Int J Clin Oncol (2004) 9:74–78
DOI 10.1007/s10147-003-0380-2

REVIEW ARTICLE

Hiroshi Goto

Clinical efficacy of ^{123}I-IMP SPECT for the diagnosis of malignant uveal melanoma

Received: December 22, 2003

Abstract The diagnostic significance of several radiopharmaceuticals for malignant uveal melanoma has been discussed in the past decade. In our study, 99 patients with clinically suspected malignant uveal melanoma were considered; 36 had been treated and 63 were untreated. Single-photon emission computed tomography (SPECT) images were obtained after the intravenous injection of N-isopropyl-*p*-[^{123}I]iodoamphetamine (^{123}I-IMP). In the 63 patients without prior treatment, 36 were negative on ^{123}I-IMP SPECT, and all 36 except for 1, were histologically or clinically confirmed as having other, benign, entities including choroidal nevus, choroidal hemangioma, metastatic choroidal tumor, and other intraocular conditions. Twenty-seven of the 63 patients showed significantly high accumulation of ^{123}I-IMP in the late phase in the area corresponding to the intraocular lesion; all except 2 of these 27 patients were histopathologically or clinically confirmed as having malignant uveal melanoma. One of these 2 ^{123}I-IMP-positive patients was histologically diagnosed with adenocarcinoma arising from the pigment epithelium of the ciliary body. The 36 patients who had undergone eye-preserving treatments such as brachytherapy showed various results on ^{123}I-IMP SPECT. We concluded that ^{123}I-IMP SPECT is useful for the diagnosis of malignant uveal melanoma, especially in patients with atypical clinical manifestations for which conventional diagnostic techniques are inadequate to arrive at a definitive diagnosis.

Key words Malignant uveal melanoma · ^{123}I-IMP SPECT · Diagnosis

H. Goto (✉)
Department of Ophthalmology, Tokyo Medical University, 6-7-1 Nishi Shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan
Tel. +81-3-3342-6111; Fax +81-3-3346-9170
e-mail: goto1115@tokyo-med.ac.jp

Introduction

Uveal melanoma, which arises in the iris, the ciliary body, or the choroid, is the most common primary intraocular malignant tumor. According to a recent report, the mean age-adjusted incidence of uveal melanoma in the United States was 4.3 per million, and most cases (97.8%) occurred in the white population.[1] In Japan, only one report with regard to the incidence of uveal melanoma has been published during the past 30 years, and it indicated that the estimated annual incidence of uveal melanoma in Japan was 0.25 per million.[2]

Despite various new concepts and methods of treatment such as radiotherapy, improvement of survival rates in patients with uveal melanoma has been limited.[3] A recent investigation of very long-term prognosis reported that uveal melanoma-related mortality was 31% by 5 years, 45% by 15 years, 49% by 25 years, and 52% by 35 years, according to cumulative incidence analysis.[4]

Dilemma in the clinical diagnosis of uveal melanoma

A diagnosis of uveal melanoma is made by characteristic ocular manifestations obtained by slit-lamp biomicroscopy, binocular fundus examination, ultrasonography, and magnetic resonance imaging (MRI). In general, the clinical diagnosis of uveal melanoma is not difficult when ocular findings and results of radiological examinations are typical. However, a clinical diagnosis of uveal melanoma may be difficult in some cases, in which the ophthalmologist may be confused by atypical ocular manifestations and/or ocular complications such as cataract, retinal detachment, and vitreous hemorrhage. Although the accuracy of the clinical diagnosis of uveal melanoma has improved, misdiagnosis still occurs today.[5] Especially, choroidal melanoma early in its natural course is difficult to distinguish from choroidal nevus.[6]

Histopathological examination without enucleating the eyeball is the ideal approach to obtain an accurate diagnosis

of uveal melanoma. Fine-needle biopsy[7,8] or excisional biopsy[9,10] following certain protocols yields a histopathological diagnosis. However, these diagnostic or therapeutic techniques are indicated in only a limited number of patients with uveal melanoma.

Scintigraphy using radiopharmaceuticals for the diagnosis of uveal melanoma

Several radiopharmaceuticals, including [^{123}I] N-(2-diethylaminoethyl)-4-iodobenzamide (^{123}I-BZA),[11] [^{123}I] N-(2-diethylaminoethyl) 4-iodobenzamide (^{123}I-IDAB),[12] 4-borono-2-[^{18}F] fluoro-D,L-phenylalanine (^{18}F-FBPA),[13] and N-isopropyl-*p*-[^{123}I]iodoamphetamine (^{123}I-IMP)[14] have been reported to be useful for the diagnosis of cutaneous, ocular, and metastatic melanomas.

