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Prophylactic Intravitreal Bevacizumab After Plaque Radiotherapy for Uveal Melanoma: Analysis of Visual Acuity, Tumor Response, and Radiation Complications in 1131 Eyes Based on Patient Age

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Purpose: The aim of this study was to determine the impact of age on radiation complications after plaque radiotherapy and prophylactic intravitreal bevacizumab for uveal melanoma.

Design: Retrospective cohort study.

Methods: Retrospective single-center study of plaque-irradiated uveal melanoma with prophylactic intravitreal bevacizumab at 4-month intervals from July 2000 to January 2018.

Results: Of 1131 eyes in 1131 patients, age was <50 years (n = 231), 50 to 70 years (n = 657), or >70 years (n = 243). Comparison by age category (<50 vs 50–70 vs >70 years) revealed the oldest group presenting with greatest tumor basal diameter (11.3 vs 11.3 vs 12.1 mm, $P = 0.03$) and worst visual acuity (20/40 vs 20/40 vs 20/50, $P = 0.02$). After plaque (mean follow-up 40 vs 42 vs 32 months, $P < 0.001$), radiation complications were most common in the youngest age group, including maculopathy (48% vs 39% vs 28%, $P < 0.001$), extramacular retinopathy (30% vs 25% vs 16%, $P = 0.002$), and papillopathy (21% vs 18% vs 12%, $P = 0.03$). The youngest age group had the highest Kaplan-Meier estimated 48-month cumulative probability for radiation maculopathy (62% vs 46% vs 47%, $P = 0.001$), extramacular retinopathy (36% vs 34% vs 29%, $P = 0.03$), and papillopathy (29% vs 26% vs 22%, $P = 0.13$). On subanalysis, the youngest age group had increased 48-month risk of developing radiation maculopathy when compared with the middle [hazard ratio (HR) = 1.5, $P = 0.001$] and older (HR = 1.6, $P = 0.005$) age groups and increased 48-month risk of developing extramacular radiation retinopathy compared with the older age group (HR = 1.5, $P = 0.04$).

Conclusions: After plaque radiotherapy for uveal melanoma and prophylactic intravitreal bevacizumab at 4-month intervals, patients younger than 50 years old have an increased 48-month risk of radiation maculopathy.

Key Words: age, anti-vascular endothelial growth factor, cystoid macular edema, plaque radiotherapy, radiation retinopathy

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Plaque radiotherapy is the most common treatment modality for uveal melanoma.[1,2] In a study of 638 patients undergoing plaque radiotherapy, the Collaborative Ocular Melanoma Study (COMS) demonstrated Kaplan-Meier estimates of tumor control in 90% and globe salvage in 88% at 5 years.[3] The COMS group also studied long-term mortality outcomes after plaque radiotherapy and showed a 12-year rate of death from uveal melanoma metastasis at 21%.[4] However, radiotherapy of uveal melanoma exposes the surrounding normal ocular tissues to potential radiation-related damage, often resulting in decreased vision.[2–6]

Several studies have previously examined visual acuity outcomes after plaque radiotherapy.[7–9] In a comprehensive study of 1106 patients with plaque-irradiated uveal melanoma, Shields et al found poor visual acuity (defined as 20/200 or worse) in 34% of patients at 5 years and 68% of patients at 10 years follow-up.[7] In a separate study of 1780 patients with small choroidal melanoma, measuring 3 mm in thickness or less, patients treated with plaque radiotherapy had a 10-year risk of experiencing ≥3 lines of Snellen visual acuity loss in 49%.[10]

More recently, anti-vascular endothelial growth factors (VEGF) have been employed to reduce tumor-related and radiation-related ischemic retinal findings. Shah et al explored the visual benefits of additional prophylactic anti-VEGF (intravitreal bevacizumab) in 292 patients with plaque-irradiated uveal melanoma compared with controls who were initially observed and found (bevacizumab group vs control group) a reduction in the 2 year rate of optical coherence tomography (OCT)-evident macular edema (26% vs 40%, $P = 0.004$), clinically evident radiation maculopathy (16% vs 31%, $P = 0.001$), moderate vision loss (33% vs 57%, $P < 0.001$), and poor visual acuity (Snellen <5/200) (15% vs 28%, $P = 0.004$),[11] suggesting the benefit of prophylactic intravitreal bevacizumab injections for prevention of radiation side effects and maintenance of visual acuity. Herein, we study a larger cohort of 1131 patients over a longer period of time to further evaluate prophylactic bevacizumab after plaque-irradiated uveal melanoma and specifically investigate visual outcomes, tumor response, and radiation complications based on patient age.

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METHODS

A retrospective chart review was performed on all patients with uveal melanoma managed with plaque radiotherapy and additional prophylactic intravitreal bevacizumab (1.25 mg in 0.05 mL) injections at the Ocular Oncology Service (Wills Eye Hospital, Philadelphia, PA) between July 7, 2000 and January 19, 2018. Patients with cystoid macular edema at presentation that required therapeutic intravitreal bevacizumab injections were excluded from analysis. The study was approved by the Wills Eye Hospital Institutional Review Board and was adherent to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants in this study. All patients had comprehensive ophthalmic examination including slit lamp biomicroscopy, indirect ophthalmoscopy, and imaging with fundus photography, ocular ultrasonography, fundus autofluorescence, and optical coherence tomography.

Patients were categorized into 3 age groups including younger (<50 years), middle aged (50–70 years, inclusive), and older (>70 years) patients. Demographic and initial clinical features included patient age, involved eye, race, sex, medical history, ocular history, best-corrected visual acuity, and presenting symptoms. Snellen visual acuity was defined as good (20/20–20/40), intermediate (20/50–20/150), and poor (20/200 and worse). LogMAR visual acuity was recorded and expressed as a Snellen visual acuity equivalent. Recorded tumor features included distance from the optic disc and foveola in millimeters (mm), largest basal diameter (millimeter), thickness (millimeter), presence of Bruch membrane rupture, episcleral sentinel vessels, extraocular extension, anteroposterior location of epicenter, quadrantic location, location of the anterior margin, and configuration. Presence of subretinal fluid was determined by clinical examination and optical coherence tomography. Presence and extent of orange pigmentation over the tumor was determined by funduscopy and autofluorescence imaging. Tumor classification was recorded based on the American Joint Committee on Cancer (AJCC) staging system, 8th edition.[12]

All patients were treated with customized Iodine-125 (I^{125}) plaque radiotherapy. Plaque features included applicator shape, total treatment duration (hours), total dose [centiGray (cGy)] to tumor apex, base, optic disc, foveola, lens, sclera, and opposite retina, and dose rate (cGy/hour) to the tumor apex, base, optic disc, foveola, lens, sclera, and opposite retina.

