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## Visualizing Ocular Melanoma Using Iodine-123-N-(2-Diethylaminoethyl)4-Iodobenzamide SPECT

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Radiolabeled benzamides have recently been introduced for the detection of melanoma. We evaluated the potential clinical applicability of <sup>123</sup>I-N-(2-diethylaminoethyl) 4-iodobenzamide (<sup>123</sup>I-IDAB) for SPECT imaging of ocular melanoma. **Methods:** Fourteen patients were studied, 10 with or suspected of malignant ocular melanoma and four with ocular naevi. All patients underwent SPECT imaging of the head and whole-body scintigraphy 4-5 hr after injection of 170 MBq [<sup>123</sup>I]IDAB. **Results:** A definite tracer hyperfixation was observed in the pathological eye in 9 of 10 (90%) patients with ocular melanoma. The pathological-to-normal eye ratio averaged 1.46 (range 1.07-2.86). The melanoma nature of the scintigraphic lesions was confirmed after enucleation in eight cases and by clinical evolution in two. A false-negative scan was reported in a patient with a small and hypochromic lesion. In patients with ocular naevi, no false-positive scintigrams were documented. **Conclusion:**

Iodine-123-IDAB scintigraphy may contribute significantly to decide about enucleation in cases where some doubt persists with conventional techniques.

**Key Words:** benzamides; ocular melanoma; SPECT

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Ocular melanomas are the most common primary intraocular malignancies in adults. The diagnosis is usually made from documented growth of a lesion on serial clinical examinations, ocular ultrasonography and/or fluoangiography. CT and MR images may be helpful for further evaluation (1). In some cases, however, the assessment of the nature of ocular lesions is troublesome. As early dissemination may occur, every effort should be made to distinguish a melanoma from a naevus as soon as possible. Biopsy offers no valid alternative because ocular tumors are not easily accessible from biopsy without the disruption of vision. A noninvasive method to help in the

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**TABLE 1**  
Patient Characteristics

Patient no.	Sex	Age (yr)	Localization	Size (mm)	IDAB	Ratio	Treatment
1	F	45	Choroidal	960	+	1.71	Protontherapy
2	F	56	Choroidal	100	+	1.87	Enucleation
3	F	57	Iris	2016	+	2.8	Enucleation
4	F	65	Choroidal	216	+	2.12	Enucleation
5	F	67	Choroidal	168	+	1.28	Enucleation
6	M	49	Iris	12	-	1	Enucleation
7	F	67	Conjunctiva	-	+	1.54	Radiotherapy
8	F	51	Iris	9	+	1.25	Enucleation
9	M	76	Choroidal	250	+	1.64	Enucleation
10	F	76	Choroidal	330	+	1.24	Enucleation
11	M	71	Naevus	-	-	1	None
12	F	89	Naevus	-	-	1	None
13	F	60	Naevus	-	-	1	None
14	M	45	Naevus	-	-	1	None

assessment of ocular tumors would therefore be the best alternative.

Recently,  $^{123}\text{I}$ -N(2-diethylaminoethyl) 4-iodobenzamide ( $^{123}\text{I}$ IDAB), a radiolabeled benzamide, has been proposed for the detection of melanoma lesions (2). This radiopharmaceutical has been used with success in patients with melanoma by Michelot et al. (3).

The aim of this study was to assess the diagnostic potential of  $^{123}\text{I}$ IDAB SPECT in patients with ocular melanoma and to determine the specificity of the test by including patients with benign lesions.

**MATERIALS AND METHODS**

**Patient Population**

Fourteen patients with ocular lesions (10 women, 4 men; age range 45–89 yr; mean age 62 yr) were included in this study. In 10 cases, ocular melanoma was strongly suspected on the basis of clinical examination and radiological staging. In eight patients, the diagnosis was confirmed by histological tests after enucleation (Table 1). In these eight patients, the size of the tumor was measured. Two patients refused surgery, one was treated with radiotherapy, the other submitted to protontherapy. In two other patients, the scan was repeated 1 mo after enucleation. Four patients with ocular naevi, not showing signs of progression on serial clinical examinations, were also tested.

