Original Investigation | CLINICAL SCIENCES Outcomes of Choroidal Melanomas Treated With Eye Physics A 20-Year Review

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IMPORTANCE The University of Southern California Eye Physics plaques compare favorably with the Collaborative Ocular Melanoma Study plaques in terms of late adverse effects from radiation, metastasis, and local tumor recurrence.

OBJECTIVE To review the University of Southern California experience using Eye Physics plaques and Plaque Simulator software to treat choroidal melanomas and compare the outcomes with published results of the Collaborative Ocular Melanoma Study.

DESIGN, SETTING, AND PARTICIPANTS A retrospective case series of 82 patients treated for medium-sized choroidal melanoma from January 1, 1990, through December 30, 2010, using iodine 125 plaques and treatment simulation software developed at the University of Southern California. The dosimetric goal was 85 Gy in 7 days to a conformal volume enclosing the apex and a 2-mm margin surrounding the tumor base. Plaque localization was guided by the Plaque Simulator computer modeling system using preoperative imaging studies.

MAIN OUTCOMES AND MEASURES Primary outcome measures were local tumor control, globe preservation, and metastases. Secondary outcome measures were late radiation adverse effects including postoperative vision changes, optic neuropathy, radiation retinopathy, and cataract.

RESULTS The median follow-up for 82 patients was 46.8 months (range, 1-171 months). Globe preservation was achieved in 80 patients (97.6%); 2 patients underwent enucleation for local recurrence. Metastatic disease developed in 9 patients (11.0%). Retinopathy was seen in 31 patients (37.8%), optic neuropathy in 12 (14.6%), and cataracts in 26 (31.7%). Postoperatively, 21 patients (25.6%) lost more than 6 lines of Snellen visual acuity.

CONCLUSIONS AND RELEVANCE When considering rates of local recurrence, metastases, and late radiation adverse effects, the University of Southern California results for medium-sized choroidal melanomas using Eye Physics plaques compared favorably with Collaborative Ocular Melanoma Study data. The Plaque Simulator 3-dimensional tumor-modeling program developed at the University of Southern California is a reliable method for determining plaque positioning preoperatively and for treating this cohort of patients.

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Corresponding Author: Jesse L. Berry, MD, Doheny Eye Institute, Department of Ophthalmology, 1450 San Pablo St, Los Angeles, CA 90033 (jesse.berrymd@gmail.com). he Collaborative Ocular Melanoma Study (COMS) established iodine 125 episceral plaque brachytherapy as an effective modality for treating medium-sized choroidal melanomas, with survival rates equal to enucleation.¹ The brachytherapy technique used in the COMS is the standard approach in the United States for globe preservation with medium-sized choroidal melanomas. The COMS plaques are placed using intraoperative techniques including transillumination, indirect ophthalmoscopy with scleral diathermy, and ultrasonography to localize the tumor.² Using these techniques, the COMS found a rate of local tumor recurrence of 10.3%; and the chance for enucleation, owing to either tumor recurrence or ocular adverse effects, was 12.5% at 5 years.³

The Plaque Simulator (PS) software used in this study was developed at the University of Southern California (USC) along with the Eye Physics (EP) plaques and have been previously described.⁴⁻⁸ Potential advantages of the EP plaque system over COMS plaques include a thinner plaque profile; a collimating slot for each iodine 125 seed; and a wider range of available shapes, sizes, and curvatures, which support customized, conformal tumor treatment.⁴ The plaque localization technique relies on computer modeling rather than traditional intraoperative methods.

The PS software fuses fundus photography, ocular ultrasonography, and computed tomography (CT) or magnetic resonance imaging (MRI) to create a 3-dimensional (3-D) model of the eye, tumor, plaque, and seeds. This simulation enables selection of seed positions to approximately conform to the tumor base. Seed orientation and collimation are selected to spare critical structures of the eye (eg, macula and optic nerve), and plaque position and orientation on the eye are determined preoperatively, obviating the need for intraoperative localization of the tumor. We presented and evaluated 20 years of clinical results with this technology.

Methods

This is a retrospective record review of all patients who underwent episcleral plaque brachytherapy with iodine 125 at USC between January 1, 1990, and December 30, 2010, for mediumsized choroidal melanomas as diagnosed by our ocular oncologist (A.L.M.). This study was approved by the institutional review board at USC.