All patients were counseled on the risks and benefits of intravitral injections and then offered prophylactic intravitreal bevacizumab injections at the time of plaque removal followed by at 4 month intervals for a duration of 2 years. Only patients who consented to prophylactic injections were included in this study to control for this variable between comparison groups. Prophylactic injections were continued at 4-month intervals as long as the ophthalmic examination was unremarkable for clinical features of radiation damage [eg, radiation maculopathy, radiation retinopathy, or cystoid macular edema (CME)]. Once features of radiation damage were detected, patients were offered therapeutic injections. Prophylactic injections were discontinued if the patient refused additional injections or required injection of anti-vascular endothelial growth factor (anti-VEGF) agents for therapeutic treatment of post-radiation complications. The total number of prophylactic injections received by each patient was recorded. Injections given to treat radiation complications (eg, cystoid macular edema) were not considered prophylactic.

Clinical outcomes included final best-corrected visual acuity, total lines of visual acuity loss, final tumor features (basal diameter and thickness), tumor recurrence, interval to recurrence, radiation complications (radiation maculopathy, nonproliferative retinopathy, proliferative retinopathy, papillopathy, cystoid macular edema, retinal vascular occlusion, iris neovascularization, neovascular glaucoma, cataract, and scleral necrosis), and interval to radiation complications. Radiation maculopathy was defined by the presence of retinal microaneurysms, exudation, hemorrhages, and/or nerve fiber layer infarction in the macular region. Radiation retinopathy was defined as similar changes found outside the macular region. Radiation papillopathy was defined by the presence of optic disc congestion, edema, surrounding retinal nerve fiber infarction, or atrophy.

Statistical Analysis

Data were analyzed using SPSS statistics software (version 18 for Windows; SPSS Inc., Chicago, IL). Continuous variables are expressed as mean (median, range). Demographic, clinical, and imaging features were compared by age group (<50 vs 50–70 vs >70 years) using Chi-square test or Fischer exact test for categorical variables and 1-way analysis of variance for continuous variables. Post hoc analysis of continuous variables with Bonferroni test was used to make pairwise comparisons between the age groups. Logistic regression analysis was used to adjust the role of potential confounders on categorical variables. Kaplan-Meier graphs depict the rate of complications after plaque therapy by age group. Hazard ratio (HR) was calculated using Cox regression analysis. A P value <0.05 was considered statistically significant.

RESULTS

There were 1131 eyes in 1131 patients with uveal melanoma. Of these, there were 231 (20%) younger, 657 (58%) middle aged, and 243 (21%) older patients. Demographic features are described in Table 1. A comparison by age category (<50 vs 50–70 vs >70 years) revealed mean age of 40 versus 61 versus 77 years ($P < 0.001$). Fewer younger patients presented with diabetes (5% vs 14% vs 21%, $P < 0.001$), systemic hypertension (16% vs 45% vs 60%, $P < 0.001$), and ocular melanocytosis (2% vs 2% vs 6%, $P < 0.03$). There was no difference in patient race, sex, or other medical and ocular history (Table 1).

Clinical features at presentation are described in Table 2. Comparison by age category revealed that a smaller proportion of younger patients presented with moderate visual acuity (20/50–20/150) (22% vs 22% vs 31%, $P = 0.04$). Presenting mean LogMAR visual acuity (expressed as Snellen visual acuity) was different among the age groups (20/40 vs 20/40 vs 20/50, $P = 0.02$). Post hoc analysis showed better presenting LogMAR visual acuity in the younger compared with the older age group ($P = 0.04$) and the middle aged compared with the older age group ($P = 0.05$). Younger patients presented with more symptoms of decreased visual acuity (40% vs 33% vs 30%, $P < 0.001$) and visual field defect (13% vs 9% vs 5%, $P < 0.001$) with fewer younger patients presenting asymptomatically (26% vs 33% vs 45%, $P < 0.001$). Younger patients were more likely to present with subretinal fluid (83% vs 78% vs 71%, $P = 0.006$) with greater extension beyond the tumor margin (32% vs 22% vs 17%, $P = 0.04$), more likely to have subretinal fluid involvement

TABLE 1. Prophylactic Intravitreal Bevacizumab After Plaque Radiotherapy for Uveal Melanoma: Analysis of Visual Acuity, Tumor Response, and Radiation Complications in 1131 Eyes per Patient Age: Demographic Features

Demographic Features	Age <50 y (n = 231) [n (%)]	Age 50–70 y (n = 657) [n (%)]	Age >70 y (n = 243) [n (%)]	*P* value	Combined (n = 1131) n (%)
Age (years) Mean (median, range)	40 (41, 20–49)	61 (61, 50–70)	77 (76, 71–97)	<0.001	60 (61, 20–97)
Race					
White	218 (94)	631 (96)	232 (95)	0.11	1081 (96)
African American	1 (<1)	1 (<1)	1 (<1)		3 (<1)
Hispanic	7 (3)	8 (1)	5 (2)		20 (2)
Asian	1 (<1)	0 (0)	0 (0)		1 (<1)
Middle Eastern	2 (1)	0 (0)	1 (<1)		3 (<1)
Other/unknown	2 (1)	17 (3)	4 (2)		23 (2)
Sex					
Male	124 (54)	317 (48)	116 (48)	0.32	557 (49)
Female	107 (46)	340 (52)	127 (52)		574 (51)
Medical history					
Dysplastic nevus syndrome	1 (<1)	1 (<1)	2 (1)	0.86	4 (<1)
Skin melanoma	4 (2)	18 (3)	14 (6)	0.67	36 (3)
Diabetes	12 (5)	92 (14)	52 (21)	<0.001	156 (14)
Hypertension	37 (16)	295 (45)	146 (60)	<0.001	478 (42)
Ocular history					
Uveal melanoma (fellow eye)	0 (0)	1 (<1)	0 (0)	0.39	1 (<1)
Conjunctival melanoma	0 (0)	0 (0)	0 (0)	NA	0 (0)
Conjunctival primary acquired melanosis	1 (<1)	1 (<1)	0 (0)	0.81	2 (<1)
Ocular melanocytosis	5 (2)	16 (2)	14 (6)	0.03	35 (3)

TABLE 2. Prophylactic Intravitreal Bevacizumab After Plaque Radiotherapy for Uveal Melanoma: Analysis of Visual Acuity, Tumor Response, and Radiation Complications in 1131 Eyes per Patient Age: Clinical Features