The study protocol was approved by the Commission of Medical Ethics of the Free University of Brussels. Informed consent was obtained from all patients.

**Tracer Preparation**

Iodine-123 labeling was performed by  $\text{Cu}^{1+}$  assisted isotopic exchange on I-IDAB in reducing and acidic conditions, a method developed by Mertens et al. (4). Seven hundred forty MBq of  $^{123}\text{I}$  was added to a reaction mixture containing 1 mg IDAB, 1 mg  $\text{SnSO}_4$ , 5 mg gentisic acid, 11 mg citric acid and  $45.5 \mu\text{g}$   $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  in  $500 \mu\text{l}$  aqua proinjection. The solution was heated in an appropriate device at  $100^\circ\text{C}$  for 60 min. A mean labeling yield of 99.5% was obtained. After adjustment of the ionic strength, by adding a solution containing 10 mg gentisic acid, 22 mg citric acid, 17 mg  $\text{Na}_2\text{SO}_4$  and 10.5 mg trisodiumcitrate in  $2000 \mu\text{l}$  aqua proinjection, sterilization was performed by means of a  $0.22 \mu$  Millex GL filter. Iodine-123-IDAB was obtained with a radiopharmaceutical purity of >99% and a specific activity of 740 MBq/mg.

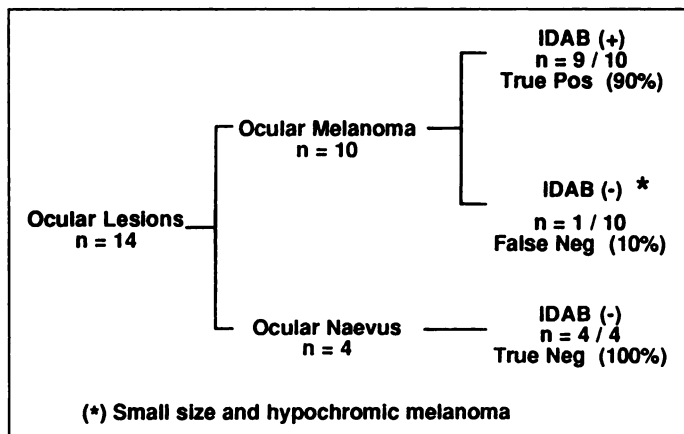


FIGURE 1. Results of the visual analysis of transverse SPECT slices.

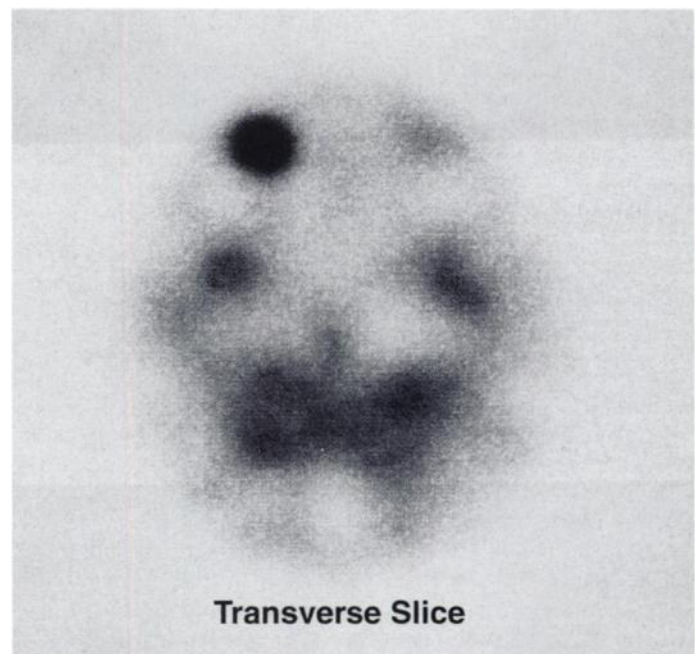
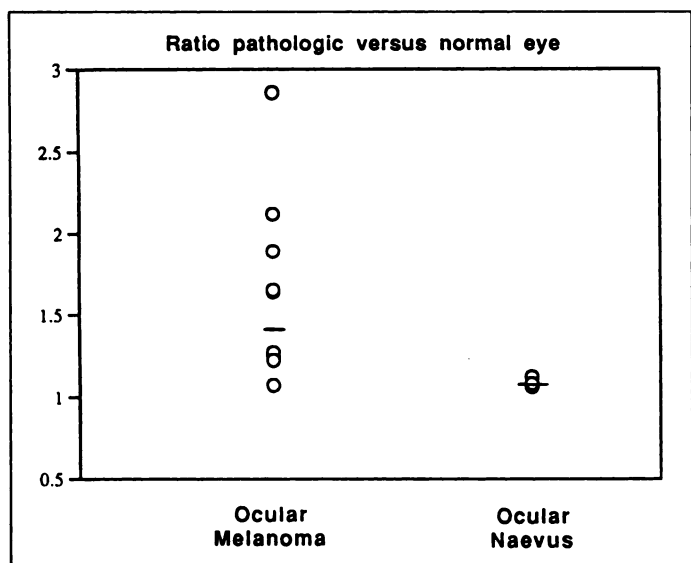


