

Scientific Article

Preliminary Results of Uveal Melanoma Treated With Iodine-125 Plaques: Analysis of Disease Control and Visual Outcomes With 63 Gy to the Target Volume



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Abstract

Purpose: Our purpose was to review the preliminary outcomes of patients with uveal melanoma treated with iodine-125 plaques using a novel treatment planning approach.

Methods and Materials: This was a single institution, retrospective review of patients treated with iodine-125 brachytherapy for uveal melanoma from November 2016 to February 2019. We used 3-dimensional treatment planning with the Eye Physics Plaque Simulator to ensure that a minimum of 63 Gy covered a 2-mm circumferential tumor margin and the apex height of the tumor over 94 hours. Primary endpoints were local failure, systemic metastasis, final visual acuity (VA), and radiation retinopathy. Associations between primary endpoints and tumor characteristics/radiation dose were performed using univariate analysis.

Results: Sixty-nine patients were included in the analysis. Mean largest basal diameter was 11.67 mm (range, 6-18; median, 12), and the average tumor thickness to the inner sclera was 3.18 mm (range, 0.5-9.3; median, 2.8). Molecular testing that was successfully performed in 59 patients revealed that 27% (16 of 59) had class 2 gene expression profile designation. Average follow-up posttreatment was 28.3 months (range, 4-46; median, 29), with 6% (4 of 69) developing local failure and 6% (4 of 69) developing metastasis over this duration. Average final VA (0.57 logMAR [Snellen 20/74]; range, 0-2.9; median, 0.3) was decreased from baseline (0.34 logMAR [Snellen 20/44]; range, 0-2.3; median, 0.1), and 48% (33 of 69) developed radiation retinopathy. Fifty percent of patients had a final VA 20/40 or better and 22% had a final VA 20/200 or worse.

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All data generated and analyzed during this study are included in this published article (and its supplementary information files).

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Conclusions: In patients with uveal melanoma, preliminary results with brachytherapy using Eye Physics plaques with a treatment plan that delivers 63 Gy to a 2-mm circumferential tumor margin and the tumor apex suggest effective disease control and favorable VA outcomes.

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Introduction

Uveal melanoma is the most common site of noncutaneous melanoma,^{1,2} with a reported incidence rate ranging from 4.9 to 5.2 cases per million.²⁻⁵ Plaque brachytherapy is the most widely used treatment for uveal melanoma, as it delivers a highly conformal radiation dose to the tumor with relatively less radiation to surrounding healthy tissues. Brachytherapy has been used as a globe-preserving treatment for intraocular tumors since 1930.⁶ High-energy cobalt-60 (⁶⁰Co) episcleral discs were popularized by Stallard in the 1960s.⁷ Since that time, several other isotopes have been used, including beta electron emitters ruthenium/rhodium-106 (¹⁰⁶Ru/¹⁰⁶Rh), strontium-90/yttrium-90 (⁹⁰Sr/⁹⁰Y) in solid plaques, and low-energy photon emitters iodine-125 (¹²⁵I), palladium-103 (¹⁰³Pd), and cesium-131 (¹³¹Cs) in seeded plaques.⁸⁻¹² Compared with solid plaques, seeded photon plaques can be adjusted to shape the radiation dose to the tumor volume, making them more customizable to tumor shape and dimensions.¹¹ In addition, photon emitting isotopes are further penetrating, so they can be used for tumor apical heights higher than 6 mm, which is typically the limit of beta electron plaques like ¹⁰⁶Ru.^{10,12}

The Collaborative Ocular Melanoma Study (COMS) study is the only randomized clinical trial of episcleral brachytherapy compared with enucleation in the treatment of medium-sized choroidal malignant melanoma, which exclusively used ¹²⁵I and demonstrated noninferiority of episcleral brachytherapy.^{13,14} This trial used COMS plaques and prescribed a dose of 85 Gy to a minimum of 5 mm from the inner sclera or to the tumor apical height if greater than 5 mm. The rate of 5-year local control for brachytherapy was approximately 90%, with an 87.5% globe-preservation rate.¹⁴ However, substantial visual acuity (VA) impairment occurred in 43% to 49% of treated eyes at 3 years, likely from radiation retinopathy or neuropathy.¹⁵

We have previously published our experience at Duke University prescribing less than 85 Gy to the tumor apex using COMS plaques. We observed acceptable disease control and decreased ocular morbidity with lower radiation doses to the tumor.¹⁶ In 2016, our team transitioned to Isoaid Eye Physics (EP) ¹²⁵I plaques from COMS plaques, which allowed us to use the 3-dimensional treatment planning software. Here, we describe our treatment planning approach with EP plaques to deliver a minimum of 63 Gy to the tumor apex and to a 2-mm circumferential

margin around the tumor (even if tumor apex is less than 5 mm) and report the preliminary oncological and visual outcomes.