Clinical Features	Age <50 y (n = 231) n (%)	Age 50–70 y (n = 657) n (%)	Age >70 y (n = 243) n (%)	*P* value	Combined (n = 1131) n (%)
Involved eye (n = 1131 patients)					
Right	118 (51)	324 (49)	123 (51)	0.88	565 (50)
Left	113 (49)	333 (51)	120 (49)		566 (50)
Snellen visual acuity (n = 1131 eyes)					
20/20–20/40	162 (70)	466 (71)	146 (60)	0.04	774 (68)
20/50–20/150	51 (22)	141 (22)	74 (31)		266 (24)
20/200 or worse	18 (8)	50 (8)	23 (10)		91 (8)
Visual acuity (Snellen) Mean (median, range)	20/40 (20/25, 20/20-HM)	20/40 (20/30, 20/20-LP)	20/50 (20/40, 20/20-LP)		20/50 (20/30, 20/20-LP)
Visual acuity (LogMAR) Mean (median, range)	0.31 (0.10, 0.00–3.00)	0.33 (0.18, 0.00–4.00)	0.43 (0.30, 0.00–4.00)	0.02	0.35 (0.18, 0.00–4.00)
Symptoms					
Decreased visual acuity	93 (40)	214 (33)	73 (30)	<0.001	380 (34)
Visual field defect	31 (13)	58 (9)	11 (5)		100 (9)
Flashes, floaters	45 (19)	157 (24)	42 (17)		244 (22)
Pain	3 (1)	11 (2)	8 (3)		22 (2)
No symptoms	59 (26)	217 (33)	109 (45)		385 (34)
Tumor Features					
Distance to optic disc, mm Mean (median, range)	4.5 (3.4, 0.0–17.0)	4.6 (3.3, 0.0–20.0)	4.9 (4, 0.0–18.0)	0.58	4.6 (3.5, 0.0–20.0)
Distance to foveola, mm Mean (median, range)	4.1 (3.0, 0.0–19.0)	4.2 (3.0, 0.0–20.0)	4.5 (3.0, 0.0–17.0)	0.53	4.2 (3.0, 0.0–20.0)
Largest base diameter, mm) Mean (median, range)	11.3 (11.0, 2.0–20.0)	11.3 (11.0, 2.5–22.0)	12.1 (12.0, 4.0–20.0)	0.03	11.5 (11.0, 2.0–22.0)
Tumor thickness, mm Mean (median, range)	5.2 (4.5, 1.4–12.3)	4.8 (3.9, 0.9–13.3)	4.7 (3.9, 2.0–13.0)	0.08	4.8 (4.0, 0.9–13.3)
Bruch membrane rupture	27 (12)	70 (11)	21 (9)	0.53	118 (10)
Sentinel vessels	13 (6)	39 (6)	9 (4)	0.41	61 (5)
Extraocular extension	1 (<1)	5 (<1)	4 (2)	0.41	10 (<1)
Tumor epicentre					
Macula	44 (19)	130 (20)	34 (14)	0.30	208 (18)

TABLE 2. (Continued)

Clinical Features	Age <50 y (n = 231) n (%)	Age 50–70 y (n = 657) n (%)	Age >70 y (n = 243) n (%)	*P* value	Combined (n = 1131) n (%)
Macula to equator	139 (60)	410 (62)	165 (68)		714 (63)
Equator to ora	38 (17)	93 (14)	37 (15)		168 (15)
Ciliary body	9 (4)	24 (4)	7 (3)		40 (4)
Iris	1 (<1)	0 (0)	0 (0)		1 (<0.1)
Quadrantic location					
Macula	44 (19)	114 (17)	27 (11)	0.15	185 (16)
Inferior	38 (17)	119 (18)	48 (20)		205 (18)
Temporal	68 (29)	179 (27)	64 (26)		311 (28)
Superior	43 (19)	141 (22)	68 (28)		252 (22)
Nasal	38 (17)	104 (16)	36 (15)		178 (16)
Anterior tumor margin					
Macula	13 (6)	47 (7)	2 (<1)	0.002	62 (6)
Macula to equator	100 (43)	276 (42)	91 (37)		467 (41)
Equator to ora	68 (29)	214 (33)	97 (40)		379 (34)
Ciliary body	49 (21)	120 (18)	53 (22)		222 (20)
Iris	1 (<1)	0 (0)	0 (0)		1 (<1)
Tumor configuration					
Dome	190 (82)	522 (80)	206 (85)	0.38	918 (81)
Mushroom	25 (11)	82 (13)	19 (8)		126 (11)
Plateau	14 (6)	48 (7)	14 (6)		76 (7)
Bilobed or multilobed	2 (<1)	5 (<1)	4 (2)		11 (1)
Subretinal fluid by optical coherence tomography/clinical examination					
Absent	39 (17)	147 (22)	71 (29)	0.006	257 (23)
Present	192 (83)	510 (78)	172 (71)		874 (77)
Extent of subretinal fluid					
Subretinal cap over melanoma	37 (16)	110 (17)	43 (18)	0.04	190 (17)
≤3 mm from tumor margin	54 (23)	194 (30)	68 (28)		316 (28)
3–6 mm from tumor margin	27 (12)	63 (10)	19 (8)		109 (10)
>6 mm from tumor margin	74 (32)	143 (22)	42 (17)		259 (23)
Quadrant of subretinal fluid					
1 Quadrant	112 (49)	344 (52)	119 (49)	0.01	575 (51)
2 Quadrants	48 (21)	116 (18)	44 (18)		208 (18)
3 Quadrants	29 (13)	39 (6)	7 (3)		75 (7)
4 Quadrants	3 (1)	11 (2)	2 (1)		16 (1)
Subfoveal fluid	81 (35)	192 (29)	47 (19)	0.001	320 (28)
Orange pigment by autofluorescence*	n = 200	n = 586	n = 208		N = 994
Absent	71 (36)	213 (36)	68 (33)	0.64	352 (35)
Present	129 (65)	373 (64)	140 (67)		642 (65)
Extent of orange pigment					
<25% of tumor surface	43 (22)	96 (16)	32 (15)	0.42	171 (17)
25%–50% of tumor surface	34 (17)	96 (16)	34 (16)		164 (16)
50%–75% of tumor surface	31 (16)	106 (18)	47 (23)		184 (19)
>75% of tumor surface	21 (11)	75 (13)	27 (11)		123 (12)
AJCC8 classification stage					
I	85 (37)	257 (39)	84 (35)	0.60	426 (38)
IIA	85 (37)	234 (36)	97 (40)		416 (37)
IIB	42 (18)	107 (16)	32 (13)		181 (16)
IIIA	13 (6)	47 (7)	22 (9)		82 (7)
IIIB	6 (3)	10 (2)	8 (3)		24 (2)
IIIC	0 (0)	1 (<1)	0 (0)		1 (<1)
IV	0 (0)	1 (<1)	0 (0)		1 (<1)

*137 patients had incomplete, poor, or no view of tumor with autoflourescence.

Visual acuity (LogMAR): post hoc analysis (Bonferroni test) showed that there was significant difference between group 1 and group 3 ($P = 0.04$) and a weakly significant difference between group 2 & 3 ($P = 0.048$). There was no significant difference between the other groups ($P > 0.05$).

