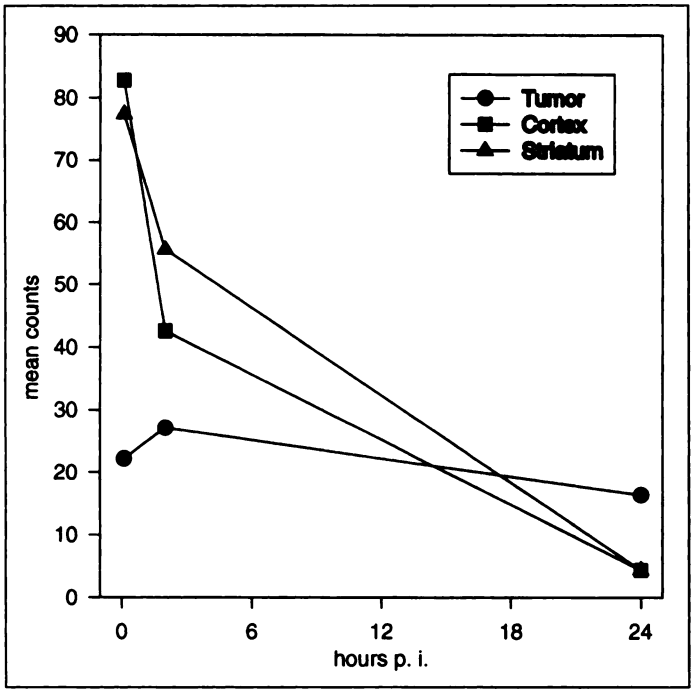


**FIGURE 2.** Time-activity curves for tumor tissue, cortex and striatum from Figure 1.

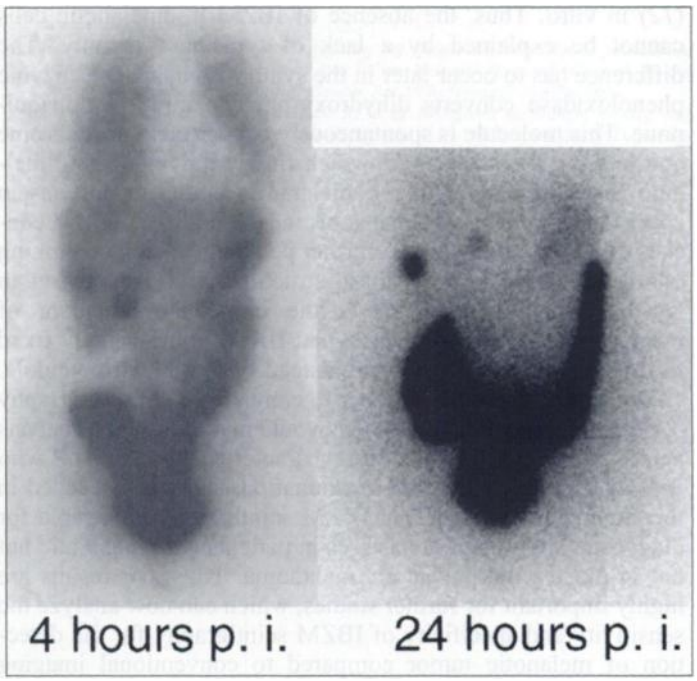


**FIGURE 3.** Planar scintigrams showing liver metastases 4 and 24 hr after injection of IBZM.

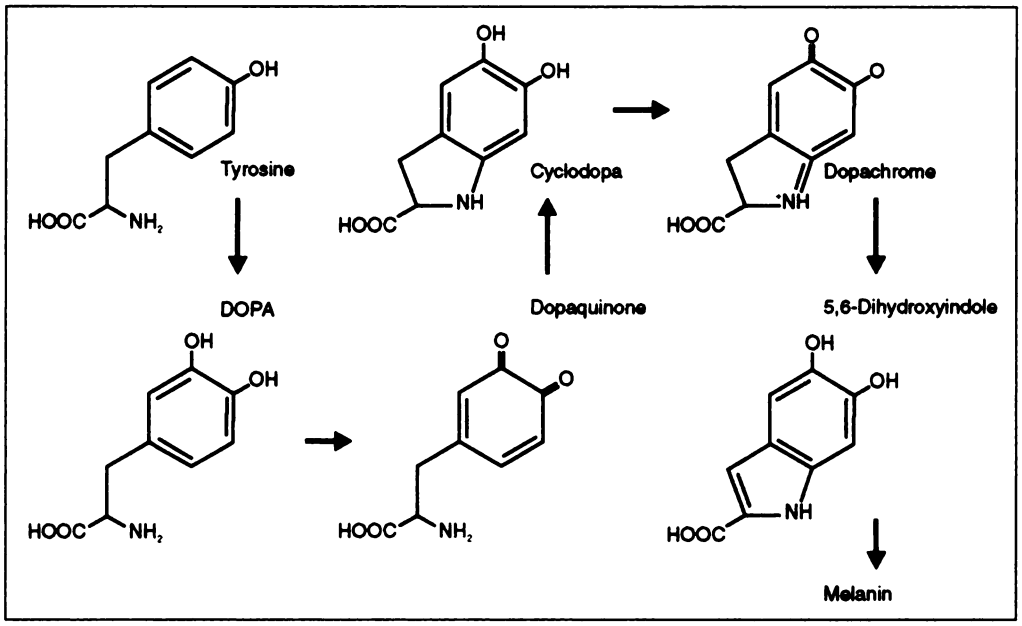


**FIGURE 4.** Biosynthesis of melanin.

Coenen et al. (*10*) showed that benzamides are taken up in melanotic melanomas in mice, in a manner that is independent of the total cell number but strongly correlated to the intracellular melanin content. Moreover, binding of benzamides was dependent on the pH of the environment and peaked when pH was optimal for cellular melanin synthesis. Additionally, melanoma cells lack dopamine D2 receptor mRNA (*7*). Additional evidence against specific D2 or sigma-1 receptor binding comes from a particularly instructive case, which we discussed in detail in the results (Figs. 1 and 2). Thus, specific IBZM binding to membrane receptors is an unlikely explanation for the observed intratumoral accumulation of the ligand.

Dopamine and melanin are biochemically derived from the amino acid tyrosine. The first and rate-limiting step of both syntheses is the hydroxylation of tyrosine to dihydroxy-phenylalanine by the tyrosinase. This enzyme seems to be present in both melanotic and amelanotic melanoma cells, as indicated by the analysis of tyrosinase mRNA (*11*) and tyrosinase activity (*12*) in vitro. Thus, the absence of IBZM in amelanotic cells cannot be explained by a lack of tyrosinase activity. The difference has to occur later in the synthesis chain. The enzyme phenoloxidase converts dihydroxy-phenylalanine to dopaquinone. This molecule is spontaneously converted to dopachrome and to 5,6-dihydroxyindole, which finally polymerizes to melanin (Fig. 4). Intracellularly, melanin