

ORIGINAL ARTICLE

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## Diagnosis and follow up of primary ocular melanoma by radioimmunoscintigraphy

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### Summary

**Purpose:** To determine the usefulness of immunoscintigraphy with Tc-99m labeled anti-melanoma antibodies in the diagnosis of primary ocular melanoma. Furthermore, to try to determine whether the treatment of ocular melanoma by contact radiotherapy had an influence on the immunoscintigraphic disease detection.

**Patients and methods:** Immunoscintigraphy was performed on 17 patients: 9 patients with newly diagnosed choroidal melanoma (group A), 6 patients with choroidal melanoma treated by ruthenium contact radiotherapy (group B) and 2 patients with melanoma conjunctivae (group C). F(ab')<sub>2</sub> fragments of 225.28S monoclonal antibody directed against a high molecular weight melanoma-associated antigen (HMW-MAA) were used. Planar scintigraphy was done 4 hours after intravenous (i.v.) injection of 300-445 MBq of labeled antibodies, in anterior Waters projection, with 95 degrees of cranial tilt of the gamma-camera head. 500,000 counts static images were acquired in 256×256 resolution matrix.

**Results:** All group A patients showed positive im-

munoscintigraphy. The maximum diameter of these tumors, measured by ultrasound, was between 9 and 18 mm, with maximal prominence between 5 and 10.5 mm. Both patients of group C showed negative immunoscintigraphy, due to the small dimensions of the tumors (less than 2.7 mm). In all 6 patients of group B immunoscintigraphy was negative although the dimensions of the tumors were sufficient enough to be visualized by immunoscintigraphy (diameter between 8.3 and 17 mm and prominence between 5 and 10.3 mm).

**Conclusion:** According to our preliminary results, we concluded that immunoscintigraphy was useful diagnostic modality in the detection of small intraocular tumors. The negative immunoscintigraphy in patients with tumors treated by contact radiotherapy could be explained by the biological regression of the tumor that precedes regression of its volume. This finding indicates that immunoscintigraphy could be useful in the follow-up of conservatively or surgically treated patients with choroidal melanoma.

**Key words:** anti-melanoma antibody, eye tumor, immunoscintigraphy, malignant melanoma, ruthenium, tumor imaging

### Introduction

Choroidal melanoma is the most common primary eye tumor. Successful treatment and good prog-

nosis of the disease depend on early disease diagnosis. Besides conventional diagnostic modalities like ultrasonography and fluorescein angiography, for several years antibody-guided scintigraphy has been used as an additional tool in the diagnosis of ocular melanoma [1]. In the majority of the cases, immunoscintigraphy of choroidal melanoma is performed with technetium-99m-labeled F(ab')<sub>2</sub> fragments of 225.28S monoclonal antibody. This antibody recognizes a human high molecular weight melanoma-associated antigen with restricted tissue distribution, which is expressed in about 90% of melanoma cells [2]. The same antibody has been widely used for the detection of metastases of cutaneous melanoma with high antigenic expression [3].

With respect to these considerations, our study

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aimed at evaluating the usefulness of immunoscintigraphy with anti-melanoma antibodies in the diagnosis of primary ocular melanoma. Furthermore, we tried to determine whether the treatment of ocular melanoma by contact radiotherapy had an influence on the immunoscintigraphic disease detection.

### Patients and methods

The investigation was carried out on 17 patients with pigmented ocular melanoma. Twelve patients were males and 5 females with a median age of 53 years (range 23-82 years). The patients were divided into 3 groups. Group A consisted of 9 patients with newly diagnosed choroidal melanoma based on clinical findings, ultrasonography and fluorescein angiography. Seven of these patients underwent eye enucleation and melanoma tissue samples were available for histology, whereas 2 patients were treated conservatively with radioactive ruthenium contact radiotherapy. Group B consisted of 6 patients with choroidal melanoma, who were treated with radioactive ruthenium contact radiotherapy. Group C consisted of 2 patients with melanoma conjunctivae.

Immunoscintigraphy was done with F(ab')<sub>2</sub> fragments of 225.28S monoclonal antibody directed against the high molecular weight melanoma-associated antigen HMW-MAA (Technemab-K-1, Fa. Sorin/Solco). The antibody labeling was performed according to the manufacturer's instructions, using 300-445 MBq of radionuclide technetium-99m. Standard planar scintigraphy was done 4 hours after the i.v. injection of the radioactive solution. Gamma camera (Siemens Orbiter 7500) was equipped with low-energy high resolute parallel-hole collimator. Computer-assisted static scintigraphy of the head was done in anterior Waters projection, with 15 degrees cranial tilt of the gamma camera head. Zoom factor of 1.5 was used and 500,000 counts static images were stored in 256×256 resolution matrix.