Patient Eligibility

Eligible patients were older than 18 years of age; had a primary, medium-sized choroidal melanoma; and otherwise had no contraindications to brachytherapy. Medium-sized tumors were defined as having an apical height between 2.5 and 10.0 mm and a basal diameter between 4.5 and 16.0 mm. Patients with clinical, laboratory, or radiologic evidence of metastatic disease (stage IV) at the time of diagnosis were not eligible for brachytherapy. Large, diffuse, ill-defined tumors; tumors contiguous with the optic nerve for more than 3 clock hours or surrounding the nerve; tumors primarily involving the ciliary body or iris; and tumors with extrascleral extension were not eligible for plaque therapy. All patients were educated on treatment options including observation, enucleation, and proton beam therapy. Patients who chose brachytherapy were treated with iodine 125 EP plaques, with a prescribed dose of 85 Gy to the tumor apex.

Data Collection and Patient Follow-up

At diagnosis, medical and ocular history and complete ophthalmic examination with measurement of visual acuity with pinhole or manifest refraction, slitlamp examination, and fundoscopy of both eyes were completed. Gonioscopy was performed when clinically indicated. Patients had A-scan and Bscan echography and color fundus photography at initial and follow-up examinations. Internal reflectivity, apical height, base diameter, and circumference were recorded with ultrasound. Patients had orbital imaging with CT or MRI. Systemic evaluation was performed by an internist or oncologist at the time of diagnosis and biannually after treatment including chest radiography, serum liver function tests, and liver imaging.

Follow-up data were collected at postoperative examinations at approximately 3 months (range, 2-4 months), 6 months (range, 5-8 months), and 12 months (range, 9-14 months) after surgery and 6- to 12-month intervals thereafter. Patients without follow-up at the end of our study were contacted by telephone. Patients and/or family members were asked about any known recurrence of melanoma or tumor-related death. Mortality data were not confirmed with pathology or autopsy reports.

Patients were monitored for adverse effects such as blepharoptosis, strabismus, cataract, radiation retinopathy/ vitreous hemorrhage, optic neuropathy, phthisis with or without pain, and local failure/recurrence. Local failure was defined (as in the COMS³) as greater than 15% increase in tumor size on ultrasound; greater than 250-µm increase of tumor border; extrascleral extension greater than 2 mm; or evidence of orbital recurrence.

Primary outcome measures were local recurrence, enucleation, and death. Secondary outcome measures were plaquerelated adverse effects and change in visual acuity.

Histopathologic evaluation was performed on all enucleated specimens.

Plaque Protocol

All brachytherapy treatment plans were completed by a single radiation oncologist (M.A.), and all surgical procedures were completed by a single ocular oncologist (A.L.M.). The PS planning software was developed by Astrahan and colleagues⁴⁻⁸ at USC and is distributed by BEBIG GmbH. The EP plaques are available from Eye Physics LLC and in preloaded, presterilized configurations from IsoAid.

Computer simulation created a 3-D model of the tumor within each patient's eye (**Figure 1**). The modeling process began with mapping the tumor base that was visible in color photographs and/or fluorescein angiography images of the retina. The images had to include the macula and optic disc for reference landmarks. The tumor height was determined from ultrasound, with confirmation from CT or MRI multiplanar reconstructions of ocular meridian planes passing through the tumor apex. The basal dimensions of the tumor measured by

Figure 1. 3-Dimensional Models and Photograph



A, Posterior tumor digitized on retinal map with a 2-mm margin, suture coordinates, and approximately conformal isodose lines. B, Conformal iodine 125 loading of plaque model 917, which is a semi-elliptical design with 1-mm-deep collimating slots and a broadly notched posterior edge with 2 seed

positions that can straddle the optic disc. C, Fusion of computed tomography, fundus, and both 2-dimensional and 3-dimensional dosimetry. D, Example of plaque placement with measurement from the limbus along meridians (clock hours) on the eye.

ultrasonography and from multiplanar reconstructions were used to confirm the photographic mapping and to estimate any portions of the tumor perimeter that were too anterior to be photographed. A multiplanar reconstruction meridian that bisects the eye through the center of the optic nerve (eg, an axial slice that bisects the eye) provided the posterior pole and optic disc reference points in 3-D CT (or MRI) space, which allowed the fusion of the fundus photographs with the 3-D model.