^{123}I-IMP and malignant melanoma

The diagnostic efficacy of ^{123}I-IMP scintigraphy for uveal melanoma was suggested over 20 years ago.[14] ^{123}I-IMP was primarily developed as a radiopharmaceutical for blood perfusion imaging[14] and it has been utilized clinically for the diagnosis and evaluation of cerebral infarction and other vascular disorders.

Since Holman et al.[15] reported a positive correlation between increased ^{123}I-IMP accumulation and melanin production, ^{123}I-IMP has been utilized clinically not only to evaluate blood perfusion but also to detect malignant melanoma. Cohen et al.[16] have shown that the in vitro ^{123}I-IMP uptake by amelanotic melanoma cells is less than that by melanotic melanoma cells, and this is compatible with the clinical data obtained from patients with skin melanoma. Although many clinical trials of ^{123}I-IMP have been conducted in the field of melanoma of the skin and other organs, few case reports have been published on its use for the diagnosis of uveal melanoma.[17–19]

We have reported the usefulness of single-photon emission computed tomography (SPECT), using ^{123}I-IMP, for the diagnosis of uveal melanomas, which were mostly pigmented melanomas in the Japanese population.[20]

Current results of ^{123}I-IMP SPECT for the diagnosis of uveal melanoma

To date, ^{123}I-IMP SPECT images have been obtained from 99 patients with clinically suspected uveal melanoma at Tokyo Medical University Hospital. Orbital SPECT images were analyzed 20 min (early phase) and 24 h (late phase) after the intravenous injection of 111 MBq of ^{123}I-IMP. Our previous study demonstrated that late-phase evaluation was critical to detect uveal melanoma.[20]

Thirty-six of the 99 patients had medical histories of eye-preserving treatments, including brachytherapy, extrabeam radiotherapy, transpupillary thermotherapy (TTT), and local resection of the tumor. The remaining 63 patients, who had had no prior treatment, were examined initially for the clinical diagnosis of uveal melanoma or for ruling out other intraocular disorders.

Table 1. ^{123}I-IMP SPECT images in patients with intraocular tumors and other intraocular disorders, except for uveal melanoma

Diagnosis	Number of patients
Iris nevus or iris melanocytoma	4
Ciliary-body tumor	3
Choroidal nevus	5
Choroidal hemangioma	3
Melanocytoma of the optic disc	6
Metastatic choroidal tumor	3
Age-related macular degeneration	2
Others	9

^{123}I-IMP SPECT, N-isopropyl-*p*-[^{123}I]iodoamphetamine single-photon emission computed tomography

Of the 63 patients without prior treatment, 36 were negative for ^{123}I-IMP SPECT images in both early and late phases, and all 36 patients, except for 1, were histologically or clinically confirmed as having other clinical entities, including choroidal nevus, choroidal hemangioma, melanocytoma of the optic disc, metastatic choroidal tumor, and other intraocular disorders (Table 1). The remaining 27 patients showed significantly high accumulation of ^{123}I-IMP in the late phase in an area corresponding to the intraocular lesion, and all except 2 of these patients were histopathologically (16 cases) or clinically (9 cases) confirmed as having uveal melanoma. All 25 patients with uveal melanoma detected by ^{123}I-IMP SPECT had a pigmented intraocular tumor. The smallest tumor among these 25 patients was 3 mm × 4 mm.

A diagnosis of uveal melanoma was ruled out in two patients who showed positive results on ^{123}I-IMP SPECT images. One of these patients was histopathologically diagnosed with adenocarcinoma arising from the pigment epithelium of the ciliary body. This case suggests that an intraocular tumor producing abnormal melanin pigment could show uptake of ^{123}I-IMP. The second of these two ^{123}I-IMP SPECT-positive patients was clinically diagnosed as having iris melanocytoma, which has remained constant in size for several years. It remains to be seen whether this tumor will maintain its size and pigmentation in the future. In fact, the possibility of transformation to malignant melanoma has been suggested in patients with melanocytoma arising from the iris or optic disc.[21,22] None of the patients with melanocytoma of the optic disc showed a positive result on ^{123}I-IMP SPECT images in our series.