Methods and Materials

This study is a retrospective review of all adult patients (>18) treated with ¹²⁵I brachytherapy with EP plaques for uveal melanoma from November 2016 to February 2019. This study was approved by the institutional review board of Duke University Medical Center (Pro00034058). Patients were identified for potential inclusion through the Duke Tumor Registry and the Duke Radiation Oncology Database. They were excluded if they had metastatic disease at presentation or if they had multiple uveal melanomas, which were previously reported in a case series by Kheir et al.¹⁷ Relevant information consisting of patient demographics, tumor characteristics, treatment data, eye plaque characteristics, oncologic outcomes (local control and distant metastasis), VA, and radiation-related toxicity data were abstracted from the electronic medical record (Maestro/EPIC and ARIA RadONC).

Planning and treatment

All patients had uveal melanoma and were treated by a single ocular oncology trained ophthalmologist (M.A.M.). Circular, notched and semielliptical EP plaques with diameters of 15, 20, and 23 mm were used. They were obtained preloaded with ¹²⁵I seeds and presterilized from Isoaid LLC (Port Richey, FL). Our medical physics team established a planning protocol using the plaque simulator (PS) treatment planning system and information about the size and location of the tumor provided by the ocular oncologist. For each patient, the ocular oncologist provided a sketch of the tumor on an azimuthal equidistant projection fundus diagram. The ocular oncologist also provided a numerical ellipsoidal approximation of the base dimensions of the tumor and an approximation of the distance from the tumor edge to both the nearest edge of the optic nerve sheath and to the foveola. The tumor apex was clinically determined using ultrasound and was also provided to the radiation oncologist (D.G.K) and medical physics team. Based on the anatomic location of the tumor and tumor size, the size and shape of the plaque were selected for adequate coverage of the tumor and to facilitate the placement

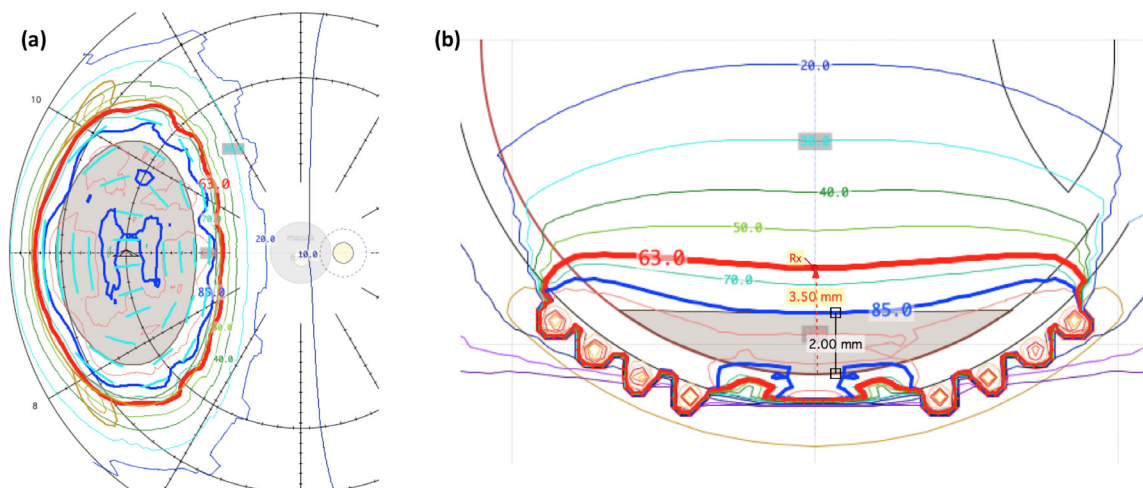


Fig. 1 Isodose lines on the inner sclera (a) and through a cross section of the eye (b) showing the deeper planning apex of 3.5 mm necessary for the 63 Gy isodose line to cover the tumor base + 2-mm circumferential margin. Isodose plots from Plaque Simulator version 6.7.1.

of the plaque over the tumor. In some cases, plaques were fully loaded with ^{125}I seeds and in other clinical scenarios a larger plaque size than required to cover the tumor was selected to facilitate placement of the plaque or suturing and only the posterior dwell positions were loaded with ^{125}I seeds (posterior loading).