Base diameter: post hoc analysis (Bonferroni test) showed that there was significant difference between group 2 & group 3 ($P = 0.03$). There was no significant difference between the other groups ($P > 0.05$).

of 3 or more quadrants (18%, 8%, 4%, $P < 0.001$), and subretinal fluid extension under the foveola (35% vs 29% vs 19%, $P = 0.001$). There was no difference by age group in tumor laterality, distance to optic disc or foveola, tumor thickness, presence of Bruch membrane rupture, sentinel vessels, or extraocular extension, anteroposterior and quadrantic location of tumor epicenter, tumor configuration, orange pigment presence and extent, and AJCC 8th edition classification.

Treatment features are described in Table 3. A comparison by age category revealed younger patients more likely to receive

TABLE 3. Prophylactic Intravitreal Bevacizumab After Plaque Radiotherapy for Uveal Melanoma: Analysis of Visual Acuity, Tumor Response, and Radiation Complications in 1131 Eyes per Patient Age: Treatment Features

Treatment Features	Age <50 y (n = 231) n (%)	Age 50–70 y (n = 657) n (%)	Age >70 y (n = 243) n (%)	*P* value	Combined (n = 1131) n (%)
Number of prophylactic injections Mean (median, range)	4 (4, 1–6)	4 (5, 1–6)	4 (4, 1–6)	0.03	4 (4, 1–6)
Plaque radiotherapy features					
Total treatment duration, h Mean (median, range)	101 (96, 72–172)	100 (96, 21–173)	101 (97, 92–172)	0.62	101 (96, 21–173)
Plaque shape					
Round	169 (73)	489 (74)	191 (79)	0.69	849 (75)
Notched	49 (21)	134 (20)	42 (17)		225 (20)
Deep notched	13 (6)	34 (5)	10 (4)		57 (5)
Total dose, Gy Mean, median (range)					
Apex	70 (70, 68–80)	70 (70, 35–80)	70 (70, 68–83)	0.44	70 (70, 35–83)
Base	196 (170, 75–475)	184 (155, 46–605)	173 (149, 80–494)	0.02	184 (156, 46–605)
Optic disc	40 (33, 4–217)	38 (29, 4–208)	34 (28, 5–158)	0.04	38 (29, 4–217)
Foveola	62 (40, 5–508)	58 (39, 4–336)	49 (34, 5–217)	0.02	57 (38, 4–508)
Lens	20 (11, 3–97)	19 (11, 2–152)	19 (12, 3–185)	0.63	19 (11, 2–185)
Sclera	196 (169, 74–475)	184 (155, 46–605)	173 (149, 80–494)	0.02	184 (155, 46–605)
Opposite retina	7 (5, 2–37)	7 (5, 1–74)	7 (5, 2–61)	0.83	7 (5, 1–74)
Dose rate, cGy/h Mean (median, range)					
Apex	72 (74, 42–99)	73 (74, 38–95)	72 (74, 42–86)	0.87	72 (74, 38–99)
Base	195 (178, 80–429)	186 (164, 50–485)	173 (157, 74–366)	0.01	185 (164, 50–485)
Optic disc	41 (34, 4–230)	39 (30, 4–219)	35 (29, 5–167)	0.07	38 (39, 4–230)
Foveola	62 (42, 4–374)	59 (40, 2–351)	51 (35, 5–210)	0.04	58 (39, 2–374)
Lens	20 (12, 3–107)	19 (12, 2–133)	18 (13, 4–113)	0.56	19 (12, 2–133)
Sclera	195 (178, 80–429)	185 (164, 50–485)	173 (157, 74–366)	0.01	185 (164, 50–485)
Opposite retina	7 (5, 2–21)	7 (5, 2–73)	6 (5, 2–17)	0.53	7 (5, 2–73)

No. prophylactic injection: post hoc analysis (Bonferroni test) there was a significant difference between group 2 and 3 ($P = 0.04$). There was no significant difference between other groups ($P > 0.05$).

Total dose to base: post hoc analysis (Bonferroni test) there was a significant difference between group 1 and 3 ($P = 0.01$). There was no significant difference between other groups ($P > 0.05$).

Total dose to disc: post hoc analysis (Bonferroni test) there was a significant difference between group 1 and 3 ($P = 0.04$). There was no significant difference between other groups ($P > 0.05$).

Total dose to fovea: post hoc analysis (Bonferroni test) there was a significant difference between group 1 and 3 ($P = 0.02$). There was no significant difference between other groups ($P > 0.05$).

Total dose to sclera: post hoc analysis (Bonferroni test) there was a significant difference between group 1 and 3 ($P = 0.01$). There was no significant difference between other groups ($P > 0.05$).

Dose rate to base: post hoc analysis (Bonferroni test) there was a significant difference between group 1 and 3 ($P = 0.004$). There was no significant difference between other groups ($P > 0.05$).

Dose rate to fovea: post hoc analysis (Bonferroni test) there was a significant difference between group 1 and 3 ($P = 0.045$). There was no significant difference between other groups ($P > 0.05$).

Dose rate to sclera: post hoc analysis (Bonferroni test) there was a significant difference between group 1 and 3 ($P = 0.004$). There was no significant difference between other groups ($P > 0.05$).

recommended bevacizumab injections (4.0 vs 4.2 vs 3.8, $P = 0.03$), with post hoc analysis revealing a greater number of injections received by the middle aged compared with the older age group ($P = 0.04$). Compared with the older age group, the younger age group had a greater total dosage of radiation directed to the tumor base (196 Gy vs 184 Gy vs 173 Gy, $P = 0.02$), optic disc (40 Gy vs 38 Gy vs 34 Gy, $P = 0.04$), foveola (62 Gy vs 58 Gy vs 49 Gy, $P = 0.02$), and sclera (196 Gy vs 184 Gy vs 173 Gy, $P = 0.02$). Younger patients also had higher dose rate to the tumor base (195 cGy/h vs 186 cGy/h vs 173 cGy/h, $P = 0.01$), foveola (62 cGy/h vs 59 cGy/h vs 51 cGy/h, $P = 0.04$), and sclera (195 cGy/hr vs 185 cGy/hr vs 173 cGy/h, $P = 0.01$).

