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Regression Patterns of Iris Melanoma after Palladium-103 (^{103}Pd) Plaque Brachytherapy

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Purpose: To evaluate the patterns of regression of iris melanoma after treatment with palladium-103 (^{103}Pd) plaque brachytherapy.

Design: Retrospective, nonrandomized, interventional case series.

Participants: Fifty patients with primary malignant melanoma of the iris.

Methods: Palladium-103 plaque brachytherapy.

Main Outcome Measures: Changes in tumor size, pigmentation, and vascularity; incidence of iris neovascularization; and radiation-related complications.

Results: The mean age in the case series was 61.2±14.9 years. The mean tumor thickness was 1.4±0.6 mm. According to the American Joint Committee on Cancer, eighth edition, staging criteria for iris melanoma, 21 tumors (42%) were T1a, 5 tumors (10%) were T1b, and 24 tumors (48%) were T2a. The tumor was melanotic in 37 cases (74%) and amelanotic in 13 cases (26%); of these, 13 tumors (26%) showed variable pigmentation. After brachytherapy, mean tumor thickness decreased to 0.9±0.2 mm. Pigmentation increased in 32 tumors (64%), decreased in 11 tumors (22%), and was unchanged in 6 tumors (12%). For intrinsic vascularity (n = 19), 12 tumors (63%) showed decrease and 7 tumors (37%) showed complete resolution. Appearance of ectropion uveae showed diminution in 15 tumors (43%); newly present corectopia was observed in 6 patients (12%). On high-frequency ultrasound imaging, of the 42 tumors (84%) with low to moderate internal reflectivity, 30 tumors (60%) showed an increase in internal reflectivity on regression. Iris stromal atrophy was noted in 26 patients (52%), progression or new-onset cataract was noted in 22 patients (44%), neovascular glaucoma was noted in 1 patient (2%), and there were no cases of corneal opacity. There was no clinical evidence (0%) of radiation-induced retinopathy, maculopathy, or optic neuropathy. Mean follow-up in this series was 5.2 years (range, 0.5–17 years).

Conclusions: The most common findings related to iris melanoma regression after ^{103}Pd plaque brachytherapy included decreased intrinsic tumor vascularity, increased tumor pigmentation, and decreased tumor thickness with synchronous increase in internal ultrasonographic reflectivity. No irreversible sight-limiting complications were noted. *Ophthalmology 2017;■:1–8 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Iris melanoma is the least common type of uveal melanoma, constituting only 2% to 3% of cases.[1,2] Early studies suggested that because of their anatomic location and tendency for slow growth, they were presumed to have low metastatic potential of 3.5% to 5%.[1–3] Thus, smaller iris and iridociliary melanomas have been observed for documentation of growth before intervention. However, a relatively recent single-center and multicenter international studies have found that biopsy-proven iris melanomas are more dangerous, with metastatic rates of 10.7% to 11%.[2,4] These findings support the treatment of iris melanomas.

Clinical signs suggesting that a pigmented iris tumor is a melanoma include intrinsic tumor vascularity, stromal involvement of more than 3 clock hours (or measuring >5 mm), thickness larger than 1 mm, sentinel vessels (iris and episcleral), sector cataract, pigment dispersion, secondary glaucoma, and extrascleral extension.[4] Although a clinical diagnosis can be acceptable, both aspiration cutter-assisted or needle biopsy have been performed safely in cases with high suspicion of malignancy or with atypical clinical features, as well as for obtaining a specimen for histopathologic and genetic studies.[5–7]

The management of iris melanoma has depended on several clinical features: tumor size, location, or extent; tumor seeding; as well as the presence of tumor-related glaucoma.[4,8] Treatment options include iridectomy, iridocyclectomy, plaque brachytherapy, proton beam radiotherapy, and enucleation.[9–19] Smaller tumors have been managed with local resection (iridectomy, iridocyclectomy) to achieve tumor-free margins, whereas larger tumors, multifocal tumors, or those tumors causing uncontrollable glaucoma were managed with plaque radiotherapy or enucleation.[13,17–19] Of these, local resection invariably causes a dysmorphic, dystonic pupil or large optical opening with associated anisocoria, accommodative symptoms, and photophobia. Local control after local resection of iris melanomas has been reported to be 90% to 94%.[18,19]

In 1991, we treated the first iris melanoma with epicorneal palladium-103 (^{103}Pd) ophthalmic plaque radiation therapy in an effort to preserve normal iris tissue and

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function.[16] More recent literature reveals a trend towards conservative treatment with radiation therapy.[10–17] In consideration of this trend, it is important to examine and document the patterns of change after plaque radiation therapy for iris melanoma.

In a search and review of National Library of Medicine and PubMed findings using the terms *iris*, *plaque*, *radiation*, and *regression*, we could find no studies describing the clinical patterns of regression of iris melanoma after plaque brachytherapy. Therefore, we describe the clinical features of regressing iris melanomas after ^{103}Pd plaque brachytherapy.

Methods

This study adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996. We obtained approval from The New York Eye Cancer Center Internal Review Board to perform a retrospective chart review of ophthalmic plaque brachytherapy for iris melanomas between 1998 and 2015. This included 50 patients with iris melanoma who underwent ^{103}Pd plaque brachytherapy with at least 6 months of follow-up. Patients diagnosed with ciliary body melanoma extending to the iris were excluded from the study.