is bound to proteins in specific organelles called melanosomes. Iodine-123-IBZM consists of a benzole ring and a further pentangular ring containing one nitrogen atom (*13*). These structures are also present in 5,6-dihydroxyindole, which is the immediate precursor of melanin. Thus, we hypothesize that IBZM is most likely fixed to the melanin macromolecule instead of 5,6-dihydroxyindole.

The aim of this study was not to compare IBZM scintigraphy to other imaging methods, which would make a blinded analysis necessary. Rather, we wanted to characterize those patients who potentially benefit from the examination, and we succeeded in this attempt. We found that IBZM scintigraphy is feasible for diagnostic analysis of metastases in patients with melanotic but not in those with amelanotic melanoma. Thus, our results are highly important for further studies, which can now analyze the sensitivity and specificity of IBZM scintigraphy for the detection of melanotic tumor compared to conventional imaging methods. The design of the study required that the results of the conventional examinations were known when the IBZM scintigraphy was analyzed, and this, of course, influenced our estimates of sensitivity and specificity of the method. As a result of these limitations, the specificity of pathologic IBZM binding for malignant melanoma cells was 100% outside the physiologic distribution. The overall sensitivity of the method for melanoma detection was 56%, and the sensitivity for the detection of melanotic metastases was 80%. Visceral metastases in liver or lung were not seen when they were smaller than 15 mm in diameter. Brain metastases with a diameter of $<10$ mm were hardly visible. Cutaneous metastases were visible down to a size of 5 mm. These results are in good agreement with the data of Maffioli et al. (*5*).