The 36 patients who had a history of eye-preserving treatments, including brachytherapy, extrabeam radiotherapy, TTT, and local resection showed various findings on ^{123}I-IMP SPECT images. No evidence of recurrence was detected in 25 patients with a negative result on ^{123}I-IMP SPECT. Eleven patients were positive for ^{123}I-IMP SPECT, and 4 of them underwent eyeball enucleation subsequently. All 4 patients revealed the recurrence of uveal melanoma histopathologically. Two patients were re-treated with

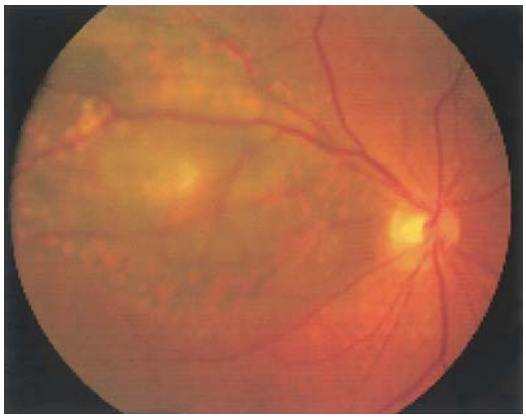

Fig. 1. Ocular fundus photograph of a 74-year-old woman. A slightly elevated intraocular lesion with orange pigment is observed in the right eye

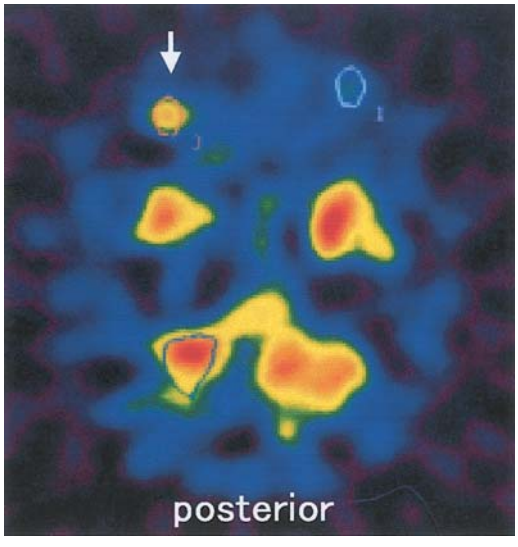

Fig. 2. N-isopropyl-*p*-[^{123}I]iodoamphetamine (^{123}I-IMP) single-photon emission computed tomography (SPECT) image in late phase. Note the moderate accumulation of ^{123}I-IMP, corresponding to the right eye (*arrow*)

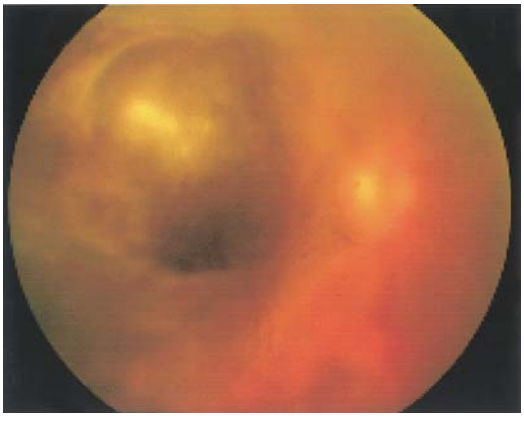

Fig. 3. Ocular fundus photograph taken 7 months after the last laser treatment. Enlargement of the tumor, with mushroom-shaped proliferation is observed

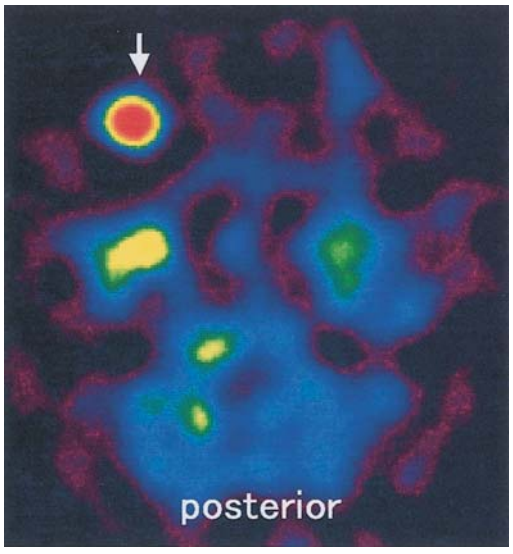

Fig. 4. ^{123}I-IMP SPECT image performed 7 months after the last laser treatment. Note the marked accumulation of ^{123}I-IMP (*arrow*) compared to that in Fig. 2

