JAMA Ophthalmology | Original Investigation

Visual Outcome and Millimeter Incremental Risk of Metastasis in 1780 Patients With Small Choroidal Melanoma Managed by Plaque Radiotherapy

Carol L. Shields, MD; Kareem Sioufi, MD; Archana Srinivasan, MD; Maura DiNicola, MD; Babak Masoomian, MD; Laura E. Barna, BS, MSc; Vladislav P. Bekerman, BS; Emil A. T. Say, MD; Arman Mashayekhi, MD; Jacqueline Emrich, PhD; Lydia Komarnicky, MD; Jerry A. Shields, MD

IMPORTANCE Early detection of choroidal melanoma at a small tumor size is emphasized in the literature. However, there is little published information on the specific risks of plaque-irradiated small choroidal melanoma on visual acuity and metastasis.

OBJECTIVE To analyze outcomes of plaque radiotherapy for small choroidal melanoma 3 mm in thickness or less.

DESIGN, SETTING, AND PARTICIPANTS This retrospective noncomparative series at a tertiary referral center included 1780 consecutive patients who had received plaque radiotherapy treatment for small choroidal melanoma.

MAIN OUTCOMES AND MEASURES Visual acuity outcomes and melanoma-associated metastasis, assessed by Kaplan-Meier analyses.

RESULTS The mean (SD) patient age at melanoma diagnosis was 58 (14) years. Of 1780 patients, 908 were female (51.0%), and 1752 were white (98.4%). Visual acuity was 20/40 OU or better in 1276 of the patients (71.7%), and the mean (SD) visual acuity was 20/40 (20/50) OU (median, 20/30; range, 20/20 to counting fingers). The mean (SD) tumor basal dimension was 8.8 (2.9) mm (median, 8.0 mm; range, 2.0-20.0 mm) and mean (SD) tumor thickness was 2.6 (0.5) mm (median, 2.7; range, 0.2-3.4 mm). Mean (SD) distance to the foveola was 3.4 (3.9) mm and to the optic disc was 3.7 (3.7) mm. The Kaplan-Meier rate of visual acuity loss (≥3 Snellen lines) was 9.5% (95% CI, 8.2%-11.0%) at 1 year, 39.2% (95% CI, 36.5%-42.0%) at 5 years, and 48.9% (95% CI, 45.6%-52.3%) at 10 years, whereas poor visual acuity (≤20/200) was 7.1% (95% CI, 5.9%-8.4%) at 1 year, 38.2% (95% CI, 35.5%-41.1%) at 5 years, and 53.5% (95% CI, 50.1%-57.1%) at 10 years. Regarding melanoma-associated metastasis, the rate was 0.2% (95% CI, 0.09%-0.6%) at 1 year, 4.5% (95% CI, 3.4%-5.9%) at 5 years, and 8.8% (95% CI, 6.9%-11.1%) at 10 years. Using 1.0-mm thickness increments, the 10-year risk for metastasis was 25.0% (95% CI, 3.9%-87.2%) at 0-mm to 1.0-mm thickness, 5.9% (95% CI, 2.5%-13.5%) at 1.1-mm to 2.0-mm thickness, 8.1% (95% CI, 5.9%-11.0%) at 2.1-mm to 3.0-mm thickness, and 13.4% (95% CI, 8.7%-20.4%) at thicknesses greater than 3.0 mm. The greater relative risk (RR) for metastasis in thinnest tumors was 1.83 (95% CI, 1.09-3.07), which likely represented more aggressive diffuse (flat) melanoma. By multivariable analysis, clinical features predictive of melanoma-associated metastasis included increasing patient age (RR, 1.32 [95% CI, 1.07-1.63] per decade; $P = .01$), tumor diameter (RR, 1.15 [95% CI, 1.06-1.24] per mm; $P < .001$), tumor thickness (RR, 2.22 [95% CI, 1.22-4.05] per mm; $P = .01$), photopsia symptoms (RR, 2.45 [95% CI, 1.35-4.43]; $P = .003$), and prior treatment before plaque radiotherapy (RR, 3.31 [95% CI, 1.31-8.33]; $P = .01$).

CONCLUSIONS AND RELEVANCE This retrospective study suggests that small choroidal melanoma treated with plaque radiotherapy has a 10-year risk for visual acuity loss of 48.9% (95% CI, 45.6%-52.3%) and a 10-risk of systemic metastasis of 8.8% (95% CI, 6.9%-11.1%). In this analysis, each millimeter of increasing thickness and diameter contributed risk for metastatic disease.

JAMA Ophthalmol. 2018;136(12):1325-1333. doi:10.1001/jamaophthalmol.2018.3881
Published online September 27, 2018.

Invited Commentary
page 1333

Supplemental content and
Journal Club Slides

Author Affiliations: Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania (C. L. Shields, Sioufi, Srinivasan, DiNicola, Masoomian, Barna, Bekerman, Say, Mashayekhi, J. A. Shields); Department of Radiation Oncology, Hahnemann University Hospital, Philadelphia, Pennsylvania (Emrich, Komarnicky).

Corresponding Author: Carol L. Shields, MD, Ocular Oncology Service, 840 Walnut St, Ste 1440, Philadelphia, PA 19107 (carolshields@gmail.com).

There is considerable attention to the early identification and treatment of small choroidal melanoma, generally defined as a tumor 3 mm or less in thickness (<3.5 mm, rounded to the whole number).[1-10] Small choroidal melanoma can clinically simulate nevus, and there are clinical, cytologic, and cytogenetic features that can serve to differentiate these conditions.[5,6,8-12]

Clinical risk factors, such as greater tumor thickness, presence of symptoms, subretinal fluid, orange pigment, ultrasonographic hollowness, and tumor location near the optic disc, among others, are routinely used to identify choroidal melanoma at its earliest point, a time when intervention could affect life prognosis.[5,8] Cytogenetic abnormalities in chromosomes 3, 6, and 8 are likewise important in melanoma risk for metastasis.[11] A recent analysis of 1059 patients with uveal melanoma revealed several clinical findings that were predictive of cytogenetic alterations associated with high-risk status for metastasis.[11,12] For chromosome 3 abnormalities, the clinical features included tumor location in the ciliary body (odds ratio [OR], 8.17 [95% CI, 3.10-21.54]), increasing tumor thickness (OR, 2.70 [95% CI, 1.92-3.81]), increasing tumor base (OR, 2.59 [95% CI, 1.92-3.49]), and older age (OR, 1.83 [95% CI, 1.40-2.40]).[12] For chromosome 8p abnormalities, the features included tumor location in the ciliary body (OR, 53.9 [95% CI, 2.86-101.6]), increasing tumor thickness (OR, 5.15 [95% CI, 2.75-9.59]), and ocular melanocytosis (OR, 3.95 [95% CI, 1.08-14.5]). For chromosome 8q abnormalities, the features included tumor location in the ciliary body (OR, 102.9 [95% CI, 6.25-169.2]), increasing tumor thickness (OR, 4.44 [95% CI, 2.89-6.83]), and ocular melanocytosis (OR, 2.75 [95% CI, 1.01-7.57]).[12] Regarding tumor size, chromosome 3 mutation was found in 35% of small melanomas (≤3 mm thickness), 52% of medium melanomas (>3 to 8 mm), and 65% of large melanomas (>8 mm), correlating with metastatic risk.[11] A recent publication[13] has demonstrated that choroidal nevi with slow growth to melanoma (>1 year) are cytogenetically less aggressive than nevi with fast growth (≤1 year). Kim et al[14] and Shields et al[15] have evaluated techniques and complications of genetic testing of small melanoma, and, despite thin tumors, a 91% yield for cytopathology was achieved.