The information from the fundus diagram was transferred into PS such that the tumor was represented with an ellipsoidal base dimension with the correct tumor apex and was placed on the appropriate position on the PS fundus diagram. An expansion of 2 mm on all sides was applied to the base dimensions of the tumor. No expansion was applied to the tumor apex depth. Unless otherwise indicated, seed strength was calculated to deliver a standard prescription of 63 Gy to cover a 2-mm circumferential tumor margin and the apex height of the tumor over 94 hours. In the COMS trial, 85 Gy was prescribed to a minimum of 5 mm or to the apex height of the tumor if it was greater than 5 mm.¹⁴ In our institutional experience using COMS plaques, we did not observe a difference in local control or metastasis when the prescription to the tumor apex varied from <69 Gy to >89 Gy.¹⁶ It is noteworthy that the silastic carrier and other physical properties in the COMS plaques decrease the prescribed dose by 10% to 15% relative to EP plaques.¹⁸ Therefore, the physical radiation dose delivered with a COMS plaque prescribed to 85 Gy may only be 72.25 to 76.5 Gy. Given this difference between the prescribed dose and the physically delivered dose with COMS plaques and our outcome data indicating adequate local control when prescribing 70 Gy to the tumor apex with COMS plaques,¹⁶ we selected a dose of 63 Gy for EP plaque prescription because these plaques lack a silastic carrier and would deliver a physical dose equivalent to a COMS plaque prescribed with a dose of 70 Gy or more to the tumor apex.

A prescription point referred to as the “planning height” was chosen to calculate the seed strengths. This point was chosen such that the tumor base with predetermined 2-mm margins received approximately 100% coverage of the prescribed 63 Gy unless a location close to the optic nerve prevented full coverage. If prescribing to the tumor apex was sufficient to obtain base + 2-mm margin coverage of 63 Gy, then the prescription height would equal the tumor apex height, even if it was less than 5 mm (Fig 1). In some cases, such as for shallow tumors, when using smaller plaques or when the tumor was near the optic nerve, a prescription height greater than the tumor apex was used to achieve full or improved base coverage with the 63 Gy isodose line. Figure 1 shows the isodose lines on the inner sclera (a) and through a cross section of the eye (b) for a 20-mm circular fully loaded plaque treating a tumor with an ellipsoidal approximated base dimension of 13 by 13 mm and a tumor apex of 2.0 mm. To obtain full coverage of base + 2 mm margin, a prescription height of 3.5 mm was required. Figure 2 shows isodose lines on the inner sclera (a) and through a cross section of the eye (b) for a 20-mm circular fully loaded plaque treating a tumor with an ellipsoidal approximated base dimension of 14 by 14 mm and a tumor apex of 4.2 mm. In this case, the prescription height was equal to the tumor apex height, with a prescription dose of 63 Gy.

At the time of plaque insertion, preplanning and seed number verification were performed by both the surgical and radiation oncology teams. Tumor localization was performed via direct visualization and marking of tumor meridian or by transillumination marking the tumor’s shadow. A dummy plaque was then positioned to ensure proper tumor coverage. When possible, a transscleral or transvitreal fine needle aspiration biopsy was performed for gene expression profile (GEP) and preferentially

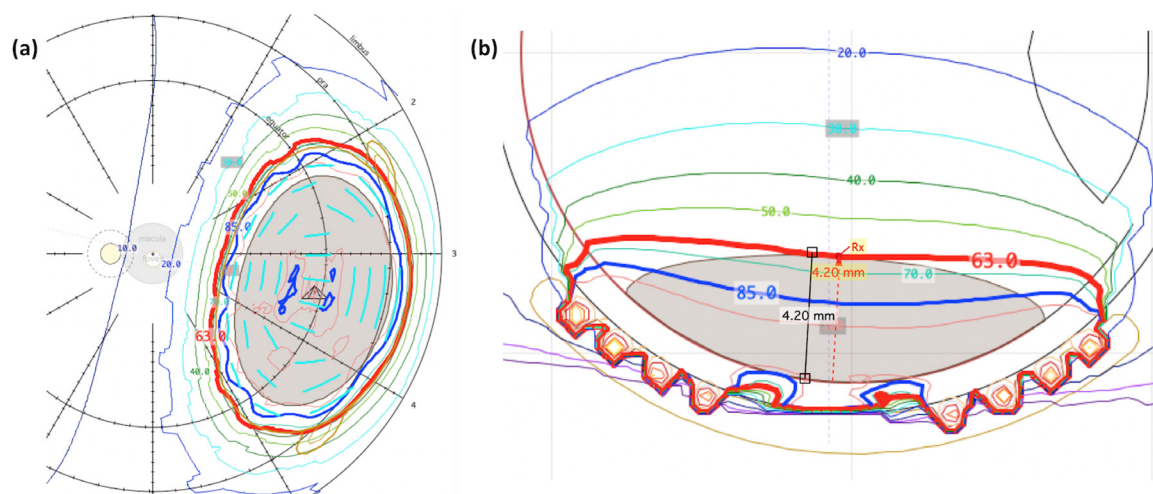


Fig. 2 Isodose lines on the inner sclera (a) and through a cross section of the eye (b) showing a planning apex of 4.2 mm, equal to tumor apex height with the 63 Gy isodose line covering the tumor base + 2-mm circumferential margin. Isodose plots from Plaques Simulator version 6.7.1.