This virtual model of the eye and tumor was used to select a plaque, locate and orient it on the eye, identify the seed positions that conformed to the tumor base, and calculate the resulting dose distribution. The location, orientation, size, and shape of the plaque and seeds were selected so as to envelop the tumor apex, base, and a 2-mm retinal margin surrounding the base within a prescribed isodose surface (eg, 85 Gy to the apex). Secondary objectives included reducing the radiation dose to critical ocular structures whenever possible with seed orientation and collimation, and positioning the suture eyelets as anteriorly as possible for ease of scleral suturing. Seed strength was selected to deliver the prescribed dose in 7 days. The lower dose rate over 7 days was chosen to decrease late radiobiological effects on normal tissues and to allow for greater flexibility

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Table 1. Baseline Characteristics of Patients Treated by Plaque Brachytherapy

Characteristic	No. (%)
Sex	
Male	49 (59.8)
Female	33 (40.2)
Age, y	
<50	18 (22.0)
50-69	39 (47.6)
≥70	25 (30.4)
Race/ethnicity	
White	77 (93.9)
Other	5 (6.1)
Laterality of affected eye	
Right	40 (48.8)
Left	42 (51.2)
Visual acuity at diagnosis	
>20/20-20/40	52 (63.4)
20/50-20/150	15 (18.3)
≤20/200	15 (18.3)
Tumor apical height, mm	
2.5-5.0	56 (68.3)
5.1-7.5	21 (25.6)
7.6-10.0	5 (6.1)
Tumor basal dimension, mm	
4.5-8.0	16 (19.5)
8.1-11.0	28 (34.1)
11.1-14.0	28 (34.1)
14.1-16.0	10 (12.3)
Location of anterior border $(n = 75)$	
Ciliary body	5 (6.7)
Anterior to equator	27 (36.0)
Posterior equator	43 (57.3)
Location of posterior border ($n = 75$)	
Anterior to equator	5 (6.7)
Posterior to equator	70 (93.3)
Follow-up, mo	
0-12	12 (14.6)
13-24	18 (22.0)
25-36	11 (13.4)
37-48	11 (13.4)
49-60	7 (8.5)
61-100	14 (17.1)
>101	9 (11.0)

in scheduling times for plaque removal. Eye Physics plaques with notched perimeters were used for tumors contiguous with the optic nerve for fewer than 3 clock hours. The most often-used EP plaque was model 917, which is a semielliptical design with 1-mm-deep collimating slots and a broadly notched posterior edge with 2 seed positions that can straddle the optic disc (Figure 1B).

Suture coordinates for plaque eyelets were expressed as a retinal map meridian (clock hour) and caliper distance from the limbus (Figure 1D). Sutures were preplaced in the sclera and a dummy (unloaded) plaque with the same design as the treatment plaque was temporarily secured. Correct plaque placement was confirmed with direct visualization via indirect ophthalmoscopy and scleral depression around the plaque. Once the position of the plaque was confirmed, the dummy plaque was removed and the treatment plaque was secured using the same preplaced sutures. No pretreatment diagnostic biopsies (fine needle or otherwise) were performed. Of the 82 treated patients, 75 plaque protocols were available for review. Radiation doses to critical ocular structures were calculated with PS software based on plaque location and treatment time.

Statistical Analysis

Snellen visual acuity was recorded and converted to logarithm of the minimal angle of resolution format. Mean, median, range, and standard deviations were computed using Microsoft Excel functions. *P* values were calculated using the χ^2 function. Kaplan-Meier curves were calculated with Intercooled Stata version 10.1 (StataCorp). Multivariate analysis could not be performed owing to the small sample size of patients with recurrent disease/enucleation.