### Results

All patients with newly diagnosed uveal melanoma (group A) showed positive immunoscintigraphy (Table 1). The measurement of tumor dimensions that was made ultrasonographically or after enucleation of the eye indicated that strongly positive immunoscintigraphy was related to large tumors with maximal diameter between 12 and 18.3 mm and maximal prominence between 9 and 11.2 mm. Nevertheless, smaller tumors with maximal diameter between 9 and 11.3

**Table 1.** Tumor dimensions and results of immunoscintigraphy in patients with newly diagnosed choroidal melanoma (group A)

Patient	Sex	Age (yrs)	Tumor dimensions		IS findings
			Max. diameter (mm)	Max. prominence (mm)	
1	F	56	14.0	9.9	++
2	M	64	18.1	9.3	++
3	M	82	18.3	11.2	++
4	M	37	9.0	5.5	+
5	F	61	9.9	6.3	+
6	M	41	15.2	9.0	++
7	M	78	10.1	5.2	+
8	M	53	11.3	7.4	+
9	M	67	9.7	5.6	+

IS: immunoscintigraphy, F: female, M: male, +: positive, ++: strongly positive

mm and maximal prominence between 5.2 and 7.4 mm were also successfully visualized.

Histopathology of tumors with strongly positive immunoscintigraphy showed numerous pathological mitoses and intense pigmentation.

All 6 patients of group B underwent contact radiotherapy with radioactive ruthenium 6 weeks to 6 months before immunoscintigraphy. Clinical examination showed slight reduction of tumor dimensions although they remained rather large, with maximum diameter between 8.3 and 17 mm and maximal prominence between 5 and 10.3 mm. Immunoscintigraphy was clearly negative in all patients of this group (Table 2). The maximal dimensions of tumors in groups

**Table 2.** Tumor dimensions and results of immunoscintigraphy in patients with choroidal melanoma treated by contact radiotherapy (group B)

Patient	Sex	Age (yrs)	Tumor dimensions		IS findings
			Max. diameter (mm)	Max. prominence (mm)	
1	M	23	8.9	5.0	neg
2	M	38	17.0	9.3	neg
3	M	41	8.3	5.7	neg
4	F	27	15.9	8.9	neg
5	M	34	16.2	10.3	neg
6	M	36	16.9	10.0	neg

For abbreviations see footnote of Table 1

**Table 3.** Tumor dimensions and results of immunoscintigraphy in patients with melanoma conjunctivae (group C)

<i>Patient</i>	<i>Sex</i>	<i>Age (yrs)</i>	<i>Max. tumor diameter (mm)</i>	<i>IS findings</i>
1	F	55	2.6	neg
2	F	59	2.4	neg

For abbreviations see footnote of Table 1

A and B were compared; no statistically significant difference was revealed ( $p > 0.05$ ).

Immunoscintigraphy in both patients of group C was negative (Table 3). The dimensions of these tumors were small, with maximal diameter of 2.6 and 2.4 mm, respectively.

## Discussion

Most often, the diagnosis of intraocular melanoma can be accurately established by clinical examination, ultrasonography and fluorescein angiography. Occasionally, in diagnostically delicate cases, there is a need for additional diagnostic methods. It has been proved that immunoscintigraphy can contribute to differential diagnosis of eye melanoma against uveal hemangioma and melanocytoma, as well as intraocular metastases of other tumors [4]. Moreover, as eye is a dual organ, immunoscintigraphy offers the possibility of using the findings from the healthy eye as an ideal control [5].

Several authors have evaluated the sensitivity and specificity of immunoscintigraphy in the diagnosis of eye tumors. Most of them report sensitivity between 76.5 and 78.5%. The specificity is higher and ranges between 94 and 100% [6-9]. Although it is obvious that larger tumors are easier to detect, smaller tumors with diameter of only 5×3 mm could also be detected, despite the limited spatial resolution of the gamma-camera [10,11]. Our results coincide with these observations. In melanomas not treated by contact radiotherapy, false-negative results were obtained only in 2 cases of small melanoma conjunctivae with base diameter of 2.6 mm and 2.4 mm. The positive findings in all group A patients was due to the large dimensions of the tumors; larger tumor dimensions resulted in more positive findings.

In case of small-sized tumors, and given their localization within the eye, it may be useful to apply single-photon emission computed tomography (SPECT) in order to discriminate between lesions situated in the

nasal quadrant from an adjacent nasopharyngeal activity [12].

A special problem in the follow-up of patients with uveal melanoma is how to monitor the effects of radiotherapy. By contact radiotherapy with radioactive ruthenium, gradual regression of melanoma is expected after longer period of time. This regression can be monitored angiographically and ultrasonographically, but most of the signs are insufficiently specific and often unreliable. Moreover, the volume reduction does not parallel biological regression and the ultrasonographic findings can not be considered as sufficiently accurate. Interpretation of fluorescein angiography findings is difficult, due to non-transparency of eye media, presence of blood and pigment. In theory, immunoscintigraphy offers the possibility to detect and monitor the biological activity of the tumor, because antigen-antibody reaction is absent in case of significant reduction of tumor viability [13, 14]. Our results comply with this assumption, because in all patients of group B immunoscintigraphy was negative although tumor dimensions allowed their visualization. This finding may indicate biological regression of the tumor, while the volume reduction had not occurred yet.

This observation should in any case be verified or dismissed by the results from a series of patients where immunoscintigraphy could be applied before and after radiotherapy. Furthermore, it would be necessary to apply quantitative analysis of scintigraphic images for better comparison of the findings [15,16].

Owing to high antigenic expression of metastases of melanoma, immunoscintigraphy is potentially useful in detecting tumor relapse or to search for tumor metastases in other organs and tissues.

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