expressed antigen in melanoma (PRAME) analysis before radioactive plaque suturing. After a predetermined plaque dwell time (around 94 hours), the plaques were removed in the operating room. The correct number of seeds was verified by both the surgical and radiation oncology teams. Radiation retinopathy prophylaxis at plaque removal was typically given in the form of intravitreal bevacizumab. Adjuvant transpupillary thermotherapy (TTT) was applied to amenable tumors (thickness <5 mm and more posterior location).

Postoperatively, patients were seen 1-day and 1-month post plaque removal. They were fully examined every 4 months in the first 2 years and every 6 months thereafter. Examinations included VA testing, fundus examination, fundus photography, and standardized echography. Screening for metastasis was performed at least yearly and every 3 to 6 months for patients with class 2 GEP or 1B designation or PRAME positivity, as these molecular features confer a higher risk for metastasis.^{19,20}

Endpoints and statistical analysis

The primary endpoints of the study were local failure, systemic metastasis, final VA (logMAR), and radiation retinopathy. Local failure was defined as regrowth after an initial period of tumor regression requiring TTT or enucleation secondary to tumor growth. Secondary endpoints included months from treatment to metastasis, months from treatment to local failure, local failure treatment, cataract development, and radiation retinopathy treatment. Descriptive statistics were performed for multiple continuous and categorical variables including but not limited to patient characteristics and vital status, radiation doses, tumor characteristics, VA outcomes, and local failure outcomes.

Categories were created for several continuous variables, including delivered tumor apex dose (≤ 7067 , >7067 to ≤ 8438 , >8438 to $\leq 10,060$, and $>10,060$ cGy), prescribed dose to the apex planning height (≤ 6263 , >6263 to ≤ 6319 , >6319 to ≤ 6409 , and >6409 cGy), largest basal diameter (≤ 9 , >9 -11, >11 -14, and >14 mm), and tumor height/thickness (≤ 2.6 , >2.6 -3.5, >3.5 -4.9, and >4.9 mm). Then, the significance of the difference among categories for each variable and categories of GEP (class 1A, class 1B, class 2) for the primary endpoints (systemic metastasis, local treatment failure, radiation retinopathy, and final VA) were assessed using Fisher's exact test. The significance of the difference between those with and without metastasis or local failure for continuous variables was assessed using the Wilcoxon rank sum test. The relationship between tumor thickness and final VA (logMAR) was examined using linear regression.

The data analysis for this article was generated using SAS/STAT software, version 9.4 of the SAS System for Windows (SAS Institute, Inc). An alpha-level of 0.05 was used to declare significance.

Results

Sixty-nine cases of uveal melanoma were treated with EP plaques from November 2016 to February 2019. The average age of patients was 63.5 years (range, 19-87; median, 65), and 52.2% (36 of 69) were male. All patients treated were white, and 1 was of Hispanic ethnicity.

Tumor characteristics are described in Table 1. The average largest basal diameter treated was 11.67 mm (range, 6-18; median, 12), and average tumor thickness to inner sclera was 3.18 mm (range, 0.5-9.3; median, 2.8). Most tumors were located in the posterior pole (42 of 69,

Table 1 Tumor characteristics

Variable	Statistic	Value
Tumor largest base diameter (mm)	n	69
	Mean (SD)	11.67 (2.98)
	Min, median, max	6.0, 12.0, 18.0
Tumor thickness (to inner sclera, mm)	n	69
	Mean (SD)	3.18 (2.02)
	Min, median, max	0.5, 2.8, 9.3
Distance from fovea (mm)	n	64
	Mean (SD)	5.13 (4.43)
	Min, median, max	0.0, 3.8, 17.0
Distance from optic nerve (mm)	n	64
	Mean (SD)	5.69 (4.37)
	Min, median, max	0.0, 4.5, 17.0
Tumor location	n (%)	
• Iris		1 (2)
• Ciliary body		3 (4)
• Ora to equator		23 (33)
• Posterior to the equator not involving the macula		30 (44)
• Posterior to the equator involving macula		12 (17)
Melanocytic	n (%)	
• No		6 (9)
• Yes		61 (90)
• Unsure		1 (1)
Bruch's membrane breakthrough	n (%)	5 (8)
Vitreous hemorrhage	n (%)	3 (4)
Subretinal fluid at diagnosis		
• No		15 (22)
• Yes (by ocular coherence tomography)		11 (16)
• Yes (grossly)		41 (61)
Extrascleral involvement	n (%)	
• No		68 (99)
• Yes		1 (1)
• Unsure		0
Lipofuscin	n (%)	
• No		36 (56)
• Yes		25 (39)
• Unsure		3 (5)
Drusen/Retinal pigment epithelium changes	n (%)	42 (66)
Gene expression profile	n (%)	59
• Class 1A		22 (37)
• Class 1B		15 (25)
• Class 2		16 (27)
• Failure to amplify		6 (10)