Clinical outcomes are described in Table 4. A comparison by age category revealed a greater follow-up time in both the younger and middle age groups (40 vs 42 vs 32 months, $P < 0.001$). Comparison showed fewer younger and middle age patients with moderate final Snellen visual acuity (20/50–20–150) (22% vs 26% vs 34%, $P = 0.02$). A greater proportion of the younger age group developed radiation complications including radiation maculopathy (48% vs 39% vs 28%, $P < 0.001$), non-proliferative extramacular radiation retinopathy (30% vs 25% vs 16%, $P = 0.002$), radiation papillopathy (21% vs 18% vs 12%, $P = 0.03$), cystoid macular edema (39% vs 38% vs 29%, $P = 0.03$), branch retinal vein occlusion (31% vs 29% vs 19%, $P = 0.03$), and cataract (25% vs 30% vs 20%, $P = 0.004$) (Figs. 1 and 2). After adjusting for potential confounding variables including distance to optic disc and foveola, tumor basal diameter and thickness at presentation, radiation dose to tumor apex, base, and

TABLE 4. Prophylactic Intravitreal Bevacizumab After Plaque Radiotherapy for Uveal Melanoma: Analysis of Visual Acuity, Tumor Response, and Radiation Complications in 1131 Eyes per Patient Age: Clinical Outcomes

Clinical Outcomes	Age <50 y (n = 231) n (%)	Age 50–70 y (n = 657) n (%)	Age >70 y (n = 243) n (%)	*P* value	Combined (n = 1131) n (%)
Follow-up time, mo Mean (median, range)	40 (34, 3–116)	42 (36, 3–117)	32 (26, 3–108)	<0.001	40 (34, 3–117)
Enucleation	3 (1)	8 (1)	4 (1)	0.88	15 (1)
Snellen visual acuity	n = 228	n = 649	n = 239		N = 1116
20/20–20/40	88 (38)	253 (39)	78 (33)	0.02	419 (38)
20/50–20/150	49 (22)	168 (26)	82 (34)		299 (27)
20/200 or worse	91 (40)	228 (35)	79 (33)		398 (36)
Visual acuity (Snellen) Mean (median, range)	20/200 (20/70, 20/20-NLP)	20/200 (20/70, 20/20-NLP)	20/200 (20/60, 20/20-NLP)		20/200 (20/70, 20/20-NLP)
Visual acuity (LogMAR) Mean (median, range)	0.98 (0.54, 0.00–5.00)	1.01 (0.51, 0.00–5.00)	1.10 (0.48, 0.00–5.00)	0.93	1.02 (0.54, 0.00–5.00)
Lines of visual acuity loss at last follow-up date Mean (median, range)	14 (3, 0–14)	4 (2, 0–14)	3 (2, 0–13)	0.14	4 (2, 0–14)
Tumor features					
Basal diameter, mm Mean (median, range)	10 (10, 3–20)	10 (10, 1–20)	11 (11, 4–20)	0.003	10.5 (10.0, 1.0–20.0)
Thickness, mm Mean (median, range)	2.7 (2.1, 1.0–9.5)	2.5 (2.1, 0.5–12.0)	2.9 (2.5, 1.0–9.9)	0.01	2.6 (2.2, 0.5–12.0)
Recurrence of tumor	3 (1)	14 (2)	6 (3)	0.64	23 (2)
Time to recurrence, mo Mean (median, range)	37 (27, 22–61)	28 (20, 4–80)	22 (17, 13–37)	0.55	28 (20, 4–80)
Radiation complications					
Radiation maculopathy	110 (48)	254 (39)	67 (28)	<0.001	431 (38)
Time to radiation maculopathy, mo Mean (median, range)	25 (20, 4–73)	30 (26, 4–114)	28 (26, 4–75)	0.03*	29 (24, 4–114)
Nonproliferative extramacular radiation retinopathy	69 (30)	161 (25)	39 (16)	0.002	269 (24)
Time to nonproliferative extramacular radiation retinopathy, mo Mean (median, range)	26 (20, 4–81)	28 (24, 5–97)	28 (27, 4–71)	0.69	28 (24, 4–97)
Proliferative radiation retinopathy	1 (<1)	6 (1)	0 (0)	0.28	7 (1)
Time to proliferative radiation retinopathy, mo Mean (median, range)	21 (21, 21–21)	36 (39, 3–55)	NA	0.49	33 (36, 3–55)
Radiation papillopathy	48 (21)	120 (18)	29 (12)	0.03	197 (17)
Time to radiation papillopathy, mo Mean (median, range)	27 (24, 4–74)	30 (26, 2–93)	30 (32, 6–60)	0.55	30 (27, 2–93)
Cystoid macular edema	90 (39)	252 (38)	71 (29)	0.03	413 (37)
Time to onset of cystoid macular edema, mo Mean (median, range)	31 (29, 3–96)	26 (21, 3–93)	26 (19, 4–98)	0.06	27 (22, 3–98)
Retinal vessel occlusion					
Branch retinal vein occlusion	71 (31)	192 (29)	47 (19)	0.03	310 (27)
Central retinal vein occlusion	0 (0)	6 (<1)	1 (<1)		7 (<1)
Branch retinal artery occlusion	2 (<1)	5 (<1)	1 (<1)		8 (<1)
Time to retinal vessel occlusion, mo Mean (median, range)	26 (25, 3–72)	29 (24, 3–103)	23 (17, 4–77)	0.08	27 (23, 3–103)
Iris neovascularization	9 (4)	16 (2)	6 (3)	0.49	31 (3)
Time to neovascularization of the iris, mo Mean (median, range)	33 (36, 4–68)	31 (30, 4–66)	35 (39, 4–69)	0.93	33 (33, 4–69)
Neovascular glaucoma	10 (4)	17 (3)	5 (2)	0.29	32 (3)
Time to neovascular glaucoma, mo Mean (median, range)	48 (43, 4–69)	31 (26, 4–60)	43 (45, 13–75)	0.16	38 (34, 4–96)
Cataract	57 (25)	197 (30)	48 (20)	0.01	302 (27)
Time to cataract, mo Mean (median, range)	32 (29, 4–116)	27 (21, 2–138)	19 (17, 3–59)	0.004	27 (21, 2–138)
Scleral necrosis	1 (<1)	9 (1)	2 (<1)	0.45	12 (1)
Time to scleral necrosis, mo Mean (median, range)	33 (33, 33–33)	41 (35, 8–81)	34 (34, 29–39)	0.86	40 (35, 8–81)

After adjusting for tumor base diameter and thickness at presentation, the dose to apex and base, and the follow-up time, the association between age and tumor base diameter at the last follow-up date disappeared ($P = 0.08$) disappeared.

After adjusting for basal diameter and thickness of tumor at presentation, dose to apex and base, and follow-up time, the association between the older age group and larger tumor thickness at last follow-up date was significant ($P = 0.02$).

After adjusting for potential confounding variables including dose to tumor apex, base, and foveola, extension of subretinal fluid, and number prophylactic bevacizumab injections, the association between age and development of radiation maculopathy ($P < 0.001$), nonproliferative radiation retinopathy ($P = 0.001$), and cystoid macular edema ($P = 0.04$). remained significant.

After adjusting for potential confounding variables including tumor basal diameter and thickness, dose to tumor apex, base, foveola, lens, and optic nerve, extension of subretinal fluid, and number prophylactic bevacizumab injections, the association between age and development of radiation papillopathy ($P = 0.06$) and cataract ($P = 0.87$) disappeared.

Follow-up time: Post Hoc analysis (Bonferroni test) showed that there was significant difference between group 1 and group 3 (p = 0.01) and between group 2 and 3 ($P < 0.001$). There was no significant difference between the other groups ($P > 0.05$).