Regardless of the effort in the early detection of uveal melanoma, there remains little information on the specific risks of plaque-irradiated small choroidal melanoma on visual acuity and metastasis. In this study, we focus on small choroidal melanoma managed conservatively with plaque radiotherapy to assess visual outcome and precise risk for metastasis for the entire patient group and by single-millimeter and partial-millimeter thickness increments.

Key Points

Question What are the vision and metastatic outcomes for patients with small choroidal melanoma treated with plaque radiotherapy?

Findings This study of 1780 patients with small choroidal melanoma who were treated with plaque radiotherapy revealed a 5-year rate of visual acuity loss (≥3 Snellen lines) at 39.2% and a 5-year rate of melanoma-associated metastasis at 4.5%. Ten-year rates were 48.9% for visual acuity loss and 8.8% for metastases.

Meaning Despite the diminutive thickness, plaque radiotherapy for small choroidal melanoma can impart substantial visual loss, but it is fairly low risk for metastatic disease.

Methods

A retrospective medical record review was performed for all patients diagnosed with small choroidal melanoma measuring 3.4 mm or less in thickness (or ≤3 mm by whole-number measurements) by ocular ultrasonography who were managed with plaque radiotherapy on the Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania, from June 27, 1977, to December 21, 2015. This study was approved by the institutional review board of the study institution and adhered to the tenets of the Declaration of Helsinki. Informed consent was waived because of the use of deidentified patient data.

Some of the patients in this analysis may have been included in previous analyses on clinical features and risk factors for tumor growth, multi-imaging features, and outcomes analyses. However, this is to our knowledge the first study from our department specifically focused on plaque radiotherapy for small choroidal melanoma.

All patients underwent slitlamp biomicroscopy of the anterior segment of the eye and indirect ophthalmoscopy of the fundus by 1 of the 2 senior authors (C.L.S. and J.A.S.), as well as imaging with ocular ultrasonography, fundus photography, fluorescein angiography, and optical coherence tomography (when available). The clinical data were collected retrospectively and included patient demographics, tumor features, treatment parameters, and outcomes for visual acuity, metastasis, and death.

At initial examination, the collected data included age, race/ethnicity, sex, and affected eye (eTable 1 in the Supplement). The clinical features included best-corrected visual acuity (by logMAR or Snellen examination), presence of ocular melanocytosis, and anterior segment abnormalities. The tumor data included tumor location by tissue (iris, ciliary body, or choroid), quadrant (macula, inferior, temporal, superior, or nasal), anteroposterior site (macula, macula-equator, equator-ora serrata, ciliary body, or iris), and distance to optic disc and foveola (millimeters). Tumor features included largest basal diameter, thickness measured on ultrasonography, and presence of associated features, such as subretinal fluid, orange pigment, drusen, Bruch membrane rupture, retinal invasion, extraocular extension, and vitreous hemorrhage (**Table 1**). Treatment parameters were listed, including previous therapies before plaque radiotherapy, radioisotope used with dose (Gray) and dose rate (1 rad/h) to tumor apex, base, optic disc, foveola, and lens (eTable 2 in the Supplement).

Outcomes were recorded regarding visual acuity and visual acuity loss of 3 or more Snellen lines, radiation-associated complications, including maculopathy, papillopathy, neovascularization of the iris, disc, or retina, neovascular glaucoma, and vitreous hemorrhage, as documented in the medical record and judged from imaging. Time to systemic metastasis and melanoma-associated death were recorded (**Table 2**). Screening

Table 1. Tumor Features of Small Choroidal Melanoma Cases Managed With Plaque Radiotherapy (N = 1780)

Characteristic	Patients Without Metastasis (n = 1689)	Patients With Metastasis (n = 91)	*P* Value	Total (N = 1780)	Relative Risk (95% CI)	*P* Value
Tumor epicenter						
Iris	0	0		0		
Ciliary body	29 (1.7)	1 (1)	>.99[a]	30 (1.7)	1 [Reference]	.48
Choroid	1660 (98.3)	90 (99)		1750 (98.3)	2.03 (0.28-14.6)	
Tumor quadrant						
Macula	518 (30.7)	23 (2)		541 (30.4)	1 [Reference]	NA
Inferior	261 (15.5)	21 (23)		282 (15.8)	1.80 (1.00-3.25)	.05
Temporal	308 (18.2)	14 (15)	.35	322 (18.1)	1.08 (0.56-2.10)	.82
Superior	389 (23.0)	22 (24)		411 (23.1)	1.29 (0.72-2.32)	.39
Nasal	213 (12.6)	11 (12)		224 (12.6)	1.08 (0.52-2.21)	.84
Anterior tumor margin						
Macula	193 (11.4)	7 (8)		200 (11.2)	1 [Reference]	NA
Macula to equator	1041 (61.6)	54 (59)		1095 (61.5)	1.38 (0.63-3.04)	.42
Equator to ora	381 (22.6)	28 (31)	.28	409 (23.0)	1.95 (0.85-4.46)	.12
Ciliary body	54 (3.2)	2 (2)		56 (3.1)	0.96 (0.20-4.63)	.96
Iris	20 (1).2	0		20 (1.1)	NE	.98
Posterior tumor margin						
Macula	952 (56.4)	47 (52)		999 (56.1)	1 [Reference]	NA
Macula to equator	679 (40.2)	41 (45)		720 (40.4)	1.22 (0.80-1.86)	.35
Equator to ora	42 (2.5)	3 (3)	.59	45 (2.5)	1.11 (0.34-3.56)	.87
Ciliary body	16 (0.9)	0		16 (0.9)	NE	.98
Iris	0	0		0	NE	NA
Tumor largest basal diameter, mm						
Mean (SD)	8.7 (2.9)	10.0 (3.4)	<.001[b]	8.8 (2.9)	1.16[c] (1.09-1.24)	<.001
Median (range)	8 (2-20)	10 (3-20)		8 (2-20)		
Tumor thickness, mm						
Mean (SD)	2.6 (0.5)	2.8 (0.5)	.002[b]	2.6 (0.5)	2.41[c] (1.50-3.85)	<.001
Median (range)	2.7 (0.2-3.4)	3.0 (0.5-3.4)		2.7 (0.2-3.4)		
Distance to foveola, mm						
Mean (SD)	3.4 (3.9)	3.7 (3.6)	.42[b]	3.4 (3.9)	1.01[c] (0.96-1.06)	.72
Median (range)	2 (0-21)	3 (0-14)		2 (0-21)		
0-3	1074 (63.6)	51 (56)	.15	1125 (63.2)	1 [Reference]	NA
>3	615 (36.4)	40 (44)		655 (36.8)	1.23 (0.81-1.86)	.33
Distance to optic nerve, mm						
Mean (SD)	3.7 (3.7)	3.4 (3.2)	.46[b]	3.7 (3.7)	1.03[d] (0.97-1.09)	.41
Median (range)	3 (0-21)	3 (0-12)		3 (0-21)		
0-3	964 (57.1)	49 (54)	.55	1013 (56.9)	1 [Reference]	NA
>3	725 (42.9)	42 (46)		767 (43.1)	1.08 (0.72-1.63)	.72
Retinal detachment						
None	334 (19.8)	10 (11)		344 (19.3)	1 [Reference]	NA
<3 mm	912 (54.0)	45 (50)		957 (53.8)	1.69 (0.85-3.36)	.13
1 quadrant	362 (21.4)	23 (25)		385 (21.6)	2.55 (1.21-5.36)	.01
2 quadrants	70 (4.1)	9 (10)	<.001	79 (4.4)	3.88 (1.58-9.56)	.003
3 quadrants	10 (0.6)	4 (4)		14 (0.8)	9.70 (3.03-31.1)	<.001
4 quadrants	1 (0.1)	0		1 (0.1)	NE	.99