(continued on next page)

Table 1 (Continued)

Variable	Statistic	Value
Preferentially expressed antigen in melanoma	n (%)	50
• Negative		32 (64)
• Positive		17 (34)
• Failure to amplify		1 (2)

Abbreviation: SD = standard deviation.

61%), with 17% (12 of 69) involving the macula, and 90% (61 of 69) were melanocytic. Subretinal fluid was present grossly in 61% (41 of 69) of cases, but could be detected only by ocular coherence tomography in 16% (11 of 69). Around 39% (25 of 69) had lipofuscin and 66% (42 of 69) had drusen or retinal pigment epithelial changes on examination. With respect to molecular testing, out of the 59 samples taken for GEP analysis, 37% (22 of 59) were class 1A, 25% (15 of 59) were class 1B, and 27% (16 of 59) were class 2. Out of 50 samples sent for PRAME analysis, 64% (32 of 50) were negative, and 34% (17 of 50) were positive.

Regarding treatment doses (Table 2), the average dose delivered to the planning height was 6343 cGy (range,

6085-7420; median, 6319), and the average dose delivered to the tumor apex was 8897 cGy (range, 6096-15170; median, 8438). The average prescription height was 4.6 mm measured from the inner sclera (range, 2-9.3; median, 4), which is higher than the average tumor thickness (3.18 mm). For tumors with short apex heights (Fig 1), a prescription height greater than the apex height was often chosen to obtain full coverage of the 63 Gy isodose line with the EP plaques of the tumor base + 2-mm circumferential margin of the tumor. In fact, the prescribed dose and apex dose were the same in only 15 of 69 treatments (22%) (Fig 2). In this subset of cases the average dose delivered to the tumor apex was 6331 cGy (range, 6096-6668; median, 6300), and the average

Table 2 Treatment characteristics

Variable	Statistic	Value
Height to prescription (mm)	n	69
	Mean (SD)	4.57 (1.56)
	Min, median, max	2.0, 4.0, 9.3
Prescription dose (cGy)	n	69
	Mean (SD)	6343 (175.0)
	Min, median, max	6085, 6319, 7420
Apex dose (cGy)	n	69
	Mean (SD)	8897 (2286)
	Min, median, max	6096, 8438, 15170
Prescription dose and apex dose are the same	n (%)	15 (22)
5-mm dose (cGy)	n	69
	Mean (SD)	5986 (2062)
	Min, median, max	3059; 5275; 13,150
Inner sclera dose (cGy)	n	69
	Mean (SD)	14,572 (5504)
	Min, median, max	7682; 12,870; 32,970
Outer sclera dose (cGy)	n	69
	Mean (SD)	15,972 (23,651)
	Min, median, max	0.0; 4468; 84,930

Abbreviation: SD = standard deviation.

Table 3 Local failure, metastasis, and treatment outcomes

Variable	Statistic	Value
Months of follow-up	n	69
	Mean (SD)	28.32 (9.96)
	Min, median, max	4.0, 29.0, 46.0
Local failure	n (%)	
• No		64 (94)
• Yes		4 (6)
Initial management of local failure	n (%)	
• Transpupillary thermotherapy		1
• Enucleation		3
Eye salvage	n (%)	
• No (enucleation)		4 (6)
• Yes		65 (94)
Reason for enucleation	n (%)	
• Neovascular glaucoma		0
• Local recurrence		4
Months from treatment to local failure	n	4
	Mean (SD)	26.25 (7.68)
	Min, median, max	18.0, 25.5, 36.0
Adjuvant transpupillary thermotherapy (for prophylaxis, not treatment)	n	39
	Mean (SD)	1.72 (0.72)
	Min, median, max	1.0, 2.0, 3.0
Metastasis	n (%)	
• No		65 (94)
• Yes		4 (6)
Months from treatment to metastasis	n	4
	Mean (SD)	20.00 (8.21)
	Min, median, max	12.0, 18.5, 31.0
Currently alive	n (%)	66 (97)
Death due to ocular melanoma metastasis	n (%)	0

Abbreviation: SD = standard deviation.

prescription height was 5.6 mm measured from the inner sclera (range, 2.8-9.3; median, 5.3).