FIGURE 2. SPECT image (transverse slice at the level of the orbitae) obtained in a patient with ocular melanoma of the right eye. Intense and homogeneous tracer fixation is seen in the pathological eye. Pathological-to-normal eye ratio 2.8.



**FIGURE 3.** Pathological-to-normal eye activity ratio in patients with ocular melanoma and patients with ocular naevi.

### Scintigraphic Protocol

One hundred seventy MBq [ $^{123}\text{I}$ ]IDAB was injected intravenously after oral intake of Lugol's solution to reduce free iodine uptake by the thyroid.

Tomographic imaging, centered on the orbitae, was performed 4–5 hr after injection of the radiotracer. Acquisition was done using a three-head gamma camera equipped with medium-energy collimators. Photopeak was set at 159 keV with a 15% window. Ninety-six projections ( $3 \times 32$  projections,  $128 \times 128$  matrix, 60 sec/projection) were obtained over  $360^\circ$ . Reconstruction was done by filtered backprojection using a Butterworth filter adapted to the count density measured.

Additional planar whole-body anterior and posterior scintigrams were acquired using a large field of view camera equipped with medium-energy, parallel-hole collimators. Scan speed was set at 15 cm/min.

### Image Analysis

SPECT images were read on a high-definition computer monitor screen using a linear gray scale and no background subtraction. A semiquantitative analysis was performed by measuring the maximal counting rate within a manually drawn region of interest around the tumor on transverse slices and calculating the pathological to normal eye and the pathological eye to cerebellum ratios. The pathological-to-normal eye ratio was compared to the size of the tumor, when available.

Visual analysis of the planar whole-body [ $^{123}\text{I}$ ]IDAB scintigrams analysis was done from hard-copy radiograph films.

### RESULTS

Neither immediate nor delayed side effects were noted after the administration of the radiopharmaceutical.

#### Normal Biodistribution

At 4–5 hr postinjection of [ $^{123}\text{I}$ ]IDAB, a considerable tracer uptake in the brain was observed on SPECT images. In contrast with this brain activity, a faint tracer uptake in normal eye may be observed in some patients. The normal biodistribution pattern of a planar whole-body scintigraphy is characterized by blood-pool activity and a homogeneous uptake in the liver, brain and lungs. The kidneys and urinary bladder were visualized as routes of tracer excretion.