History and Ophthalmic Examination

All patients were referred to The New York Eye Cancer Center with a history of iris lesion with (1) evidence of documented growth or (2) suspicion of malignant melanoma. The demographic data involving age at presentation, gender, race, and associated ocular and systemic diseases (hypertension, diabetes mellitus, cardiac illness, and malignancies involving other systems) were recorded.

Ophthalmologic examinations were inclusive of, but not limited to, visual acuity with the Early Treatment Diabetic Retinopathy Study charts and rooms, slit-lamp biomicroscopy with photography, tonometry, gonioscopy, scleral transillumination, high-frequency ultrasonography (20–50 MHz), and indirect ophthalmoscopy. Of these, visual acuity, slit-lamp photography, gonioscopic photography, high-frequency ultrasound imaging, and ophthalmoscopy testing were performed at each visit.

Informed Consent, Biopsy, and Systemic Evaluations

All patients were counselled about the most common methods of management (observation for growth, confirmation of histopathologic diagnosis with biopsy, radiation therapy, iridectomy or iridocyclectomy, and enucleation). Biopsy was performed in 37 eyes (74%) having either atypical morphologic features or after patient request for a histopathologic diagnosis using the Finger Iridectomy Technique (FIT).[5] A histopathologic diagnosis of malignant melanoma was established in all 37 eyes. All 50 patients subsequently underwent treatment with ^{103}Pd plaque brachytherapy.

Pretreatment radiographic metastatic surveys (initial whole-body 18-fluorodeoxyglucose positron emission tomography/computed tomography [PET/CT]) imaging or contrast-enhanced chest and abdominal radiographic imaging (computed tomography or magnetic resonance imaging) were performed. Follow-up systemic examinations were repeated every 6 months for the first 5 years and every year thereafter and typically were limited to radiographic abdominal imaging.[7]

Primary Data Parameters

Ocular data at presentation included initial best-corrected visual acuity, anterior segment findings, iris color, intraocular pressure, tumor pigmentation (melanotic, amelanotic [e.g., tapioca colored]), nature of pigmentation (uniform, variable), tumor epicenter quadrant (superior, temporal, inferior, nasal, or diffuse), anterior and posterior tumor margins (pupil, midzone, iris root, angle), tumor configuration (nodular, dome, diffuse), tumor base measurements (in millimeters), tumor thickness (in millimeters), intrinsic vascularity, pigment dispersion, corectopia, ectropion uveae, tumor seeds in the anterior chamber angle, ciliary body invasion, and extraocular extension. Ultrasound characteristics included tumor thickness (in millimeters), defined as the highest tumor height as measured by high-frequency ultrasound. We also determined and recorded internal tumor reflectivity (low, moderate, high), iris pigment epithelium (IPE) anterior displacement or posterior bowing, iris pigment epithelium erosion, and invasion of supraciliary space. The radiation prescription point was defined by ultrasonography as the effective tumor height in millimeters or the distance from the corneal epithelium to deepest intraocular tumor extension as measured by high-frequency ultrasonography after mydriasis.

Palladium-103 Plaque Radiation Therapy

After careful analysis of the comparative intraocular radiation distribution to critical structures (iodine 125 [^{125}I] vs. ^{103}Pd]), the latter was the radionuclide selected for every case.[20] The radiation parameters included plaque shape (round, custom-designed shape), plaque diameter, number of seeds used, duration of treatment (hours), prescribed radiation dose (Gray), and radiation rate (Gray per hour) to tumor apex, lens, optic disc, and foveola.

Plaque surgery was comprised of tumor localization and plaque insertion. Scleral transillumination and preoperative high-frequency ultrasound measurements were used to define tumor margins. Each plaque was placed as to cover the entire tumor plus a 2- to 3-mm tumor-free margin. Epicorneal plaque touch was buffered with a 0.1-mm thick amniotic membrane held in position by the plaque. The anterior aspect of the plaque was covered by conjunctiva to form a Gunderson flap. This buffering technique was used for all cases (74%) after its discovery in 2008.[21] All patients received continuous radiation starting at insertion and ending when the prescription dose was delivered to the point of deepest intraocular tumor extension (as measured by high-frequency ultrasonography after mydriasis) over 5 to 7 days. Periocular steroid injection, topical Atropisol 1% (Iolab, USA), and epibulbar antibiotic–steroid ointment were placed at the end of surgery. Topical Cyclogyl 1% (Alcon Laboratories, Inc, Fort Worth, TX) and antibiotic–steroid drops were instilled 4 times daily during the treatment interval.

Follow-up

Follow-up examinations were performed at 4 to 6-month intervals during the first 5 years and then at 6 to 12-month intervals thereafter. A detailed clinical evaluation and photographic documentation were performed at each visit. The outcome measures were changes in tumor size, pigmentation, vascularity, intraocular pressure, incidence of iris neovascularization, and radiation-related complications.

Results

Analysis of the 50 cases of iris melanoma revealed that their median follow-up was 48 months (mean, 63 months; range, 6–204 months). Demographic characteristics are described in Table 1.