Treatment outcomes and patient vital status are summarized in Table 3. Patients were followed for 28.3 months on average (range, 4-46; median, 29). In this cohort of patients, and during this initial follow-up period, most patients showed clinical response as measured by decreasing tumor basal diameter and height (Fig E1). However, 4 (6%) had local failure (Table E1). These local recurrences were treated initially with enucleation in 3 eyes and TTT in 1 eye, but the TTT failed and that eye was eventually enucleated. There were no eyes enucleated due to radiation side effects. Time from treatment to local failure was on

average 26.3 months (range, 18-36; median, 25.5). Four patients (6%) developed metastasis, all of which had a GEP of class 2. The average time from treatment to metastasis was 20 months (range, 12-31; median, 18.5). Only 1 patient had both local failure and metastasis, with metastasis preceding local failure by 11 months. Sixty-six patients (97%) are currently alive, and no deaths occurred due to melanoma metastasis.

With respect to visual outcomes (Table 4), average final VA (0.57 logMAR [Snellen 20/74]; range, 0-2.9; median, 0.3) was worse than baseline (0.34 logMAR [Snellen 20/44]; range, 0-2.3; median, 0.1). Cataract development occurred in 5 of the 54 phakic patients (9.3%). Seventy-six percent (52 of 69) received posttreatment

Table 4 Visual outcomes and radiation side effects

Variable	Statistic	Value
Baseline visual acuity (logMAR)	n	69
	Mean (SD)	0.34 (0.49)
	Min, median, max	0.0, 0.1, 2.3
Final visual acuity (logMAR)	n	66
	Mean (SD)	0.57 (0.65)
	Min, median, max	0.0, 0.3, 2.9
Cataract development	n (%)	
• No		49 (72)
• Yes		5 (7)
• Initially pseudophakic		14 (21)
Posttreatment radiation retinopathy prophylaxis	n (%)	52 (76)
Number injections for prophylaxis	n	52
	Mean (SD)	1.83 (1.12)
	Min, median, max	1.0, 1.0, 6.0
Radiation retinopathy	n (%)	
• No		31 (45)
• Yes		33 (48)
• Other variables		5 (7)
Months from treatment to radiation retinopathy	n	22
	Mean (SD)	14.45 (5.87)
	Min, median, max	3.0, 14.0, 24.0
Treatment for radiation retinopathy	n (%)	14 (21)
Number injections for treatment	n	14
	Mean (SD)	3.07 (2.23)
	Min, median, max	1.0, 3.0, 8.0
Duration of treatment with injections (months)	n	14
	Mean (SD)	5.07 (5.55)
	Min, median, max	1.0, 3.0, 20.0
Intravitreal injections (treatment or prophylaxis)	n (%)	59 (86)
Anti-vascular endothelial growth factor injection	n	59
• Intravitreal Avastin	n (%)	59 (100)
• Intravitreal aflibercept	n (%)	3 (5)
• Intravitreal triamcinolone	n (%)	1 (2)
Scatter laser (treatment or prophylaxis)	n (%)	11 (16)
Subtenon steroids	n (%)	1 (1)

Abbreviation: SD = standard deviation.

radiation retinopathy prophylaxis in the form of intravitreal bevacizumab. On average, patients received 1.8 injections (range, 1-6; median, 1) for prophylaxis. Around 48% (33 of 69) developed radiation retinopathy, which was defined at our center as changes on ocular coherence tomography of the macula associated with a drop in best corrected VA. Radiation retinopathy occurred at an

average of 14.5 months after treatment (range, 3-24; mean, 14). Fourteen patients required treatment for radiation retinopathy in the form of intravitreal injections and required a mean of 3 injections (range, 1-8; median, 3) over an average 5 months duration (range, 1-20; median, 3). A list of interventions for both treatment and prophylaxis is listed in [Table 4](#).

On comparison of different categories of variables to our main endpoint measures (Tables E2–E4), there was no statistically significant difference in radiation dose to tumor apex, tumor height, distance to optic nerve head, or PRAME positivity between the patients who developed metastasis and those who did not. There was a trend that approached statistical significance ($P = .056$) for patients with metastasis to have tumors with a largest basal diameter greater than 11 mm, and the average largest basal diameter was significantly higher in patients who developed metastasis (14.8 mm) versus those who did not (11.1 mm) ($P = .021$). The other variable that met our criteria for statistical significance ($P < .05$) in the group that developed metastasis was class 2 GEP ($P = .017$) (Tables E3 and E4). Regarding local failure, there was no significant difference between groups found in any of the mentioned variables.