### Data Analysis

The results of the visual analysis of transverse SPECT slices is shown in Figure 1. Nine of 10 (sensitivity of 90%) patients with ocular melanoma were identified as abnormal. There was a definite tracer hyperfixation in the pathological eye on transverse slices (Fig. 2). One patient with a small and hypochromic lesion presented no tracer hyperfixation in the pathological eye. Follow-up SPECT studies performed in two patients 1 mo after enucleation were normal. All patients with ocular naevi showed symmetrical tracer uptake in the orbitae. On whole-body images ocular lesions could only be detected in some patients as a faint hot spot. No distant metastases were identified in any patient.

### Semiquantitative Analysis

In patients with ocular melanoma, the pathological-to-normal eye activity ratio averaged 1.46 (range 1.07–2.86). This ratio averaged 1.08 (range 1.06–1.12) in patients with ocular naevi (Fig. 3).

The pathological eye-to-cerebellum ratio averaged 1.03 (range 0.54–1.48) in patients with ocular melanoma. This ratio averaged 0.77 (range 0.74–0.81) in patients with ocular naevi. The normal eye-to-cerebellum ratio averaged 0.67 (range 0.44–0.81).

### DISCUSSION

Although the number of patients in our study was limited, the estimated figures on sensitivity (90%) and positive predictive value (100%) of [ $^{123}\text{I}$ ]IDAB SPECT images in regard to the assessment of ocular melanoma lesions is promising. The only false-negative case in our study was noted in a very small and hypopigmented lesion. This was not unexpected because of the small size of the tumor and the knowledge that the affinity of benzamides for amelanotic lesions is considerably lower (3). For small tumors, the measured activity is very likely to be underestimated because of the partial volume effect. The smallest size of the tumor that could be detected was  $3 \times 3 \times 3$  mm.

The results obtained in our study are in good agreement with data presented by Michelot et al. (3) who reported a sensitivity of 95% using [ $^{123}\text{I}$ ]IDAB scintigraphy in patients ( $n = 19$ ) with primary ocular melanoma. Our study, however, differs in some aspects from the one mentioned above. We performed both SPECT and planar images early after tracer injection instead of a delayed planar imaging at 20 hr after administration. At 4–5 hr postinjection ocular melanoma lesions in our experience could be detected as faint hotspots on planar images in some cases. For the majority of patients tracer accumulation in the brain represented an important factor of disturbance and obscures the detection of ocular lesions on planar images. Provided, however, that a SPECT camera is used, lesions could be clearly visualized as early as 4–5 hr postinjection. A second point of difference was the inclusion of patients with benign ocular lesions to determine the specificity of the [ $^{123}\text{I}$ ]IDAB scintigraphy. The fact that none of the ocular naevi was reported as false-positive supports the assumption that [ $^{123}\text{I}$ ]IDAB scintigraphy may be useful in the differential diagnosis in cases where ocular melanoma is suspected among other possibilities.

Theoretically [ $^{123}\text{I}$ ]IDAB whole-body scintigraphy offers the possibility of detecting metastatic spread. In this study, however, none of the patients presented metastases. This may be related to the number of patients selected for the study. In a study performed by Lorigan et al. (5), distant disease at the time of diagnosis of ocular melanoma was observed in only 3/110 patients. The liver was the most common site of tumor recurrence in these patients. Detection of lesions by means of [ $^{123}\text{I}$ ]IDAB scintigraphy is difficult in this organ due to the important hepatic activity. Attempts have been made to synthe-

size benzamides characterized by a lower lipophilicity and lower liver uptake than IDAB to enhance the tumor-to-background ratio. Experiments conducted by John et al. (6) using [ $^{131}\text{I}$ ]IPAB (2-piperidinylaminoethyl) 4-iodobenzamide in nude mice bearing human melanoma are promising. At present, however, planar images acquired early after administration of [ $^{123}\text{I}$ ]IDAB must be interpreted with extreme caution.