Five lesions proved to be false-negative despite the presence of melanin (Table 2): lesions 9 and 32 were located in brain and lung, respectively. The high background activity of these organs results in a poor tumor-to-background ratio. Lesion 36 had a diameter of only 3 mm. Its tumor volume obviously was too low to allow sufficient aggregation of activity. Lesion 17 had a size of 40 mm but had already been subjected to an external radiation. Finally, lesion 33 was located in the vagina and could not be differentiated from urinary radioactivity.

It is well known that the intestinal uptake of IBZM due to hepatobiliary excretion obscures the detection of intra-abdominal metastases (*5*). Lesions surrounding the gallbladder and urinary bladder are almost impossible to visualize. Additionally, in our experience, metastases in the lung and brain are often only visible using SPECT at various times up to 24 hr postinjection.

The benzamide $^{123}$I-BZA (*2,3*) shows a comparable sensitivity of 81% and also a specificity of 100%. However, only 2 of 17 lesions were visible using $^{123}$I-IBF (*6*). Although former studies report a sensitivity of immunoscintigraphy using $^{111}$In- or $^{99m}$Tc-labeled monoclonal antibodies of approximately 80% (*14,15*), a more recent study only found 9 of 34 melanoma metastases, which accounts for <30%, with 2 false-positive results when using a $^{99m}$Tc-labeled antibody (*16*). A large multicenter study of 1245 patients reported a sensitivity of 73% by immunoscintigraphy with $^{99m}$Tc- and $^{111}$In-labeled antimelanoma antibodies or $^{131}$I- and $^{111}$In-labeled anticarcinoembryonic antigen F(ab')$_2$ fragments derived from antibodies 225.28S and F023C5, respectively (*17*). The potency of somatostatin receptor scintigraphy for the detection of melanoma metastases remains to be evaluated. However, specificity of this method

should be considerably lower because $^{111}$In-octreotide also has a high affinity for various other tumors. PET using $^{18}$F-fluorodeoxyglucose comprises superior sensitivity, but lower specificity, in its tumor-seeking ability compared to most other methods (*18*). However, the availability of PET scanners is currently limited to a few centers. Additionally, PET hardly allows screening of the whole-body in a reasonable time because of its limited axial field of view. Therefore, the efficacy of IBZM scintigraphy seems at least to be comparable to other nuclear medicine imaging modalities.

According to a definition from Patton (*19*), an examination is cost-effective if its benefits are worth the additional costs. The costs of IBZM are in the same price group as are other radiopharmaceuticals for the detection of melanoma metastases. The effectiveness of the method was not examined in this study. However, we know now that IBZM can only be effective for the detection of melanotic metastases and that a sensible examination can last as long as 24 hr after injection. Therefore, we propose to perform further studies on the cost-effectiveness of IBZM scintigraphy and alternative radiologic and nuclear medicine methods based on these findings.

IBZM scintigraphy for the detection of melanoma metastases has clinical applications: first, the very high specificity of the method enables it to clarify pathologic CT findings in patients with a history of melanoma. In particular, suspected lymph node metastases are suitable for IBZM scintigraphy, which also allows for an overview of the entire body without further radiation exposure. Second, in patients with a malignant melanoma and a second tumor, chemotherapy is often the superior treatment in the case of a recurrence. However, the kind of chemotherapy may depend on the histology of the recurrence, which is sometimes hard to obtain. In these cases, IBZM scintigraphy could prove the tumor to be a melanoma and, thus, enable the differential diagnosis in vivo with high specificity. We strongly recommend performing whole-body scans 4 and 24 hr after injection of the tracer because tumor-to-background ratios increased in this study in the late scans. We further recommend SPECT scans, especially when abdominal or cerebral metastases are suspected.

## CONCLUSION

IBZM binding to malignant melanoma is likely to reflect melanin synthesis or content in melanotic melanomas and not dopamine D2 or sigma-1 receptor binding. Future studies should focus on IBZM accumulation in melanotic melanomas in quantitative terms as a marker of prognosis and as an index of responsiveness to chemotherapy and radiotherapy.


## ACKNOWLEDGMENTS

We thank E. Paech and her colleagues at the Clinic of Nuclear Medicine, University of Düsseldorf, Düsseldord, Germany, for their expert technical assistance during the scintigraphic studies. We also thank R. Clauss, Institute of Medicine, Research Center Jülich GmbH, for editorial assistance.


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