(continued)

Table 1. Tumor Features of Small Choroidal Melanoma Cases Managed With Plaque Radiotherapy (N = 1780) (continued)

Characteristic	Patients Without Metastasis (n = 1689)	Patients With Metastasis (n = 91)	*P* Value	Total (N = 1780)	Relative Risk (95% CI)	*P* Value
Other clinical features						
Diffuse	194 (11.5)	18 (20)	.03[a]	212 (11.9)	1.83 (1.09-3.07)	.02
Bruch rupture	40 (2.4)	2 (2)	>.99[a]	42 (2.4)	1.08 (0.27-4.40)	.91
Extraocular extension	12 (0.7)	0	>.99[a]	12 (0.7)	NE	.98
Retinal invasion	19 (1.1)	3 (3)	.01[a]	22 (1.2)	2.47 (0.78-7.82)	.12
Vitreous hemorrhage	18 (1.1)	1 (1)	>.99[a]	19 (1.1)	1.67 (0.23-12.0)	.61
Orange pigment	1042 (61.7)	47 (52)	.06	1089 (61.2)	0.85 (0.57-1.29)	.45
Drusen	375 (22.2)	15 (17)	.24[a]	390 (21.9)	0.62 (0.36-1.08)	.09
Halo	96 (5.7)	1 (1)	.06[a]	97 (5.4)	0.23 (0.03-1.65)	.14
Subfoveal fluid	524 (31.0)	26 (29)	.73	550 (30.9)	0.88 (0.56-1.38)	.57

Abbreviations: NA, not applicable; NE, not estimable.

[a] By Fisher exact test.

[b] By *t* test.

[c] Per 1-mm increase.

[d] Per 1-mm decrease.

Table 2. Kaplan-Meier Analysis of Outcomes of Plaque Radiotherapy for Small Choroidal Melanoma (N = 1780)

Outcomes	Kaplan-Meier Estimates, No. of Affected Patients/No. of Unaffected Patients (%) [95% CI]					
	1-y	3-y	5-y	10-y	15-y	20-y
Visual outcome						
Moderate to severe visual acuity loss (≥3 Snellen lines)	159/1416 (9.5) [8.2-11.0]	398/839 (27.0) [24.7-29.3]	518/498 (39.2) [36.5-42.0]	576/177 (48.9) [45.6-52.3]	589/57 (55.0) [50.7-59.5]	591/20 (58.2) [52.3-64.3]
Poor visual acuity ≤20/200	119/1454 (7.1) [5.9-8.4]	354/885 (24.4) [22.2-26.7]	492/519 (38.2) [35.5-41.1]	585/164 (53.5) [50.1-57.1]	603/50 (61.9) [57.3-66.6]	608/14 (67.4) [61.4-73.3]
Radiation-associated complications						
Maculopathy	101/1466 (6.2) [5.1-7.4]	459/787 (32.3) [29.9-34.8]	600/450 (46.4) [43.5-49.3]	679/155 (59.0) [55.7-62.4]	693/50 (64.8) [60.7-68.8]	697/16 (68.4) [63.3-73.3]
Papillopathy	29/1531 (1.8) [1.2-2.6]	190/967 (13.8) [12.1-15.8]	255/616 (20.6) [18.4-23.1]	303/214 (30.1) [26.9-33.6]	316/66 (36.9) [32.3-41.9]	318/22 (39.3) [33.9-45.2]
Neovascularization						
Of the iris	1/1555 (0.1) [0.01-0.4]	15/1103 (1.1) [0.7-1.9]	19/741(1.6) [1.0-2.5]	27/277 (3.3) [2.1-5.0]	27/96 (3.3) [2.1-5.0]	27/35 (3.3) [2.1-5.0]
Of the disc	0/1555	12/1104 (0.9) [0.5-1.6]	23/742 (2.1) [1.4-3.2]	29/279 (3.1) [2.1-4.5]	29/96 (3.1) [2.1-4.5]	29/35 (3.1) [2.1-4.5]
Elsewhere	4/1548 (0.3) [0.1-0.7]	32/1091 (2.4) [1.7-3.4]	54/727 (4.7) [3.6-6.2]	69/267 (7.4) [5.8-9.5]	70/ 94 (8.0) [6.1-10.5]	71/35 (9.6) [6.5-14.1]
Neovascular glaucoma	0/1555	9/1105 (0.7) [0.4-1.3]	15/742 (1.4) [0.8-2.3]	24/281 (3.2) [2.1-4.9]	27/96 (5.2) [3.0-8.7]	27/35 (5.2) [3.0-8.7]
Vitreous hemorrhage	17/1540 (1.0) [0.6-1.6]	94/1054 (6.9) [5.7-8.4]	140/688 (11.7) [10.0-13.7]	166/254 (16.5) [14.1-19.2]	176/84 (22.2) [18.2-26.9]	178/31 (24.8) [19.8-30.8]
Systemic outcome						
Metastasis	4/1561 (0.2) [0.09-0.6]	24/1127 (1.7) [1.1-2.6]	50/762 (4.5) [3.4-5.9]	74/290 (8.8) [6.9-11.1]	88/97 (16.0) [12.1-20.8]	91/35 (19.5) [14.5-25.9]
Death	4/1560 (0.2) [0.09-0.6]	16/1133 (1.2) [0.7-1.9]	41/771 (3.8) [2.7-5.0]	65/290 (8.3) [6.4-10.7]	77/100 (13.6) [10.3-17.8]	79/36 (16.0) [11.7-21.5]

for metastasis was performed by a general medical physician or medical oncologist with twice-yearly physical examination and liver function tests (lactate dehydrogenase, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase) and once-yearly liver imaging (magnetic resonance, computed tomography, or ultrasonography) and chest radiograph.