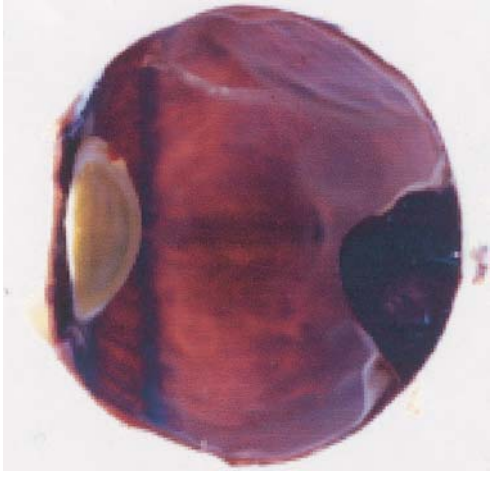

Fig. 5. A brownish intraocular tumor is observed at the posterior pole in the enucleated eyeball

brachytherapy or TTT, and the other 5 patients have been followed with careful observation.

Representative case reports

Case 1

Figure 1 shows an ocular fundus photograph of case 1, a 74-year-old woman who had been treated and managed for a diagnosis of age-related macular degeneration for several months. ^{123}I-IMP SPECT, performed to rule out uveal melanoma, showed abnormal uptake in the right eye (Fig. 2). Although she underwent repeat laser treatment, the elevated intraocular lesion became enlarged (Fig. 3), and ^{123}I-

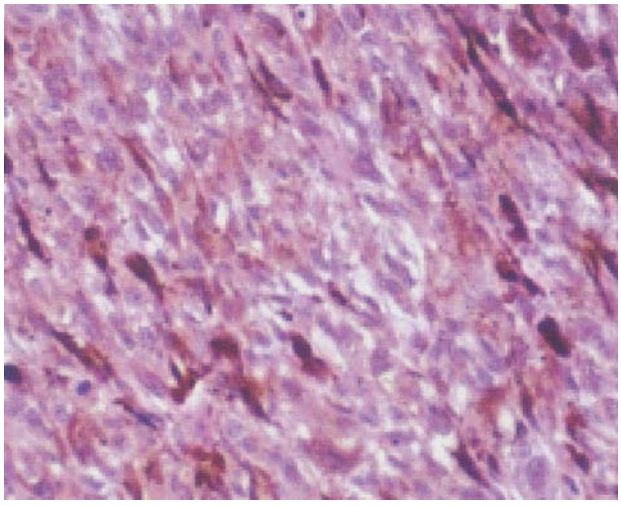

Fig. 6. Histopathological diagnosis was compatible with choroidal melanoma, with the tumor composed mainly of spindle cells. Original magnification, ×132

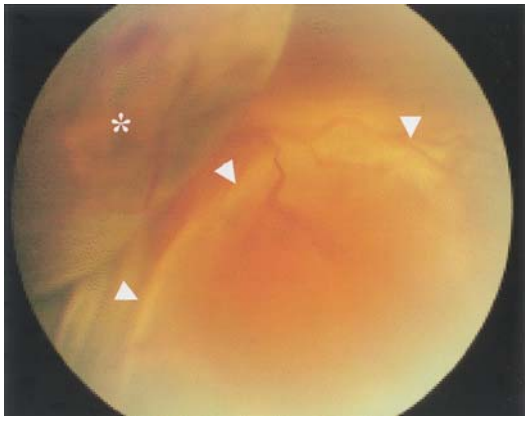

Fig. 7. Ocular fundus photograph of a 57-year-old man. Intraocular tumor (*asterisk*) and bullous retinal detachment (*arrowheads*) are noted. Metastatic choroidal tumor was suspected, due to a medical history of lung cancer

IMP SPECT performed 7 months after the last laser treatment revealed marked accumulation of ^{123}I-IMP (Fig. 4). Eventually, she underwent eyeball enucleation. Macroscopic and histopathological examination of the enucleated eyeball was compatible with choroidal melanoma (Fig. 5, 6).

