Iris and Anterior Chamber Angle Neovascularization after Iodine 125 Brachytherapy for Uveal Melanoma

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Purpose: Iris neovascularization (INV) and anterior chamber angle neovascularization after radiotherapy for uveal melanoma may lead to neovascular glaucoma and enucleation. However, neovascularization of the anterior ocular segment may respond favorably to treatment with panretinal photocoagulation. The purpose of this study was to evaluate the frequency, interval to development, and predisposing factors of anterior ocular segment neovascularization following iodine 125 (I^{125}) brachytherapy for uveal melanoma.

Design: Retrospective, interventional, consecutive case series.

Participants: Sixty-five patients (65 eyes), consecutively treated with I^{125} brachytherapy for uveal melanoma from 1995 through 2000 and followed up after radiation therapy for 24 months or more.

Methods: Clinical findings and ultrasonography characteristics as well as treatment parameters were analyzed.

Main Outcome Measures: The frequency of INV was determined and the interval to development of INV as well as the predisposing factors were analyzed statistically.

Results: In 15 of 65 eyes (23%), INV was detected after I^{125} brachytherapy at a mean ± standard deviation of 26.66±11.63 months (median, 24 months; range, 9–48 months). Risk factors displaying the stronger correlation with INV were greater maximal tumor height ($P<0.01$), greater tumor vascularity ($P<0.01$), and disinsertion of horizontal rectus muscles ($P = 0.01$).

Conclusions: After I^{125} brachytherapy for choroidal melanoma, INV developed in 23% of eyes and was correlated with larger tumor size, greater tumor vascularity, and disinsertion of a horizontal rectus muscle. *Ophthalmology 2005;112:505–510 © 2005 by the American Academy of Ophthalmology.*

Radiotherapy, in the form of external beam (teletherapy) or radioactive plaque (brachytherapy), has proven effective for the local control of uveal melanoma.[1,2] However, radiotherapy may be associated with ocular complications, such as neovascularization of the retina, iris, and anterior chamber angle.[1,3,4] The development of the latter is often devastating, because it can lead to neovascular glaucoma (NVG), a common reason for performing enucleation at a later stage.[3,4] The prevention or early detection of the development of anterior ocular segment neovascularization, including iris neovascularization (INV) and anterior chamber angle neovascularization (ANV), is very important because it may be more effectively treated if recognized early.[5] Previous studies have identified risk factors associated with the development of INV after teletherapy for the treatment of uveal melanoma.[3,4] In the case of brachytherapy, INV is well documented, although probably less common compared with teletherapy.[1,6] The present study examined risk factors associated with the development of anterior ocular segment neovascularization after iodine 125 (I^{125}) brachytherapy for the treatment of uveal melanoma. Results could prove useful for the early detection of INV and ANV in patients treated with I^{125} brachytherapy for uveal melanoma.

Patients and Methods

The archived medical charts of patients with uveal melanoma treated consecutively with I^{125} brachytherapy at the Ocular Oncology Center of Jules Stein Eye Institute during a 5-year period (1995–2000) were examined. Only patients with a minimum follow-up period of 24 months were included to allow for adequate postoperative observation period, as described elsewhere.[4] Furthermore, patients with recurrent tumors (having previously undergone other forms of treatment, including teletherapy) were excluded to rule out changes not directly related to brachytherapy. The protocol was approved by the Institutional Review Board in conformity with the tenets of the Declaration of Helsinki.

On presentation, no patient was diagnosed with INV or ANV. Furthermore, no patient was using any topical medications. In all cases, the diagnosis of uveal melanoma was based on history, fundus photography, indirect ophthalmoscopy, transillumination,

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Table 1. Pretreatment Clinical and Ultrasound Examination Parameters Recorded and Respective Scoring Method