DLS base diameter: post hoc analysis (Bonferroni test) showed that there was significant difference between group 1 and group 3 ($P = 0.02$) and between group 2 and 3 ($P = 0.003$). There was no significant difference between the other groups ($P > 0.05$).

DLS thickness: post hoc analysis (Bonferroni test) showed that there was significant difference between group 2 and group 3 ($P = 0.01$). There was no significant difference between the other groups ($P > 0.05$).

Time to rad mac: post hoc analysis (Bonferroni test) showed that there was significant difference between group 1 and group 2 ($P = 0.03$). There was no significant difference between the other groups ($P > 0.05$).

Time to cataract: Post Hoc analysis (Bonferroni test) showed that there was significant difference between group 1 and group 3 ($P = 0.003$). There was no significant difference between the other groups ($P > 0.05$).

*Estimated time to the development of radiation maculopathy: After adjusting for potential confounders (dose to apex, base, and foveola and thickness of tumor), the association between the younger age group and lower mean time to radiation maculopathy development remained significant ($P = 0.004$, HR = 1.5, 95% CI = 1.1–2.1).

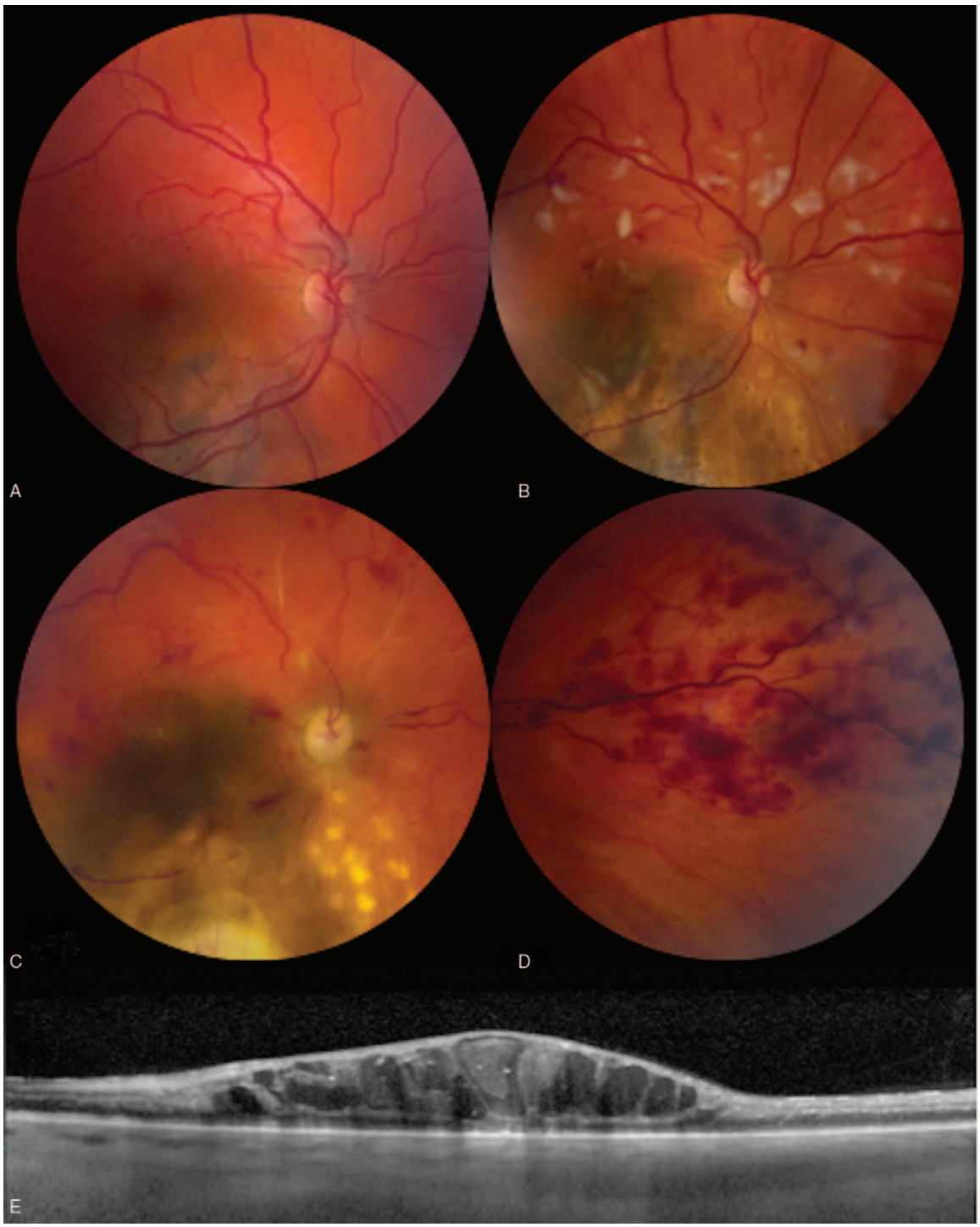

FIGURE 1. Impact of younger age category on radiation complications. (A) A 29-year-old female with uveal melanoma in the right eye, 0.5 mm from the foveola and 2 mm from the optic disc, (B) developed retinal hemorrhages and nerve fiber layer infarctions 9 months after plaque radiotherapy. (C) At 48 months, radiation-related optic atrophy and vascular sclerosis, (D) sectoral peripheral retinal hemorrhages, and (E) optical coherence tomography-evident cystoid macular edema were noted.

foveola, extent of subretinal fluid, and number of prophylactic bevacizumab injections using logistic regression analysis, the association between age and radiation maculopathy ($P < 0.001$), nonproliferative extramacular radiation retinopathy ($P = 0.001$), and cystoid macular edema ($P = 0.04$) remained significant, but the associations between age and radiation papillopathy ($P = 0.06$) and cataract ($P = 0.87$) were nonsignificant. The younger patients had the shortest time to onset of radiation maculopathy (25 vs 30 vs 28 months, $P = 0.03$) and longest time to cataract development (32 vs 21 vs 17 months, $P = 0.03$). There was no difference by age group in need for enucleation, lines of visual acuity lost at last follow-up, and presence of (and interval to) tumor recurrence, proliferative radiation retinopathy, iris neovascularization, neovascular glaucoma, and scleral necrosis.