Statistical Analysis

All data were tabulated using Microsoft Excel 2016 version 15.24 (Microsoft Corporation). Subgroup analysis (metastasis vs no metastasis) was performed and comparison of demographics (eTable 1 in the Supplement) and tumor (Table 1) features was conducted using χ^2 test, *t* test, and Fischer exact tests, as appropriate. Hazard ratios (HR), 95% CIs, and *P* values were calculated using Cox regression analysis.

Kaplan-Meier estimates were calculated for time to event (visual acuity loss of ≥3 Snellen lines, visual acuity of ≤20/200, radiation-associated complications [maculopathy; papillopathy; neovascularization of the iris, disc, or retina; neovascular glaucoma; or vitreous hemorrhage], and systemic outcomes [metastasis and death]) (Table 2). Kaplan-Meier estimates were calculated for time to metastasis per 0.5-mm and 1.0-mm tumor thickness increments and compared across tumor thickness categories using the log-rank test (**Table 3**).

A series of univariable Cox regression analyses were performed to identify the factors associated with melanoma metastasis and death in the 1780 included patients, based on clinical features at presentation (**Table 4** and **Table 5**). All of the variables were analyzed as discrete variables except for patient age at presentation, tumor basal dimension, tumor thickness, and dis-

Table 3. Metastasis by 0.5-mm and 1.0-mm Increments After Plaque Radiotherapy for Small Choroidal Melanoma (N = 1780)

Tumor Size	No. (%)		Kaplan-Meier Estimates, No. of Affected Patients/No. of Unaffected Patients (%) [95% CI]						
	Total Patients (N = 1780)	Patients With Metastasis (n = 91)	1-y	3-y	5-y	10-y	15-y	20-y	*P* Value[a]
Using 0.5-mm increments									
0.5-1.0	6 (0.3)	1 (1)	0/5	0/4	1/2 (25.0) [3.9-87.2][b]	1/1 (25.0) [3.9-87.2][b]	1/1 (25.0) [3.9-87.2][b]	NE	.003
1.1-1.5 mm	29 (1.6)	0	0/23	0/18	0/16	0/8	0/6	0/5	
1.6-2.0 mm	231 (13.0)	8 (9)	2/197 (0.9) [0.2-3.7]	4/157 (2.1) [0.8-5.5]	5/113 (2.9) [1.2-7.1]	7/39 (6.7) [2.8-15.6]	8/17 (10.3) [4.3-23.6]	8/6 (10.3) [4.3-23.6]	
2.1-2.5 mm	521 (29.3)	17 (19)	1/462 (0.2) [0.03-1.4]	3/337 (0.7) [0.2-2.2]	10/227 (3.3) [1.8-6.1]	15/88 (6.3) [3.7-10.3]	17/33 (8.5) [5.0-14.2]	17/10 (8.5) [5.0-14.2]	
2.6-3.0 mm	615 (34.6)	39 (43)	1/538 (0.2) [0.02-1.2]	10/383 (2.1) [1.1-3.8]	19/264 (4.8) [3.0--7.5]	29/110 (9.7) [6.6-14.0]	37/34 (21.4) [14.1-31.6]	39/10 (27.3) [17.8-40.5]	
>3.0 mm	377 (21.2)	26 (29)	0/335	7/228 (2.5) [1.2-5.1]	15/140 (6.9) [4.2-11.4]	22/44 (13.4) [8.7-20.4]	25/6 (28.0) [13.9-51.4]	26/4 (42.4) [19.7-75.0]	
Using 1-mm increments									
0-1.0 mm	7 (0.4)	1 (1)	0/6	0/4	1/2 (25.0) [3.9-87.2]	1/1 (25.0) [3.9-87.2]	1/1 (25.0) [3.9-87.2]	NE	.01
1.1-2.0 mm	260 (14.6)	8 (9)	2/220 (0.8) [0.2-3.3]	4/175 (1.9) [0.7-4.9]	5/129 (2.6) [1.1-6.3]	7/47 (5.9) [2.50-13.5]	8/23 (8.8) [3.7-20.0]	8/11 (8.8) [3.7-20.0]	
2.1-3.0 mm	1136 (63.8)	56 (62)	2/1000 (0.8) [0.05-0.7]	13/720 (1.4) [0.8-2.5]	29/421 (4.1) [2.8-5.9]	44/198 (8.1) [5.9-11.0]	54/67 (15.5) [11.0 - 21.6]	56/20 (19.3) [13.2 - 27.7]	
>3.0 mm	377 (21.2)	26 (29)	0/335	7/228 (2.5) [1.2-5.1]	15/140 (6.9) [4.2-11.4]	22/44 (13.4) [8.7-20.4]	25/6 (28.0) [13.9-51.4]	26/4 (42.4) [19.7-75.0]	
All tumors	1780 (100)	91 (100)	4/1561 (0.2) [0.1-0.6]	24/1127 (1.7) [1.1-2.6]	50/762 (4.5) [3.4-5.9]	74/290 (8.8) [6.9-11.1]	88/97 (16.0) [12.1-20.8]	91/35 (19.5) [14.5-25.9]	

Abbreviation: NE, not estimable.

[a] Log-rank test.

[b] Diffuse configuration.

tance of tumor to optic disc margin and foveola, which were evaluated as continuous variables. Subsequent multivariable analyses were performed using Cox proportional hazard model forward stepwise method for the factors identified as significant at the 5% level of significance. All significant analysis was performed using SAS version 13.2 (SAS Institute).

Results

In this analysis, there were 1780 consecutive patients with small choroidal melanoma treated with plaque radiotherapy. The results are tabulated in Tables 1 through 5 and eTables 1 through 5 in the Supplement.

The patient demographic and visual acuity features are listed in eTable 1 in the Supplement. Briefly, visual acuity was 20/40 OU or better in 1276 of the patients (71.7%), and the mean (SD) visual acuity was 20/40 (20/50) OU (median, 20/30; range, 20/20 to counting fingers). The mean (SD) patient age at initial presentation was 58 (14) years (median, 59 years; range, 10-93 years). Most patients were white (n = 1752; 98.4%), and male and female participants were equally represented (n = 908 [51.0%] were female). Based on categorizations of patients by their ultimate development of melanoma-associated metastases, there were no significant differences in demographic features, presence of melanocytosis, and visual acuity at study entry.