Parameter	Method of Evaluation
Best-corrected visual acuity	Snellen acuity converted to logMAR values
Intraocular pressure	Recorded in millimeters of mercury
Tumor laterality	Right eye scored as 1, left eye scored as 2
Tumor location	Macula (within the vascular arcades) scored as 1, midperiphery (vascular arcades to equator) scored as 2, anterior choroid (equator to ora serrata) scored as 3, ciliary body scored as 4, and iris scored as 5
Tumor infiltration of the optic nerve or anterior chamber angle	Absence scored as 0, presence scored as 1 for the respective finding
Lipofuscin, drusen, pigment, hemorrhage (intraretinal, subretinal or intravitreal), local or remote subretinal fluid	Absence scored as 0, presence scored as 1 for the respective finding
Maximal tumor height (MTH) and largest tumor diameter (LTD)	Recorded in millimeters, based on A-scan (MTH) and B-scan (LTD) ultrasound examination
Tumor reflectivity	Recorded as low (0), intermediate (1), or high (2), based on the height of the internal spikes of sound reflectivity (A-scan)
Tumor vascularity	Recorded on a scale of 1–4, based on the speed of spike flickering within the tumor, in comparison with the respective flickering behind the tumor (A-scan)

logMAR = logarithm of the minimum angle of resolution; LTD = largest tumor diameter; MTH = maximal tumor height.

ultrasound evaluation (A-scan and B-scan ultrasonography and high-frequency ultrasound biomicroscopy in the case of anteriorly located tumors), fluorescein angiography, and occasionally indocyanine green angiography. After an informed consent to undergo brachytherapy, the tumor was measured, based on ophthalmoscopy, ultrasonography, and a standard Collaborative Ocular Melanoma Study chart with intraocular cord diameters. Subsequently, a custom I^{125} plaque was constructed. Size and dosimetry characteristics were based on standard Collaborative Ocular Melanoma Study guidelines[7–9] and included an apex dose of 85 Gy and a safety margin of 3 mm beyond the visible tumor. Subsequently, I^{125} brachytherapy was administered. The technique included conjunctival peritomy, retraction of Tenon's capsule, identification and marking of the tumor with transillumination, and disinsertion of an extraocular muscle where appropriate. In the latter case, the insertion of the muscle was anchored to the sclera for identification and repositioning on removal of the plaque. A dummy plaque then was placed, and subsequently, the radioactive plaque was sutured in place. The correct position in relation to the tumor was examined with indirect ophthalmoscopy and transillumination as well as with intraoperative ultrasound evaluation (B scan). Conjunctiva and Tenon's capsule then were reapproximated with sutures, and the eye was covered with a lead shield. The patient was discharged on the following day (with instructions for protection against radioactivity), and the plaque was removed at a predetermined date, when delivery of the appropriate dosage according to the protocol had been completed (usually 4 to 5 days later). Immediately after the removal of the plaque, the levels of radioactivity again were examined to verify complete removal of the radioactive material.

After surgery, patients were examined at regular intervals (0.5 month, 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, and at 6-month intervals for 5 years after treatment). Apart from a comprehensive ophthalmologic examination, other studies also were performed at selected intervals, including ultrasonography, ophthalmic photography, and fluorescein angiography, to confirm local tumor control and to detect the development of complications, including INV and ANV. The detection of INV or ANV in the treated eyes was examined with high magnification biomicroscopy as well as gonioscopic evaluation (before the instillation of mydriatic drops). Laboratory tests, including liver function tests and liver imaging studies (ultrasonography, computed tomography, or magnetic resonance imaging) also were performed at regular intervals to detect metastasis.

Demographic and social information collected included age, gender, race, and smoking habits, scored in pack-years. Information from the medical history collected included the presence of diagnosed arterial hypertension and diabetes mellitus. Pretreatment parameters recorded as well as respective scoring methods are presented in Table 1. Treatment parameters recorded included plaque diameter (millimeters), total radioactivity (millicuries), duration of application (hours), and total dose delivered (grays).

On completion of data recording, a statistical analysis of results was performed with SPSS software version 8.0.[10] Survival analysis, using a univariate Cox regression model, was applied to evaluate the statistical correlation between individual risk factors and the development of INV. The intervals of postoperative examinations were calculated in days (based on the exact date of visits) and then converted to months by dividing the number of days by 30 to facilitate analysis and comparison with previous studies. The independent correlation of parameters examined with the development of INV and the respective relative risk ratios were explored using a multivariate Cox proportional hazard model with a forward stepwise procedure (with a probability for entry into the

Table 2. Radioactive Plaque Characteristics

Plaque Characteristic	Mean	Standard Deviation	Median	Range
Plaque diameter (mm)	17.47	0.24	18	10–23
Total radioactivity (millicuries)	49.99	1.9	48.11	17.65–110
Duration of application (hrs)	128.31	1.55	120.08	113.68–188.83
Total dose delivered (Gy)	85.58	0.16	85.04	81.89–104.77