Results

Patient Population

From January 1, 1990, to December 30, 2010, 82 patients with medium-sized choroidal melanomas were treated using PS software and EP plaques loaded with iodine 125 seeds. Baseline patient demographic and tumor characteristics are described in Table 1. Forty-nine patients (59.8%) were male. The median age at the time of treatment was 62 years (range, 23-87 years). Forty patients (48.8%) had tumor in the right eye. Seventy-seven patients (93.9%) were white (self-designation). Tumor height at diagnosis ranged from 2.5 to 9.6 mm with average (SD) apical height of 4.6 (1.5) mm. Basal diameter at diagnosis ranged from 5.9 to 15.8 mm with an average (SD) of 10.7 (2.6) mm. Most tumors were located in the posterior pole, with the posterior border behind the equator in 70 (93.3%) patients. The median follow-up was 46.8 months (range, 1-171 months). Fifty-two patients (63.4%) had greater than 24 months follow-up.

After treatment, 80 patients (97.6%) retained their eyes. Two eyes (2.4%) were enucleated secondary to local tumor recurrence based on a 2.4-mm increase in apical size in 1 patient (on ultrasound) and significant subretinal bleeding with doubling of tumor size in another. No patient underwent enucleation for a blind painful eye. The Kaplan-Meier estimate of local tumor control at 5 years was 97% (95% CI, 89-99) (**Figure 2**). Time to enucleation was 8 months and 15 months in the 2 eyes that had local recurrence.

Nine (10.9%) of 82 patients developed metastatic disease. The mean (SD) time to development of metastatic disease was 41.0 (34.7) months (range, 6-106 months). All patients who developed metastatic disease (9 of 9) were found to have metastases to the liver. Metastatic disease was also found in the bones (3 of 9), brain (1 of 9), adrenal gland (1 of

Figure 2. Kaplan-Meier Curves of Enucleation Postplague Brachytherapy









The estimate of survival without metastatic disease at 60 months is 89% (95% CI. 77-95).

9), and breast (1 of 9). The Kaplan-Meier estimate of survival without metastatic disease at 60 months was 89% (95% CI, 77-95) (Figure 3).

Radiation Dose and Related Adverse Effects

The radiation dose delivered to the tumor and critical ocular structures was calculated using the PS software. The average (SD) dose to the tumor apex was 85.6 (13.1) Gy (range, 70.8-102.6 Gy). The average (SD) dose to the optic nerve was 46.6 (37.5) Gy (range, 5.2-113.4 Gy); 66.6 (66.2) Gy to the macula (range, 4.2-312.4 Gy); and 15.2 (11.6) Gy to the lens (range, 3.7-73.6 Gy) (Table 2). Twenty-two patients received a dose greater than 55 Gy to the optic nerve; 7 of 22 patients developed optic neuropathy. Thirty-six patients received a dose greater than 40 Gy to the macula; 17 of 36 patients developed radiation retinopathy.

The adverse effects of brachytherapy included blepharoptosis in 7 patients (8.5%), diplopia in 10 (12.2%), cataract in 26 (31.7%), radiation retinopathy in 31 (37.8%), and optic neuropathy in 12 (14.6%). These rates were compared with radiation-related ocular adverse effects in the COMS (Table 2).9

University of Southern California Melanoma Study **Baseline Clinical Characteristics** Patients. No. 638 82 Median follow up, mo 67 47 Patients, % White 98 94 Male 50 60 Mean tumor height, mm 4.2 4.6 Mean basal diameter, mm 11.5 10.7 Anterior border posterior to 55 57 equator, % **Tumor Control** Dose to tumor apex, Gy 85 85 Dose to optic nerve, Gy 52.1 46.6 Dose to macula/fovea, Gy 79 66.6 Dose to lens, Gy 15.6 15.2 Kaplan-Meier-estimated tumor 3.0 10 recurrence at 5 v. % Enucleation at 5 v. % 3.0 13 Metastatic disease at 5 y, % 10 11 Visual and Ocular Outcomes, % Preoperative visual acuity 63 20/40 or better 70 20/200 or worse 10 18 Postoperative visual acuity 35 20/40 or better 34 20/200 or worse 43 43 Optic neuropathy 27 15 Radiation retinopathy 49 38 Cataracts 83 32

Table 2. Collaborative Ocular Melanoma Study vs University of Southern

Collaborative Ocular

Vision

At diagnosis, Snellen visual acuity better than or equal to 20/40 was measured in 52 patients (63.4%). Visual acuity worse than or equal to 20/200 was measured in 15 patients (18.3%).