There was no relation between tumor apex radiation dose and final VA or the development of radiation retinopathy. However, patients treated with higher doses at 5 mm were more likely to have worse visual outcomes. Patients who developed radiation retinopathy had tumors that were located, on average, closer to the fovea (3.10 vs 7.36 mm; $P = .001$) and optic nerve (3.84 vs 7.97 mm; $P < .001$) (Table E5). Moreover, in patients who developed radiation retinopathy the average radiation dose was higher to the fovea (5401 vs 2907 cGy; $P = .004$) and optic nerve (2830 vs 1739 cGy; $P = .004$) (Table E5). There was a significant difference in final vision among the defined tumor thickness categories and according to the radiation dose at 5-mm height. The relationship between tumor thickness and final VA (logMAR) was assessed using linear regression (Fig E2A). As the largest height/thickness increased by 1 mm, vision acuity in logMAR units increased by 0.1384 logMAR units ($P < .001$). An increase in logMAR indicates a decrease in vision (logMAR of 0 = 20/20 vision in Snellen). However, the adjusted *r*-squared value was 0.198, indicating that 20% of the variation in final VA was explained by the tumor thickness. Regarding the relationship between 5-mm dose and final VA, for each 1 Gy increase in 5-mm dose, logMAR final VA increased by 0.000154 units, corresponding to a decrease in final VA. The adjusted *r*-squared value was 0.239, indicating that 24% of the variation in final VA was explained by the 5-mm dose (Fig E2B).

Discussion

We present the preliminary results of a retrospective analysis of a series of 69 patients with uveal melanoma treated with low-dose brachytherapy using EP ^{125}I plaques. Using our planning protocol with a goal to deliver a physical dose of 63 Gy to a 2-mm circumferential margin around the tumor and at least 63 Gy to the tumor apex, the rate of local failure (6%) and distant metastasis (6%)

were within a comparable range to those reported in the COMS trial.^{14,21} The mean follow-up time in this study was around 28 months (median, 29). For comparison, in the COMS trial brachytherapy arm after 25 to 30 months the local treatment failure cumulative percentage was 6.6%.¹⁴ In the COMS trial, the 2-year metastasis rate was 10%²¹ and mortality was around 2.9%.²² Within the follow-up period, we observed no deaths due to melanoma metastasis in our cohort.

In the 4 patients who developed metastasis, all of the tumors had a largest base diameter >11 mm and a GEP class 2 designation. This is consistent with the results of a study by Demirci et al,²³ which showed worse prognosis for class 2 tumors with largest base diameter ≥ 12 mm. Interestingly, we observed no statistically significant difference in PRAME expression in tumors that developed metastasis, which may be related to the relatively small cohort, the relatively short duration of follow-up, or to the role of PRAME expression in prognostication for metastasis in class 1 tumors,²⁰ which have not metastasized thus far. These results suggest that the development of metastasis is related to intrinsic clinical and biological differences in these tumors rather than failure of brachytherapy. Taken together, these results suggest that when using EP plaques, prescribing a treatment dose of 63 Gy as done using our planning protocol does not promote treatment failure from metastasis.

Compared with the COMS trial, the distribution of the initial VA at presentation was similar, with 70% of patients with VA of 20/40 or better (equal to COMS) and 7% with VA of 20/200 or worse (vs 10%). In contrast, the postbrachytherapy VA distribution was better than in the COMS trial. We observed 50% of patients with VA 20/40 or better (vs 34% in COMS) and 22% with VA 20/200 or worse (vs 45% in COMS), the latter including enucleated eyes. The average drop in vision in our study was between 2 to 3 lines, despite 48% of eyes developing radiation retinopathy. This may be due to our high rate of retinopathy prophylaxis (76%) and our low threshold for treatment with anti-vascular endothelial growth factor injections. Regarding enucleation, all 4 cases reported in our study were due to local failure, and no enucleations were performed due to blind, painful eyes. In contrast, 40% of eyes enucleated in COMS at 5 years were due to pain and/or low VA.¹⁴ However, most of the enucleations for painful eyes in the COMS study occurred >3 years after treatment, so it is possible that with longer follow-up some of our patients may also develop pain in the treated eye.