The tumor features are listed in Table 1. Overall, tumor quadrant location included the macula (n = 541 [30.4%]), the inferior quadrant (n = 282 [15.8%]), the temporal quadrant (n = 322 [18.1%]), the superior quadrant (n = 411 [23.1%]), and the nasal quadrant (n = 224 [12.6%]), with no significant difference regarding metastatic disease. The mean (SD) tumor basal diameter was 8.8 (2.9) mm (median, 8 mm; range, 2-20 mm) and mean (SD) tumor thickness was 2.6 (0.5) mm (median, 2.7 mm; range, 0.2-3.4 mm), with risk for metastasis greater with larger base (relative risk [RR], 1.16 [95% CI, 1.09-1.24] per 1-mm increase) and larger thickness (RR, 2.41 [95% CI, 1.50-3.85] per 1-mm increase; eFigures 1 and 2 in the Supplement). The mean (SD) tumor proximity to the foveola was 3.4 (3.9) mm (median, 2 mm; range, 0-21 mm) and to the optic disc was 3.7 (3.7) mm (median, 3 mm; range, 0-21 mm), with no difference on rates of metastasis. Other features associated with metastatic disease included presence of the retinal detachment of 1 quadrant (RR, 2.55 [95% CI, 1.21-5.36]; $P = .01$), 2 quadrants (RR, 3.88 [95% CI, 1.58-9.56]; $P = .003$), or 3 quadrants (RR, 9.70 [95% CI, 3.03-31.1]; $P < .001$), as well as diffuse configuration (RR, 1.83 [95% CI, 1.09-3.07]; $P = .02$).

The treatment parameters are listed in eTable 2 in the Supplement. Previous treatment was performed in 61 patients (3.4%), including transpupillary thermotherapy, plaque radiotherapy (at a center other than the one in which this study was conducted), photodynamic therapy, and laser photocoagulation. The median interval from first examination to plaque radiotherapy was less than 1 month (range, 0-1 month). The radioactive isotope used was generally iodine 125, and the calculated dose to the tumor apex was 84 Gy; to the base, 183 Gy;

Table 4. Clinical Features Associated With Metastasis After Plaque Radiotherapy for Small Choroidal Melanoma (N = 1780)

Features	No. (%)		Univariable Analysis		Multivariable Analysis	
	Metastasis (n = 91)	No Metastasis (n = 1689)	*P* Value	Relative Risk (95% CI)	*P* Value	Relative Risk (95% CI)
Age, mean (SD), y	60 (12)	58 (14)	<.001	1.33[a] (1.13-1.57)	.01	1.32[a] (1.07-1.63)
Ocular symptoms						
Photopsia	19 (21)	188 (11.1)	.01	1.94 (1.17-3.21)	.003	2.45 (1.35-4.43)
Tumor basal diameter, mm						
Median (range)	10.0	8.0	<.001	1.16[b] (1.09-1.24)	<.001	1.15[b] (1.06-1.24)
Mean (SD)	10.0 (3.4)	8.7 (2.9)				
Tumor thickness, mm						
Median (range)	3.0	2.7	<.001	2.41[b] (1.50-3.85)	.01	2.22[b] (1.22-4.05)
Mean (SD)	2.8 (0.5)	2.6 (0.5)				
Subretinal fluid						
1 Quadrant	23 (25)	362 (21.4)	.01	2.55 (1.21-5.36)	NA	NA
2 Quadrants	9 (10)	70 (4.1)	.003	3.88 (1.58-9.56)	NA	NA
3 Quadrants	4 (4)	10 (0.6)	<.001	9.70 (3.03-31.1)	NA	NA
Diffuse configuration	18 (20)	194 (11.5)	.02	1.83 (1.09-3.07)	NA	NA
Prior treatment	8 (9)	53 (3.1)	.01	2.48 (1.20-5.13)	.01	3.31 (1.31-8.33)
Radiation dose rate, median (range)						
At optic disc, rad/h	39.5 (8.86-236.2)	30.8 (1.98-310.4)	.03	1.06[c] (1.01-1.12)	NA	NA
At lens, rad	9.95 (3.5936.9)	7.01 (2.24-98.8)	.03	1.23[d] (1.02-1.49)	NA	NA
At lens, rad/h	10.5 (2.97-37.4)	7.29 (1.00-103.0)	.03	1.23[c] (1.02-1.48)	NA	NA
Tumor thickness at last visit, mm, mean (SD)	1.80 (0.5)	1.79 (0.5)	.03	1.59[b] (1.05-2.41)	NA	NA
Visual acuity ≤20/200[e]	27 (30)	583 (34.5)	.002	2.07 (1.32-3.25)	NA	NA
Moderate vision loss[e]	27 (30)	567 (33.6)	.01	1.80 (1.14-2.82)	NA	NA
Radiation maculopathy[e]	29 (32)	668 (39.6)	<.001	2.24 (1.44-3.49)	NA	NA
Radiation papillopathy[e]	11 (12)	307 (18.2)	.002	2.66 (1.41-5.00)	NA	NA
Local recurrence	21 (23)	91 (5.4)	<.001	2.84 (1.73-4.64)	NA	NA
Enucleation	17 (19)	56 (3.3)	<.001	4.21 (2.49-4.15)	NA	NA
Death	41 (45)	39 (2.3)	<.001	22.0 (14.4-33.5)	NA	NA

Abbreviation: NA, not applicable.
[a] Per 10-year increase.
[b] Per 1-mm increase.
[c] Per 10–cGy/h increase.
[d] Per 10-cGy increase.
[e] No vs yes.

to the optic disc, 41 Gy; to the foveola, 67 Gy, and to the lens, 9 Gy (eTable 2 in the Supplement).

The mean (SD) follow-up time for this cohort was 74 (59) months (median, 55; range, 0-380 months). The number of patients followed up per length of time (in year increments) is listed in eTable 3 in the Supplement. Patient demographics and tumor features were evaluated based on follow-up of less than 5 years vs 5 years or more (eTables 4 and 5 in the Supplement).

Kaplan-Meier analyses of outcomes are listed in Table 2 and eFigures 3, 4, and 5 in the Supplement. The Kaplan-Meier rate of visual acuity loss (≥3 Snellen lines) was 9.5% (95% CI, 8.2%-11.0%) at 1 year, 39.2% (95% CI, 36.5%-42.0%) at 5 years, and 48.9% (95% CI, 45.6%-52.3%) at 10 years, whereas poor visual acuity (≤20/200) was 7.1% (95% CI, 5.9%-8.4%) at 1 year, 38.2% (95% CI, 35.5%-41.1%) at 5 years, and 53.5% (95% CI, 50.1%-57.1%) at 10 years. The rate of melanoma-associated metastases was 0.2% (95% CI, 0.09%-0.6%) at 1 year, 4.5% (95% CI, 3.4%-5.9%) at 5 years, and 8.8% (95% CI, 6.9%-11.1%) at 10 years. The 10-year risk was estimated for maculopathy (59.0% [95% CI, 55.7%-62.4%]), papillopathy (30.1% [95% CI, 26.9%-33.6%]), neovascularization of the iris (3.3% [95% CI, 2.1%-5.0%]), neovascularization of the disc (3.1% [95% CI, 2.1%-4.5%]), neovascularization of the retina (7.4% [95% CI, 5.8%-9.5%]), neovascular glaucoma (3.2% [95% CI, 2.1%-4.9%]), and vitreous hemorrhage (16.5% [95% CI, 14.1%-19.2%]). Kaplan-Meier analysis at 5 and 10 years showed tumor recurrence at 6.5% (95% CI, 5.2%-8.0%) and 10.8% (95% CI, 8.7%-13.3%), and the need for enucleation (for any reason) at 4.0% (95% CI, 3.0%-5.3%) and 7.6% (95% CI, 5.8%-10.0%).