Case 2

Figure 7 shows an ocular fundus photograph of case 2, a 57-year-old man who was difficult to diagnose clinically due to the presence of bullous retinal detachment masking an uveal tumor. Initially, metastatic uveal tumor was suspected because of his medical history of lung cancer. However, the ^{123}I-IMP SPECT image was positive (Fig. 8) and the histopathological diagnosis obtained after enucleation of the eyeball was compatible with choroidal melanoma, with no evidence of metastatic lung cancer.

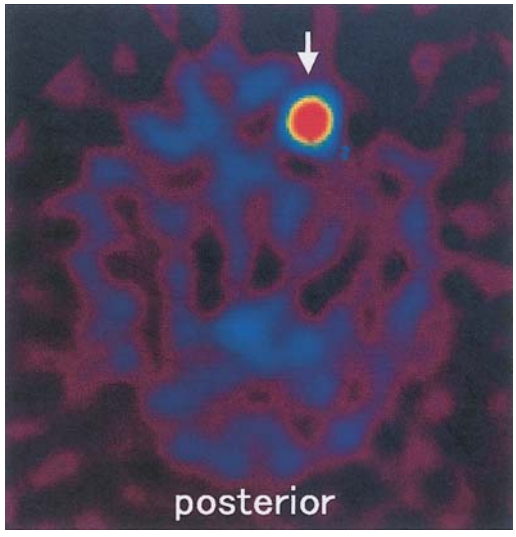

Fig. 8. ^{123}I-IMP SPECT image is positive (*arrow*) in late phase. The histopathological diagnosis of the enucleated eyeball was choroidal melanoma

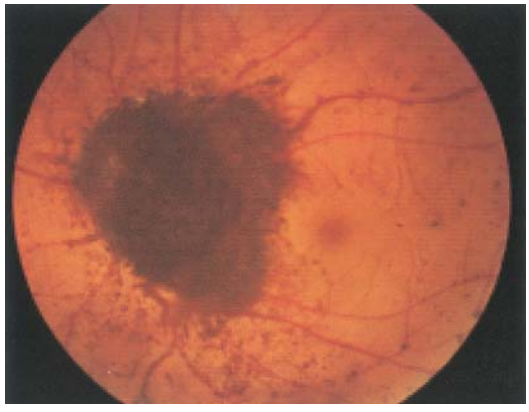

Fig. 9. Ocular fundus photograph, showing melanocytoma of the optic disc, with marked dispersion of melanin pigment into the vitreous. The ^{123}I-IMP SPECT image was negative

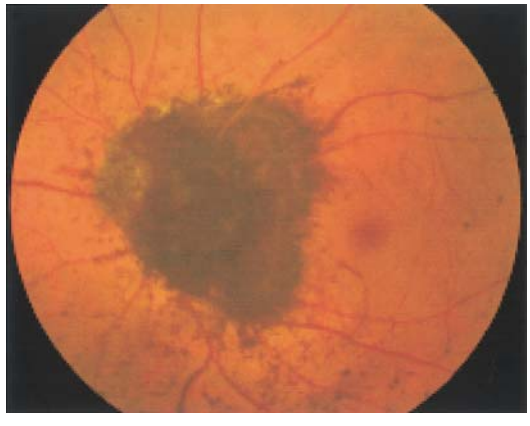

Fig. 10. Ocular fundus photograph taken 5 years after the initial visit. No significant changes were observed at this time

Case 3

Figure 9 shows an ocular fundus photograph of case 3, a 62-year-old man with melanocytoma of the optic disc. Transformation to malignant melanoma was initially considered because of the marked melanin pigmentation around the optic disc, with vitreous dispersion. However, the ^{123}I-IMP SPECT image was negative, and no intraocular abnormalities have been observed for 5 years since the initial examination (Fig. 10).

Conclusions

^{123}I-IMP SPECT is an effective procedure for the diagnosis of uveal melanoma, especially in patients with atypical clinical manifestations for which conventional diagnostic techniques are inadequate to arrive at a definitive diagnosis. The high rate of detection by the ^{123}I-IMP images in patients with uveal melanoma, compared to the rate of detection in skin melanoma described previously,[16] may be explained by the abundant vascularization in the uveal tissue. In addition, the high resolution obtained with SPECT images may contribute to the determination of localized tumors. The ^{123}I-IMP SPECT technique will be applied more often in the future to evaluate the therapeutic effects of eye-preserving treatments.