At final follow-up, the number of patients with visual acuity better than or equal to 20/40 decreased to 29 (35.4%) and those with visual acuity worse than or equal to 20/200 increased to 35 (42.7%). After brachytherapy, 21 patients (25.6%) lost 5 or more lines of vision compared with visual acuity at diagnosis.

Discussion

The COMS was a national, multicenter, randomized trial that used iodine 125 brachytherapy to treat 650 patients with medium-sized (2.5- to 10-mm apical height and 5- to 16-mm basal dimension) choroidal melanomas from 1986-1998. The COMS established episcleral plaque radiotherapy as a viable treatment option, with survival rates equal to enucleation.¹ Treatment failure at 5 years was reported in the COMS as 10.3% of local recurrence, with a 12.5% rate of all-cause enucleation.³

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Figure 4. Enucleated Specimen



Almost half of the treated eyes lost 6 lines of vision from their pretreatment level or had vision worse than 20/200 at 3 years post-therapy.¹⁰

The COMS plaques are available in standard circular and notched sizes from 10- to 22-mm diameters. The COMS plaques use Silastic silicone inserts to hold the radioactive seeds. Use of silicone resulted in greater attenuation of low-energy radiation from iodine 125 than was intended. When calculating dose for COMS plaques, if the silicone carrier is modeled as being water equivalent, the delivered dose will be 15% to 50% less than expected.⁸ According to COMS protocol, the diameter of the plaque includes a 2-mm physical margin between the tumor base and lip of the plaque. The prescription isodose coverage to the retina typically lies outside the lip of the plaque for tumors greater than 5-mm tall. The COMS plaques are localized by the surgeon using intraoperative techniques and have been adopted as standard of care for medium-sized choroidal melanomas at most ocular oncology centers.

The EP/PS system uses 3-D image-based computer modeling to determine plaque position preoperatively. The clinical results demonstrated in this series suggest that by using this treatment simulation, tumor location can be accurately determined and plaque location planned in advance of surgery. Using COMS data as historical controls, the clinical results of our series compared favorably when considering rates of tumor recurrence, distant metastasis, and adverse effects. The rate of intraocular tumor recurrence at 5 years in our series was 2.4%, lower than the 10.3% rate found in COMS.3 Both enucleated eyes were evaluated by an ocular histopathologist. One of our 2 local recurrences was associated with a doubling of tumor thickness and vitreous hemorrhage, which may have been secondary to intratumor hemorrhage causing apparent tumor regrowth rather than a true recurrence. Histopathologic evaluation of the enucleated specimen showed tumor necrosis, hemorrhage, and pigment-laden macrophages (Figure 4).

With equivalent baseline characteristics, the rates of patient survival and metastatic disease were similar in both series (10.9%).¹¹ In our series, retinopathy was seen in 37.8% of patients, optic neuropathy in 14.6%, and cataracts in 31.7% (Table 2). Regarding final visual outcomes, percentages of patients with 20/40 or better vision or 20/200 or worse vision were essentially the same between the 2 groups (Table 2). Rates of ocular adverse effects following brachytherapy appeared to be Enucleation performed owing to increase in tumor size. A, Low-power image shows posteriorly located pigmented mass with significant hemorrhage. B, High-power image of specimen shows tumor necrosis and pigment-laden macrophages.

lower in our series compared with the COMS; however, our sample size was significantly smaller and any advantages in visual outcomes with the EP system remain unproven. Overall clinical results of our series compared favorably with other nonrandomized single-surgeon series: Char et al¹² reported a 15% risk of enucleation at 4 years, Gündüz et al¹³ reported a 9% 5-year risk for local tumor recurrence, and Quivey et al¹⁴ reported an 18% rate of local recurrence at 5 years.

The combination of EP plaques and PS software offers advantages over COMS plaques. The system is surgeon-friendly as plaque localization is performed preoperatively using clinical data. Using transillumination and/or indirect ophthalmoscopy to define plaque placement has been the standard technique for many years. However, difficulties associated with this method include poor visualization owing to opaque media, surgeon error in judgment on localization, poor transillumination owing to the absence of inherent pigmentation, and difficulty indenting the posterior margin of the tumor. Additionally, obviating the need for performing tumor localization intraoperatively has several theoretical advantages including faster operative times, lack of scleral and retinal scarring from diathermy and other marking methods, and avoidance of potential light damage to the eye from prolonged transpupillary transillumination.