Metastatic rates per thickness increments are listed in Table 3. Using the patients' tumor thicknesses at study entry in 0.5-mm increments, we found that the 10-year rate of metastasis were 25.0% (95% CI, 3.9%-87.2%) for those with 0.5-mm to 1.0-mm

Table 5. Clinical Features Associated With Death After Plaque Radiotherapy for Small Choroidal Melanoma (N = 1780)

Feature	No. (%)		Univariable Analysis		Multivariable Analysis	
	Death (n = 80)	No Death (n = 1700)	*P* Value	Relative Risk (95% CI)	*P* Value	Relative Risk (95% CI)
Age, mean (SD), y	63 (14)	58 (14)	<.001	1.66 (1.37-2.00)[a]	<.001	1.60 (1.33-1.93)[a]
Tumor quadrant						
Macula vs nasal[b]	26 (33)	515 (30.3)	.03	3.76 (1.14-12.4)	NA	NA
Superior vs nasal[b]	21 (26)	390 (22.9)	.02	4.04 (1.21-13.6)	NA	NA
Inferior vs nasal[b]	17 (21)	265 (15.9)	.01	4.81 (1.41-16.4)	NA	NA
Tumor basal diameter, mm						
Mean (SD)	9.5 (2.9)	8.7 (2.9)	.01	1.11 (1.03-1.19)[c]	NA	NA
Median (range)	9.0 (5.0-17.0)	8.0 (2.0-20.0)			NA	NA
Tumor thickness, mm						
Mean (SD)	2.8 (0.5)	2.6 (0.5)	<.001	2.37 (1.44-3.89)[c]	.01	2.03 (1.24-3.31)[c]
Median (range)	3.0 (0.5-3.4)	2.7 (0.2-3.4)				
Subretinal fluid in 1 quadrant	23 (29)	362 (21.3)	.03	2.19 (1.08-4.42)	NA	NA
Plaque type (iridium vs iodine 125[b])	5 (6)	32 (1.8)	.04	2.59 (1.03-6.49)	NA	NA

Abbreviation: NA, not applicable.

[a] Per 10-year increase.

[b] Nasal is the reference category for these comparisons.

[c] Per 1-mm increase.

thicknesses, 0% for those with 1.1-mm to 1.5-mm thicknesses, 6.7% (95% CI, 2.8%-15.6%) for those who were tumors were 1.6 mm to 2 mm thick, 6.3% (95% CI, 3.7%-10.3%) for those with tumors between 2.1 mm and 2.5 mm thick, 9.7% (95% CI, 6.6%-14.0%) for those with 2.6-mm to 3.0-mm tumor thicknesses, and 13.4% (95% CI, 8.7%-20.4%) for those whose tumors were more than 3.0 mm. The 10-year rate of metastasis using 1.0-mm tumor thickness increments was 25.0% (95% CI, 3.9%-87.2%) for patients with tumors between 0 and 1.0 mm in thickness, 5.9% (95% CI, 2.5%-13.5%) for patients with tumors between 1.1 and 2.0 mm in thickness, 8.1% (95% CI, 5.9%-11.0%) for patients whose tumors between 2.1 and 3.0 mm thick, and 13.4% (95% CI, 8.7%-20.4%) for patients whose tumors were more than 3.0 mm thick. The thinnest tumors (0-1.0 mm in thickness) revealed mean basal dimension of 7.8 mm (median, 7.8 mm; range, 2-11.5 mm), while mean thickness-to-base ratio was 12%, suggestive of diffuse choroidal melanoma.

Univariable and multivariable risks for metastasis are listed in Table 4. The clinical features predictive of metastasis by multivariable analysis included increasing patient age (RR, 1.32 [95% CI, 1.07-1.63] per 10-year increase; $P = .01$), ocular symptoms of photopsia at presentation (RR, 2.45 [95% CI, 1.35-4.43]; $P = .003$), increasing tumor diameter (RR, 1.15 [95% CI, 1.06-1.24] per 1-mm increase; $P < .001$), increasing tumor thickness (RR, 2.22 [95% CI, 1.22-4.05] per 1-mm increase; $P = .01$), and prior treatment (RR, 3.31 [95% CI, 1.31-8.33]; $P = .01$).

Univariable and multivariable risks for death are listed in Table 5. The clinical features associated with death by multivariable analysis included increasing patient age (RR, 1.60 [95% CI, 1.33-1.93] per 10-year increase) and increasing tumor thickness (RR, 2.03 [95% CI, 1.24-3.31] per 1-mm increase).

Discussion

The management of small choroidal melanoma continues to stimulate debate, and the controversy rests on the balance between tumor potential for metastasis and treatment effects on visual acuity. It is understood that increasing melanoma thickness is correlated with increasing risk for metastasis.[1] Diener-West et al[4] have provided a meta-analysis of 8 published studies on metastasis of uveal melanoma managed with enucleation and found the combined weighted estimate of 5-year mortality based on tumor size was 16% for cases of small melanoma (0-3 mm thickness), 32% for cases of medium-sized melanoma (3.1-8 mm thickness), and 53% for cases of large melanoma (>8 mm thickness). Later, results from the Collaborative Ocular Melanoma Study[16] (COMS) have revealed that 10-year melanoma-associated mortality for patients with large melanomas who had undergone enucleation was 40% vs 45% for those who had undergone enucleation combined with preenucleation radiotherapy. Additional data from COMS revealed that 12-year melanoma-associated mortality for patients who had had plaque radiotherapy for medium-sized melanoma was 21%, similar to that of patients who had undergone enucleation (17%).[17]

There are to our knowledge relatively few data on outcomes after observation or treatment of small choroidal melanoma. In 1997, the COMS provided data on 204 patients with possible small choroidal melanoma (vs nevus) who were initially followed up because their tumors were not considered large enough to qualify for the clinical trial.[7] These tumors measured 5 mm or more in basal dimension and 1.0 to 3.0 mm in thickness, and 33% eventually required treatment because of growth within 5 years. The 8-year melanoma-specific mortality was 4%, but this figure included the 67% of tumors that did not qualify for treatment, so the true risk specific to the active, growing melanomas could be substantially greater.[7] In 2009, Shields et al[1] provided analysis of 8033 patients with uveal melanoma, of which 1992 had active small choroidal melanoma managed with plaque radiotherapy, and the 10-year risk for melanoma-related metastasis was 12%.