Acknowledgments The author thanks Dr. Akihiro Kaneko and Dr. Shigenobu Suzuki, National Cancer Institute, Tokyo, Japan for referring patients with malignant uveal melanoma.

References

1. Singh AD, Topham A (2003) Incidence of uveal melanoma in the United States: 1973–1997. Ophthalmology 110:956–961
2. Kaneko A (1979) Incidence of malignant melanoma of the eye in Japan. Jpn J Clin Ophthalmol 33:941–947
3. Singh AD, Topham A (2003) Survival rates with uveal melanoma in the United States: 1973–1997. Ophthalmology 110:962–965
4. Kujala E, Makitie T, Kivela T (2003) Very long-term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis *Sci* 44:4651–4659
5. Margo CE (1997) The accuracy of diagnosis of posterior uveal melanoma. Arch Ophthalmol 115:432–433
6. Shields CL, Shields JA (2002) Clinical features of small choroidal melanoma. Curr Opin Ophthalmol 13:135–141
7. Shields JA, Shields CL, Ehya H, et al. (1993) Fine-needle aspiration biopsy of suspected intraocular tumors. Ophthalmology 100:1677–1684
8. Folberg R, Augsburger JJ, Gamel JW, et al. (1985) Fine-needle aspirates of uveal melanomas and prognosis. Am J Ophthalmol 100:654–657
9. Peyman GA, Juarez CP, Diamond JG, et al. (1984) Ten years' experience with eye wall resection for uveal malignant melanoma. Ophthalmology 91:1720–1725
10. Damato B, Foulds WS (1996) Indications for trans-scleral local resection of uveal melanoma. Br J Ophthalmol 80:1029–1030
11. Bacin F, Michelot J, Bonafous J, et al. (1998) Clinical study of [^{123}I] N-(2-diethylaminoethyl)-4-iodobenzamide in the diagnosis of primary and metastatic ocular melanoma. Acta Ophthalmol Scand 76:56–61
12. Lodewijks H, Everaert H, Hennekes R, et al. (1996) I-123-IDAB: a new tracer for scintigraphic visualisation of malignant melanoma. Bull Soc Belge Ophtalmol 263:109–113
13. Ishiwata K, Ido T, Kawamura M, et al. (1991) 4-Borono-2-[^{18}F] fluoro-D, L-phenylalanine as a target compound for boron neutron capture therapy: tumor imaging potential with positron emission tomography. Int J Rad Appl Instrum [B] 18:745–751
14. Winchell HS, Baldwin RM, Lin TH (1980) Development of I-123-labeled amines for brain studies: localization of I-123 iodophenylalkyl amines in rat brain. J Nucl Med 21:940–946
15. Holman BL, Hill TC, Polak JF, et al. (1984) Cerebral perfusion imaging with iodine 123-labeled amines. Arch Neurol 41:1060–1065
16. Cohen MB, Saxton RE, Lake RR, et al. (1988) Detection of malignant melanoma with iodine-123 iodoamphetamine. J Nucl Med 29:1200–1206
17. Wada M, Ichiya Y, Katsuragi M, et al. (1985) Scintigraphic visualization of human malignant melanoma with N-isopropyl-p-[I-123]iodoamphetamine. Clin Nucl Med 10:415–417
18. Ono S, Fukunaga M, Otsuka N, et al. (1988) Visualization of ocular melanoma with N-isopropyl p-[^{123}I]-iodoamphetamine. J Nucl Med 29:1448–1450
19. Watanabe N, Seto H, Yokoyama K, et al. (1996) Scintigraphic study of malignant melanoma with ^{123}I-iodoamphetamine. Nucl Med Commun 17:153–159
20. Goto H, Usui M, Ishi I (2001) Efficacy of N-isopropyl-*p*[^{123}I]-iodoamphet-amine single photon emission computed tomography for the diagnosis of uveal malignant melanoma. Am J Ophthalmol 108:937–939
21. Cialdini AP, Sahel JA, Jalkh AE, et al. (1989) Malignant transformation of an iris melanocytoma. A case report. Graefes Arch Clin Exp Ophthalmol 227:348–354
22. Meyer D, Ge J, Blinder KJ, et al. (1999) Malignant transformation of an optic disk melanocytoma. Am J Ophthalmol 127:710–714