In comparison to several other studies on scintigraphic detection of ocular melanoma the results presented are superior. Immunoscintigraphy with a commercially available radiolabeled monoclonal antibody,  $^{99\text{m}}\text{Tc}$ -225.28S, has been evaluated by several groups. Loffler et al. (7) performed both planar and SPECT imaging in 28 patients clinically suspected of ocular melanoma. In 16 cases, the tumor was examined histologically. A positive immunoscintigraphy was observed in 56% of the histologically proven cases (and in 42% of the total group). In a study performed by Schaling et al. (8) 43 patients with ocular melanoma, six with a lesion suspected of being an ocular melanoma and seven with a benign lesion simulating an ocular melanoma were included. The detection rate of planar scintigraphy was 49%, and this was not increased by the use of SPECT techniques. Detectability by scintigraphy was correlated to the size of the lesions. They conclude that immunoscintigraphy with  $^{99\text{m}}\text{Tc}$ -225.28S is of limited value especially in small lesions (8). Czachonska et al. (9) studied 60 patients with suspicion of ocular melanoma. In all patients with positive results the diagnosis of ocular melanoma was confirmed; a sensitivity of 83% was reported. Lietzenmayer et al. (10) studied 15 patients with ocular melanoma lesions using  $^{18}\text{F}$ FDG-PET, 10 (67%) presented positive scan findings.

## CONCLUSION

Iodine-123-IDAB scintigraphy might play a role as a noninvasive tool for the imaging of ocular melanoma. In our study, none of the patients with ocular naevi demonstrated increased tracer accumulation. Therefore, [ $^{123}\text{I}$ ]IDAB scintigraphy may be used in the differential diagnosis in cases where ocular melanoma is suspected among other possibilities. Future studies in larger patient cohorts will have to be conducted to determine the role of [ $^{123}\text{I}$ ]IDAB scintigraphy in the diagnostic arsenal more precisely.

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# Thallium-201 SPECT in the Diagnosis of Head and Neck Cancer

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The accuracy of SPECT with  $^{201}\text{Tl}$ -chloride for the diagnosis of primary tumors, lymph node metastases and recurrences in head and neck cancer was evaluated for clinical applicability. **Methods:** SPECT images, obtained 60 min after administration of 150 MBq  $^{201}\text{Tl}$ -chloride, were compared with clinical, CT and/or MRI and histology results. In addition, whole-body images were obtained to detect distant metastases. **Results:** In 79 patients studied for primary tumors (principally larynx, hypopharynx, oropharynx, nasopharynx and oral cavity),  $^{201}\text{Tl}$  SPECT correctly identified 69 of 73 (95% versus 88% for CT/MRI) histologically confirmed malignancies including 63 squamous-cell carcinomas. The method localized four occult naso- and oropharynx carcinomas not seen on CT/MRI and was correctly negative in two patients without tumor and in three of four patients with no confirmed primary tumor in the head and neck. With respect to regional spread, only patients who had cervical lymph node dissection were evaluated, and the findings were recorded per side of the neck. Thallium-201 SPECT correctly identified metastases in 31 of 36 neck dissections with proven lymph node

involvement (86%), was correctly negative in nine and false-positive in one. Although the sensitivity of CT/MRI was clearly higher (97%), considerably more false-positive cases affected its accuracy (81% versus 87% for SPECT). In 30 patients investigated for recurrences,  $^{201}\text{Tl}$  SPECT correctly identified 27 of 29 microscopically confirmed tumor sites (93%) and was correctly negative in seven. Sensitivity of CT/MRI was lower (76%), and a greater number of false-positives (seven versus three for SPECT) further decreased its accuracy (64% versus 87% for SPECT). Distant metastases were detected in five patients. **Conclusion:** Thallium-201 SPECT appears to be an accurate method for the diagnosis of head and neck cancer. The method is particularly useful for detection of occult head and neck tumors and for assessing recurrences. It also may be of complementary value in the staging of primary tumors, in the differentiation of metastatic from reactive lymph nodes in the neck and, on the basis of whole-body scanning, for screening of distant metastases.

**Key Words:** head and neck cancer; SPECT; thallium-201-chloride  
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With more than 500,000 new cases projected annually worldwide, head and neck cancer constitutes approximately 5% of all

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