In this analysis, we focused specifically on small choroidal melanoma outcomes following plaque radiotherapy. We found median tumor basal dimension at 8.0 mm and thickness at 2.7 mm, and multivariable risk factors for metastasis included older

age, symptoms of photopsia, larger tumor base, greater tumor thickness, and evidence of previous treatment.

After plaque radiotherapy, the 10-year rate of metastasis using 1.0-mm thickness increments was 25% for tumors 0 to 1.0 mm thick, with lower values for thicker tumors. The spike in metastasis in the thinnest tumors could be because of the exceptionally small cohort (n = 6, with only 1 event of metastasis), or this could represent the ominous diffuse choroidal melanoma, a subset of melanoma that demonstrates thin tumor with extensive basal dimension.

In fact, the mean basal dimension of these tumors was 7.8 mm (median, 7.8 mm, range, 2 mm-11.5 mm), while mean thickness/base (percentage) ratio was 12%, supporting the clinical definition of diffuse uveal melanoma.[18] These patients often are followed up for a prolonged period under the diagnosis of choroidal nevus, and later, after documented growth, are referred for treatment. A previous study[18] comparing diffuse vs nondiffuse small choroidal melanoma revealed 15-year melanoma-associated death at 16% vs 6% ($P < .001$), and the disparity persisted even in the thinnest tumors (≤2 mm; 16% vs 4%; $P = .01$). Diffuse choroidal melanoma represents only 3% of all melanomas and is defined as tumor thickness of 20% or less relative to the tumor base (with a mean thickness of 2.0 mm), giving the tumor a flat or placoid appearance with a prominent basal diameter.[19] Font et al[20] evaluated 54 patients enucleated with diffuse melanoma and found aggressive features of epithelioid cell type (85%), extrascleral extension (39%), and melanoma-associated death in 44%, with a mean survival of 20 months in patients with lethal tumors.

Regarding visual outcome, Shields et al[21] reviewed long-term visual acuity in 1106 eyes with uveal melanoma treated with plaque radiotherapy and found the 5-year rate of poor visual acuity (≤20/200 OU) was 24% for patients with small melanoma, 30% for patients with medium-sized melanoma, and 64% for patients with large melanoma. Based on multivariable analysis, 5 important clinical factors associated with poor visual acuity included older age, posterior location of tumor, proximity to the foveola, subretinal fluid, and increasing tumor thickness. These authors concluded that visual acuity was most effectively preserved in eyes with small melanoma outside a radius of 5 mm from the optic disc and foveola.[21] The COMS[22] subsequently provided 3-year visual outcomes for 623 patients randomized to plaque radiotherapy for medium-sized melanoma and found that visual acuity declined to less than or equal to 20/200 in 43% of those whose acuity had been better than 20/200 at initial presentation.

In this retrospective analysis, we found 5-year and 10-year rate of visual acuity loss equivalent to 3 or more Snellen lines at 39.2% and 48.9%, respectively. The 5-year and 10-year rates of poor visual acuity (≤20/200 OU) were 39.2% and 53.5%, respectively. Much of the vision loss was associated with radiation maculopathy (46.4% at 5 years and 59.0% at 10 years), radiation papillopathy (20.6% at 5 years and 30.1% at 10 years), and vitreous hemorrhage (11.7% at 5 years and 16.5% at 10 years), as well as features at initial presentation, including submacular tumor location and foveal serous retinal detachment. The median distance from the posterior tumor margin to the foveola was 2.0 mm and to the optic disc was 3.0 mm, which was typical for small choroidal melanoma because most are postequatorial in location. However, this location puts the eye at high risk for ultimate visual loss from radiation-associated ischemia and swelling.

Limitations

There are limitations in this retrospective analysis, including the unavailability of some data because of patient follow-up remote from our facility, a period of data collection that extended longer than 4 decades (during which time treatment philosophies and approaches have changed over this interval), and the possibility that patients might have intermittently received various treatments to improve visual acuity. In addition, even with the robust number of patients, the points of 15 and 20 years had relatively small numbers of patients, so these data should be interpreted with caution. Despite these drawbacks, this large cohort could prove useful for comparison to newer treatment regimens.

Conclusions

In summary, small choroidal melanoma can potentially be dangerous, with a 10-year risk for metastasis at 8.8%. This risk is highest in tumors with larger bases, greater thicknesses, increasing retinal detachment, and diffuse (flat) configurations. By comparison, this rate is far less than that of medium-sized or large melanomas, which had 10-year rates of metastasis at 25.4% and 48.7%, respectively.[1] We suggest that patients with potential small choroidal melanoma be evaluated by a qualified ophthalmologist or ocular oncologist for a timely diagnosis and prompt therapeutic intervention.

ARTICLE INFORMATION

Accepted for Publication: July 12, 2018.

Published Online: September 27, 2018. doi:10.1001/jamaophthalmol.2018.3881

Author Contribution: Dr C. Shields has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: C. Shields, Sioufi, Masoomian, Mashayekhi, J. Shields.
Acquisition, analysis, or interpretation of data: C. Shields, Sioufi, Srinivasan, Di Nicola, Barna, Bekerman, Emrich, Komarnicky, J. Shields.
Drafting of the manuscript: C. Shields, Sioufi, Masoomian, J. Shields.
Critical revision of the manuscript for important intellectual content: C. Shields, Sioufi, Srinivasan, Di Nicola, Barna, Bekerman, Mashayekhi, Emrich, Komarnicky, J. Shields.
Statistical analysis: C. Shields, Sioufi.
Obtained funding: J. Shields.
Administrative, technical, or material support: C. Shields, Sioufi, Srinivasan, Di Nicola, Masoomian, Bekerman, Emrich.
Supervision: C. Shields, Di Nicola, Bekerman, Mashayekhi, Emrich, Komarnicky, J. Shields.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No disclosures were reported.

Funding/Support: Support was provided by a grant from the Eye Tumor Research Foundation (Dr C. Shields).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: Presented in part by Dr C. Shields as the 2018 Jules C. Stein, MD, Lecture; June 8, 2018; Los Angeles, CA.

Additional Contributions: We thank the following individuals who contributed to data collection for this article: Marian Pauly, MD, Nivas Govindarajan, BS, Vera Yarovaya, MD, Jason L. Chien, BS, Maxwell R. Harley, BA, and Mark P. Seraly, BS, Ocular Oncology Service, Wills Eye Hospital. Rishita Nutheti, PhD, Ocular Oncology Service, Wills Eye Hospital, provided statistical analysis. These individuals were not compensated for their contributions.

REFERENCES

1. Shields CL, Furuta M, Thangappan A, et al. Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. *Arch Ophthalmol*. 2009;127(8):989-998. doi:10.1001/archophthalmol.2009.208

2. Shields JA, Shields CL. *Intraocular Tumors: An Atlas and Textbook*. 3rd ed. Philadelphia, PA: Lippincott Wolters Kluwers; 2016:95-127.