Figure 3 depicts the 48-month Kaplan-Meier estimates of radiation maculopathy, radiation retinopathy, radiation papillopathy, cystoid macular edema, and poor visual acuity. Comparing younger versus middle aged versus older age groups, the younger

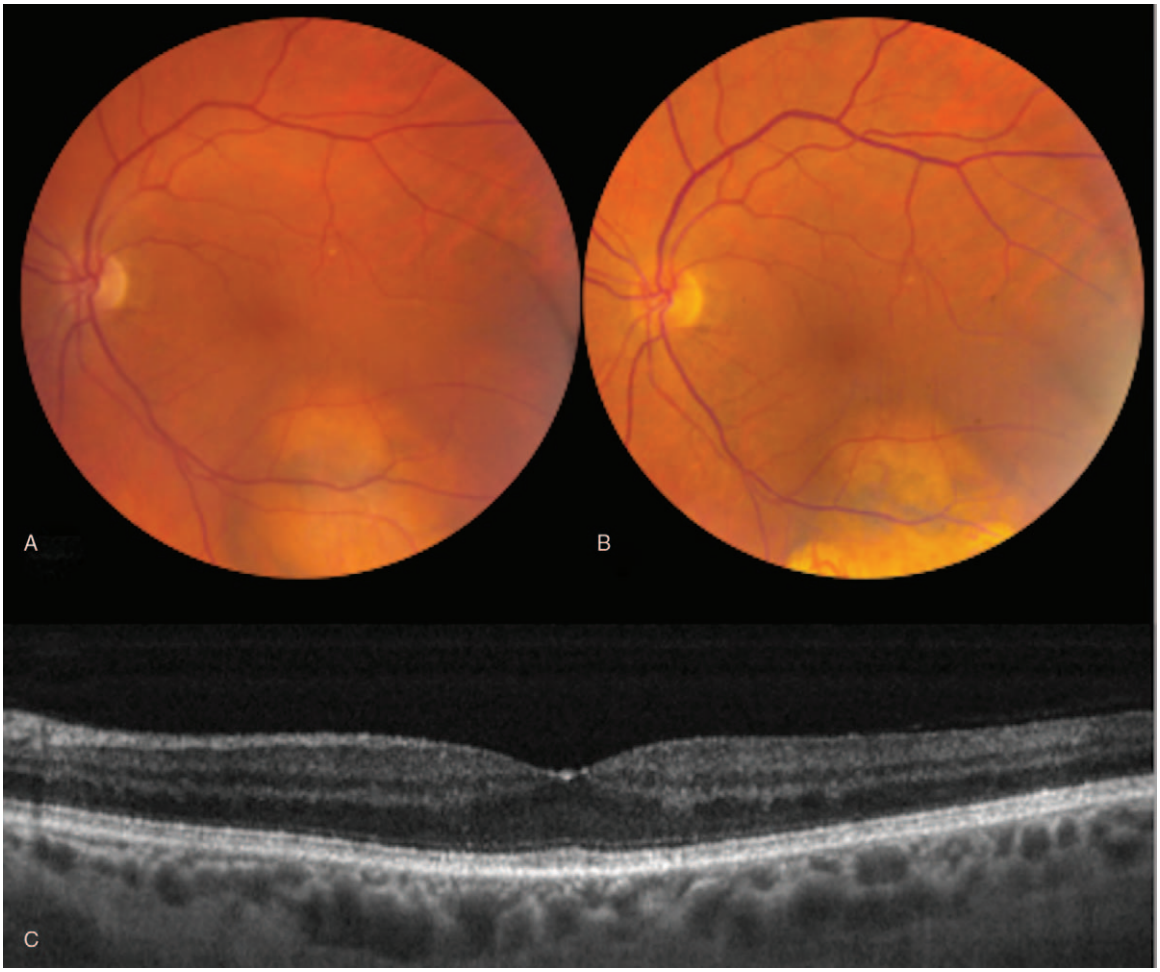

FIGURE 2. Impact of older age category on radiation complications. (A) A 73-year-old male with uveal melanoma in the left eye, 1 mm from the foveola and 4 mm from the optic disc, (B) remained free of clinically evident radiation complications, and (C) optical coherence tomography-evident cystoid macular edema at 48 months following plaque radiotherapy.

age group showed a higher 48-month probability of radiation maculopathy (62% vs 46% vs 47%, $P = 0.001$) and extra-macular radiation retinopathy (36% vs 34% vs 29%, $P = 0.03$). After adjusting for tumor base at presentation, location of tumor anterior margin, distance of plaque from macula, number of prophylactic intravitreal injections, and length of follow-up, Cox regression analysis showed that the 48-month HR for the development of radiation maculopathy between younger versus middle-aged was 1.5 ($P = 0.001$), younger versus older was 1.6, ($P = 0.005$), and middle-aged versus older was 1.2 ($P = 0.31$). After adjusting for tumor base at presentation and number of prophylactic injections, the 48-month HR for radiation retinopathy between younger versus middle-aged patients was 1.2 ($P = 0.17$), younger versus older patients was 1.5 ($P = 0.04$), and middle-aged versus older patients was 1.3 ($P = 0.15$). There were no differences between age groups across the 48-month follow-up period regarding the estimated risk of radiation papillopathy, cystoid macular edema, and poor visual acuity.

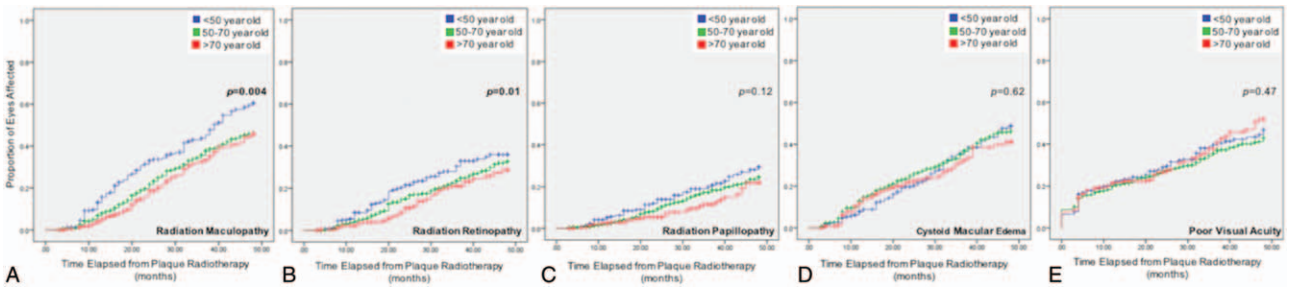

FIGURE 3. Radiation complications following plaque radiotherapy and prophylactic intravitreal bevacizumab for uveal melanoma by age of presentation. Comparison of younger (<50 years) versus middle-aged (50–70 years) versus older (>70 years) age groups showed younger patients had a higher 48-month rate of, (A) radiation maculopathy (62% vs 46% vs 47%, $P = 0.001$) and, (B) extramacular radiation retinopathy (36% vs 34% vs 29%, $P = 0.01$). No differences were detected between age groups for, (C) radiation papillopathy, (D) cystoid macular edema, or, (E) poor visual acuity.