Our preliminary results suggest that treating uveal melanoma with a lower treatment dose is safe and may lead to improved visual outcome and eye salvage. This supports our experience at Duke University Medical Center with COMS plaques. Radiation doses less than 85 Gy, prescribed to the tumor apex only rather than a minimum of 5 mm, resulted in acceptable disease control and decreased ocular morbidity.^{16,24} In 2014, Perez et al published the

findings of a retrospective study of 190 patients treated for uveal melanoma with prescribed ^{125}I brachytherapy at doses ranging from 63 to 85 Gy to tumor apex. In this analysis, no effect on tumor control outcomes was observed with lower prescription doses. Increasing tumor apex doses were associated with worsened VA and radiation side effects.¹⁶ In 2017, Oellers et al published a retrospective interventional case series comparing low (67.5–81 Gy) versus high dose (>84.35 Gy) treatment in juxtapapillary choroidal melanoma. Local and distant failure rates were comparable between these groups, with decreased radiation toxicity in the low dose group.²⁴

Several other investigators have also published their experiences with dose de-escalation in the treatment of uveal melanoma.^{25–29} Sacconn et al²⁶ reported on 62 patients with uveal melanoma treated with apex doses of 56 to 69 Gy using ^{125}I COMS plaques. They had comparable survival and local failure outcomes to COMS with better VA at 5 years. Naseripour et al²⁷ found similar results with less than recommended apex radiation dose using ^{106}Ru plaque brachytherapy. Dose de-escalation using proton beam²⁵ and gamma knife²⁸ radiation therapy have also been studied with similar success. In a randomized, double-masked trial, Gragoudas et al²⁵ treated 188 choroidal melanomas with proton beam therapy at either 50 or 70 cobalt gray equivalent. Although the local failure and metastatic outcomes in both groups were similar, the lower dose group had better preserved visual field but no difference in the loss of VA. A retrospective review of 15 studies on uveal melanoma treatment by Echeagaray et al²⁹ found no statistically significant difference in local recurrence rate with varying apex radiation doses (62.5–104 Gy).

In 2016, we switched to EP plaques exclusively at our center. Advantages for the EP plaques include a greater variety of plaque shapes and sizes, which when used with the EP software and our planning protocol, allowed us to design 3-dimensional brachytherapy plans to customize treatment to the tumor and its margins. Marwaha et al³⁰ reported on a type of EP plaque (EP917) that uses fewer radiation seeds on average with less radiation exposure to the optic disc and macula while maintaining a therapeutic dose to the tumor. Other studies have reported no difference in outcomes using EP plaques compared with COMS plaques,^{31,32} suggesting that the choice of plaque can be made based on cost or surgeon preference.³² It is worth emphasizing that key differences between COMS and EP plaques preclude a comparison of outcomes based on prescribed radiation doses. It is estimated that the silastic insert in which the ^{125}I seeds are loaded in COMS plaques attenuates around 10% of the prescribed dose.¹⁸ Therefore, to deliver a physical radiation dose to a uveal melanoma with an EP plaque that is similar to the physical dose delivered with a COMS plaque, the radiation prescription should be reduced by at least 10%.

Our study has several limitations that include the retrospective design, a relatively small patient cohort,

and a short follow-up. Therefore, these results are preliminary and additional follow-up is needed to show that this treatment approach provides durable local control similar to the COMS trial. Despite allowing almost 2 years for posttreatment follow-up, some patients were lost to follow-up or elected to receive their continuation of care elsewhere. As we are a large referral center, many patients travel from long distances to reach our clinic and choose to have some or all of their postbrachytherapy care closer to home. However, these patients are generally referred back to our center when there is a suspicion of local failure or metastasis. The COVID-19 pandemic may have also prevented some patients from presenting for their scheduled follow-up appointments due to travel restrictions or general health concerns. It is conceivable that 1 of these patients had an unrecorded local recurrence or distant metastasis. In addition, our satisfactory VA outcomes may be due to a shorter follow-up time in comparison to the COMS trial, as late radiation side effects can occur 3 years or more after treatment.

Conclusion

In this retrospective study of 69 patients with uveal melanoma treated with episcleral ^{125}I EP plaque brachytherapy with 3-dimensional treatment planning to deliver a minimum of 63 Gy to the tumor with a 2-mm circumferential margin at the base, our initial local failure and metastasis rates were similar to the outcomes in the COMS study. Using our treatment protocol, lower prescription doses do not necessarily correspond to lower tumor apex doses for short tumors, but assure a minimum of 63 Gy is delivered to the tumor apex. We also observed improved VA and eye salvage outcomes compared with the outcomes in the COMS study, which are important patient factors in choosing plaque brachytherapy over enucleation. This is especially true when the unaffected eye has poor vision or is threatened by another ocular condition. We will follow this patient cohort over the next few years to present more mature outcomes with longer follow-up time. In the meantime, these preliminary results support testing our treatment approach in a multicenter, randomized trial, in which uveal melanomas are treated with the EP plaque at higher or lower radiation dose prescriptions.

Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.adro.2021.100869](https://doi.org/10.1016/j.adro.2021.100869).

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