Additional advantages of using the EP plaques include ease of insertion from a thinner profile, less collateral radiation damage from individual seed collimation, and greater selection of shapes and sizes to facilitate placement and tumor coverage. A recent publication by Marwaha et al¹⁵ from the Cleveland Clinic reviewed 100 consecutive patients treated with COMS plaques for choroidal melanoma. Using the PS software, they recalculated radiation exposure to critical ocular structures for the model 917 EP plaque. While the results were theoretical, based on calculated dosimetry, the authors found a benefit for the EP plaque system, with lower doses of radiation delivered to the optic disc and macula compared with COMS plaques. The location of tumors in the study by Marwaha et al¹⁵ is not presented in the same manner as our study and only 1 model of plaque (EP 917) was studied, making a direct comparison impossible. However, our dosimetric calculations were similar for the lens (15.1 Gy compared with 17.07 Gy) but higher for the optic nerve and macula. Based on our calculations, the average dose to the optic nerve was 46.6 Gy, under threshold

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Variation in dose for a choroidal melanoma with 5-mm height and 12-mm diameter. Dose to the macula is 48 Gy with the COMS plaque vs 30 Gy with the EP plaque. Additionally with the COMS plaque, a larger area underlying the tumor receives 200 Gy (orange) compared with the EP plaque, although the EP plaque is thinner and the seeds are closer to the sclera.

dose for optic neuropathy (<55 Gy).¹⁶ Twenty-two patients received a dose greater than 55 Gy; 7 of 22 patients developed optic neuropathy, which accounted for 58% (7 of 12) of those patients who developed optic neuropathy. The average dose to the macula was 66.6 Gy, higher than threshold dose of 40 Gy for maculopathy, and likely represents the posterior location of most of the tumors in our series.^{17,18} Thirty-six patients received a dose greater than 40 Gy to the macula; 17 of 36 developed radiation retinopathy which accounts for 54.8% (17 of 31) of patients who developed this complication. When comparing radiation levels to critical ocular structures in the COMS, the EP system used in this group of patients demonstrated lower doses to the 3 main ocular landmarks studied (optic nerve, fovea, and lens).¹⁶ A comparison of modeled isodose lines between the COMS and EP plaques for a theoretical tumor is shown in **Figure 5**.

This study demonstrates that PS plaque planning software and design of the EP plaques produced excellent tumor control and acceptable rates of ocular adverse effects. When considering rates of local recurrence, enucleation, survival, and visual outcomes, the results of using the PS/EP combination for choroidal melanomas compared favorably with results from the COMS. From the surgeon's perspective, the PS/EP system simplifies plaque placement with preoperative planning rather than by intraoperative methods. The clinical results obtained from this long-term series suggest that EP plaques and PS software are a valid and accurate method for treating mediumsized choroidal melanomas.

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Study concept and design: Berry, Astrahan, Murphree, Kim.

Acquisition of data: All authors.

Analysis and interpretation of data: Berry,

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Conflict of Interest Disclosures: Dr Astrahan holds an ownership position in Eye Physics LLC, which was incorporated in 2007 to continue development of the Plaque Simulator software and Eye Physics plaques following Dr Astrahan's emeritus retirement from the University of Southern California (USC) in 2010. During 1990-2010, no outside funding for development or material support for any of his contributions was received by USC. No compensation was received for any patient in this study. From 1995-2010, USC and Dr Astrahan shared a royalty derived from licensed distribution of the Plaque Simulator software to other institutions. No other disclosures were reported.

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OPHTHALMIC IMAGES

Stromal Duplication of the Iris

Ladan Espandar, MD, MS; R. Rand Allingham, MD; Natalie A. Afshari, MD



A 53-year-old man who received a clinical diagnosis of anterior segment dysgenesis and hyperopia presented with high intraocular pressure (26 mm Hg in each eye) and narrow angles determined by gonioscopy, corneal guttae, and stunning partial duplication of the central iris and mid-iris (A) confirmed by anterior segment optical coherence tomographic imaging (B). Best-corrected visual acuity was 20/25 in each eye, and corneal thickness was 625 µm OD and 562 µm OS. The patient underwent a laser peripheral iridotomy. His intraocular pressure was successfully controlled with prostaglandin analogues.

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