3. McLean IW, Foster WD, Zimmerman LE. Uveal melanoma: location, size, cell type, and enucleation as risk factors in metastasis. *Hum Pathol*. 1982;13(2):123-132. doi:10.1016/S0046-8177(82)80116-0

4. Diener-West M, Hawkins BS, Markowitz JA, Schachat AP. A review of mortality from choroidal melanoma, II: a meta-analysis of 5-year mortality rates following enucleation, 1966 through 1988. *Arch Ophthalmol*. 1992;110(2):245-250. doi:10.1001/archopht.1992.01080140101036

5. Shields CL, Shields JA, Kiratli H, De Potter P, Cater JR. Risk factors for growth and metastasis of small choroidal melanocytic lesions. *Ophthalmology*. 1995;102(9):1351-1361. doi:10.1016/S0161-6420(95)30864-0

6. The Collaborative Ocular Melanoma Study Group. Factors predictive of growth and treatment of small choroidal melanoma: COMS report No. 5. *Arch Ophthalmol*. 1997;115(12):1537-1544. doi:10.1001/archopht.1997.01100160707007

7. The Collaborative Ocular Melanoma Study Group. Mortality in patients with small choroidal melanoma: COMS report No. 4. *Arch Ophthalmol*. 1997;115(7):886-893. doi:10.1001/archopht.1997.01100160056009

8. Shields CL, Cater J, Shields JA, Singh AD, Santos MCM, Carvalho C. Combination of clinical factors predictive of growth of small choroidal melanocytic tumors. *Arch Ophthalmol*. 2000;118(3):360-364. doi:10.1001/archopht.118.3.360

9. Singh AD, Mokashi AA, Bena JF, Jacques R, Rundle PA, Rennie IG. Small choroidal melanocytic lesions: features predictive of growth. *Ophthalmology*. 2006;113(6):1032-1039. doi:10.1016/j.ophtha.2006.01.053

10. Damato BE, Heimann H, Kalirai H, Coupland SE. Age, survival predictors, and metastatic death in patients with choroidal melanoma: tentative evidence of a therapeutic effect on survival. *JAMA Ophthalmol*. 2014;132(5):605-613. doi:10.1001/jamaophthalmol.2014.77

11. Shields CL, Say EAT, Hasanreisoglu M, et al. Personalized prognosis of uveal melanoma based on cytogenetic profile in 1059 patients over an 8-year period: the 2017 Harry S. Gradle lecture. *Ophthalmology*. 2017;124(10):1523-1531. doi:10.1016/j.ophtha.2017.04.003

12. Shields CL, Say EAT, Hasanreisoglu M, et al. Cytogenetic abnormalities in uveal melanoma based on tumor features and size in 1059 patients: the 2016 W. Richard Green Lecture. *Ophthalmology*. 2017;124(5):609-618. doi:10.1016/j.ophtha.2016.12.026

13. Shields CL, Pefkianaki M, Mashayekhi A, Shields JA, Ganguly A. Cytogenetic results of choroidal nevus growth into melanoma in 55 consecutive cases. *Saudi J Ophthalmol*. 2018;32(1):28-32. doi:10.1016/j.sjopt.2018.02.004

14. Kim RS, Chevez-Barrios P, Divatia M, Bretana ME, Teh B, Schefler AC. Yield, techniques, and complications of transvitreal and transscleral biopsies in small uveal melanoma. *JAMA Ophthalmol*. 2018;136(5):482-488. doi:10.1001/jamaophthalmol.2018.0561

15. Shields CL, Mashayekhi A, Shields JA. By sleight of hand, prognosis determined—even for small choroidal melanoma. *JAMA Ophthalmol*. 2018;136(5):488-489. doi:10.1001/jamaophthalmol.2018.0196

16. Hawkins BS; Collaborative Ocular Melanoma Study Group. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma, IV: 10-year mortality findings and prognostic factors. COMS report No. 24. *Am J Ophthalmol*. 2004;138(6):936-951. doi:10.1016/j.ajo.2004.07.006

17. Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, V: twelve-year mortality rates and prognostic factors. COMS report No. 28. *Arch Ophthalmol*. 2006;124(12):1684-1693. doi:10.1001/archopht.124.12.1684

18. Shields CL, Kaliki S, Furuta M, Shields JA. Diffuse versus nondiffuse small (≤ 3 mm thickness) choroidal melanoma, comparative analysis in 1,751 cases: the 2012 F. Phinizy Calhoun lecture. *Retina*. 2013;33(9):1763-1776. doi:10.1097/IAE.0b013e318285cd52

19. Shields CL, Shields JA, De Potter P, Cater J, Tardio D, Barrett J. Diffuse choroidal melanoma: clinical features predictive of metastasis. *Arch Ophthalmol*. 1996;114(8):956-963. doi:10.1001/archopht.1996.01100140164009

20. Font RL, Spaulding AG, Zimmerman LE DIFFUSE MALI. Diffuse malignant melanoma of the uveal tract: a clinicopathologic report of 54 cases. *Trans Am Acad Ophthalmol Otolaryngol*. 1968;72(6):877-895.

21. Shields CL, Shields JA, Cater J, et al. Plaque radiotherapy for uveal melanoma: long-term visual outcome in 1106 consecutive patients. *Arch Ophthalmol*. 2000;118(9):1219-1228. doi:10.1001/archopht.118.9.1219

22. Melia BM, Abramson DH, Albert DM, et al; Collaborative Ocular Melanoma Study Group. Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma, I: visual acuity after 3 years. COMS report No. 16. *Ophthalmology*. 2001;108(2):348-366. doi:10.1016/S0161-6420(00)00526-1

Invited Commentary

Treating Small Choroidal Melanoma
Smaller Is Better

H. Culver Boldt, MD; Elaine Binkley, MD

Over the last several decades, ocular oncologists have set a goal to identify and treat smaller uveal melanomas. Another way to rephrase this goal would be to state that we want to identify melanocytic lesions that are likely to spread at some future time and ablate them before they do so. Ocular oncologists are very accurate in diagnosing medium and large uveal melanomas. Differentiation of small melanomas from high-risk choroidal nevi has been more challenging. Approximately 8% of people in the United States have a choroidal nevus. The malignant transformation rate is estimated at about 1 in 9000 per year.[1] This translates into about 2400 new cases of uveal melanoma each year in the United States, and the incidence seems to be increasing. Only about 30% of these lesions are diagnosed while they are small melanomas.

Related article page 1325

So how does one differentiate the occasional small uveal melanoma from the thousands of benign choroidal nevi? In the past, significant documented growth of a small lesion often was used as a surrogate for malignant transformation. However, in a study of risk factors for metastasis,[2] growth of a lesion was associated with an 8-fold increase in metastasis. Identification of those lesions that will grow in the future is the goal. In addition,