DISCUSSION

The retinal vasculature is prone to pathologic changes after hypoxic events from an underlying disease or an environmental insult.[13] Similar to other ophthalmic vascular diseases, such as diabetic retinopathy, radiation toxicity can cause retinal capillary leakage, nonperfusion, and sometimes, neovascularization, predisposing the retinal vasculature to leakage and bleeding.[13] The risk of developing such complications, in the setting of diabetes or after radiation therapy, has been associated with younger patient age.[14–16]

Radiation-induced vasculopathy manifests with retinal microaneurysms, exudation, hemorrhages, edema, and nerve fiber layer infarction after an average latent period of 14 months.[15–17] Disruption of the retinal capillary endothelium leads to downstream activation of the clotting cascade, resulting in nonperfusion and ultimate retinal and optic disc ischemia.[16] These complications are fairly common after treatment of uveal melanoma with plaque radiotherapy. In a series of 630 patients treated with plaque radiotherapy for macular uveal melanoma, Gündüz et al reported the 5-year risk of developing radiation maculopathy and papillopathy at 40% and 13%, respectively.[18] In a separate study of 1300 patients treated with plaque radiotherapy for posterior uveal melanoma, Gündüz et al found a 46% 5-year risk of nonproliferative radiation retinopathy.[19] These reports date back to the pre-anti-VEGF era when bevacizumab or similar drugs were not available for prevention or treatment of radiation maculopathy.

Age as a predictive factor for the development of radiation-induced vascular complications has been reported in both the systemic and ophthalmic literature.[14–16,20] In a study of 2232 patients who received mediastinal radiotherapy for Hodgkin lymphoma, the risk of fatal acute myocardial infarction was higher in patients younger than 19 years compared with patients older than 50-years (relative risk of 45 vs 1.5, $P < 0.001$).[20] In a cohort of 1117 patients with diabetes mellitus, younger age at presentation with systemic diabetes (<15 years) was associated with a higher long-term risk of proliferative diabetic retinopathy compared with older patients (≥15 years old).[14] Based on a series of 558 patients with uveal melanoma treated with proton beam radiotherapy, evaluated by Gragoudas et al, younger age at presentation, along with presence of diabetes mellitus, hypertension, and shorter tumor distance to the foveola and/or optic disc, was identified as a predictive factor for development of radiation maculopathy and papillopathy.[15] Later, Krema et al, from a cohort of 300 patients with uveal melanoma treated with I^{125} plaque radiotherapy, identified similar predictive factors, including young patient age, for the development of radiation retinopathy.[16] However, little is known about the specific effect of patient age at presentation on the risk of development of the spectrum of radiation complications after plaque radiotherapy of uveal melanoma, especially in this era of prophylactic intravitreal bevacizumab injection.

In this study, we focused only on the impact of patient age regarding the outcomes of radiation complications after plaque radiotherapy of uveal melanoma in the anti-VEGF era in which patients were prescribed to receive a total of 7 prophylactic intravitreal injections spread uniformly over a 2-year period. We did not find differences in final visual acuity or lines of visual acuity lost between age groups. However, we found a greater proportion of younger patients developed complications including radiation maculopathy, extramacular retinopathy, papillopathy, branch retinal vein occlusion, and cystoid macular edema, even after adjusting for radiation dosages. Only cataract formation was found to be higher in older patients. By survival analysis over a 48-month period, the younger age group had a greater risk of developing radiation maculopathy compared with the middle-aged (HR = 1.5) and older (HR = 1.6) age groups and a greater risk of developing extramacular radiation retinopathy compared with the older age group (HR = 1.5).

Vascular endothelial growth factor (VEGF) is an important inflammatory marker released in response to hypoxia, with higher levels in eyes after a vascular insult, such as radiation.[13,21] Missotten et al found higher intraocular VEGF levels in eyes with uveal melanoma after radiation (median 364 pg/mL) compared with nonirradiated eyes (median of 146.5 pg/mL).[21] Although an appropriate physiologic stress response to elicit angiogenesis, increased exposure to VEGF can cause pathologic changes in the retinal vasculature.[13] Rivard et al described age-related variations in VEGF expression and found that the *in vitro* VEGF levels in vascular smooth muscle cells exposed to hypoxic conditions in old rabbits was significantly lower than young rabbits (100% vs 213%, $P < 0.05$).[22] Greater intraocular VEGF levels in younger patients after radiotherapy could be partly responsible for the higher risk of radiation complications in this age group.

Currently, we offer intravitreal bevacizumab at 4-month intervals over a 2-year period as prophylaxis for prevention or reduction of radiation-induced side effects after plaque radiotherapy for uveal melanoma. Intravitreal bevacizumab injections have been previously studied for the treatment of radiation complications with varying results on visual acuity.[6,23] When beginning treatment, injections are typically administered at 1-month intervals. Although the ideal interval for use of intravitreal bevacizumab injections as prophylaxis has not been thoroughly investigated, our group has studied the efficacy of intravitreal bevacizumab for prevention of these side effects with promising results when used at a 4-month interval.[11] Of 292 patients receiving prophylactic intravitreal bevacizumab in our early series, fewer radiation complications of CME (26% vs 40%, $P = 0.004$) and radiation maculopathy (16% vs 31%, $P = 0.001$) were observed compared with controls managed without bevacizumab over a 2-year period.[11] Later, we continued this study over a 4-year period and found a lower 4-year Kaplan-Meier estimated risk of developing clinically evident radiation maculopathy in patients receiving prophylactic intravitreal bevacizumab compared with a control group managed with bevacizumab (HR = 1.39, $P = 0.03$).[24] Furthermore, over the 4-year period, the bevacizumab group demonstrated better median visual acuity compared with the control group (20/70 vs counting fingers, $P < 0.001$).

Herein, we have studied the impact of age on radiation complications in the setting of prophylactic anti-VEGF therapy after plaque radiotherapy. The age factor has been previously studied regarding intravitreal bevacizumab for neovascular age-related macular degeneration. Wang et al documented an association of older age with better treatment response and younger age with poorer response.[25] In this analysis, we found that younger-aged patients had a greater risk of developing radiation maculopathy and extramacular retinopathy despite the use of prophylactic intravitreal anti-VEGF. However, whether there is

an age-related difference with anti-VEGF response for the prevention of post-radiation complication deserves further study.

Limitations of this study include its retrospective design and lack of complete 48-month follow-up in all patients. In addition, not all patients received a total of 6 prophylactic injections for several reasons including, most commonly, patient co-management elsewhere and patient preference. We also recognize that our results could be confounded by presence of cataract or age-associated changes in visual acuity. This could explain why no difference was detected in the visual acuity outcome by age group despite differences in frequency of radiation side effects. Strengths of this study, however, were the large number of patients and long-term follow-up at a single-center with robust statistical analysis.

In summary, we have studied the impact of age on radiation complications and visual outcomes in patients with plaque-irradiated uveal melanoma and additional prophylactic intravitreal bevacizumab and have documented a greater frequency of radiation complications, including radiation maculopathy, extra-macular retinopathy, papillopathy, and cystoid macular edema, in the younger age category (<50 years). The mechanisms underlying the observed higher risk of post-radiation complications in younger patients deserve further study.

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