Metastasis of Uveal Melanoma Millimeter-by-Millimeter in 8033 Consecutive Eyes

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Objective: To determine the rate of metastasis of uveal melanoma on the basis of tumor thickness in millimeters.

Methods: Retrospective medical record review.

Results: The mean (median) patient age was 58 (59) years. A total of 8033 eyes were examined. Of the 285 eyes with iris melanoma, the mean tumor thickness was 2.7 mm and metastasis occurred in 0.5%, 4%, and 7% at 3, 5, and 10 years, respectively. Of the 492 eyes with ciliary body melanoma, the mean tumor thickness was 6.6 mm and metastasis occurred in 12%, 19%, and 33% at 3, 5, and 10 years, respectively. Of the 7256 eyes with choroidal melanoma, the mean tumor thickness was 5.5 mm and metastasis occurred in 8%, 15%, and 25% at 3, 5, and 10 years, respectively. For all uveal melanoma, metastasis at 5, 10, and 20 years was 6%, 12%, and 20% for small melanoma (0-3.0 mm thickness), 14%, 26%, and 37% for medium melanoma (3.1-8.0 mm), and 35%, 49%, and 67% for large melanoma (>8.0 mm). More specifically, metastasis per millimeter increment at 10 years was 6% (0-1.0 mm thickness), 12% (1.1-2.0 mm), 12% (2.1-3.0 mm), 16% (3.1-4.0 mm), 27% (4.1-5.0 mm), 28% (5.1-6.0 mm), 29% (6.1-7.0 mm), 41% (7.1-8.0 mm), 50% (8.1-9.0 mm), 44% (9.1-10.0 mm), and 51% (>10.0 mm). Clinical factors predictive of metastasis by multivariate analysis included increasing patient age, ciliary body location, increasing tumor diameter, increasing tumor thickness, having a brown tumor, and the presence of subretinal fluid, intraocular hemorrhage, or extraocular extension.

Conclusion: Increasing millimeter thickness of uveal melanoma is associated with increasing risk for metastasis.

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In 1962, Paul et al[1] from the Armed Forces Institute of Pathology reported the demographic data and prognosis of 3852 patients with uveal melanoma, the largest collection of patients with intraocular melanoma then. Their data revealed the following information: mean age at diagnosis of 55 years, approximately 54% male, and less than 1% African American. On the basis of the follow-up of 2652 cases, mortality rate by actuarial method was 29% at 5 years, 40% at 10 years, and 46% at 15 years, with a median survival of 15+ years. Ten-year mortality was lower in younger patients (aged 20-39 years) at 26% vs older patients (aged >70 years) at 51%. In 1992, Diener-West et al[2] provided a meta-analysis of 8 published articles that further refined our understanding of uveal melanoma prognosis by general tumor size. The combined weighted estimate of 5-year mortality was 16% for small tumors, 32% for medium tumors, and 53% for large tumors. Later, the Collaborative Ocular Melanoma Study disclosed melanoma-related mortality at 10 years to be 17% to 18% for medium melanoma and 40% to 45% for large melanoma.[3-6]

Uveal melanoma prognosis has been shown to be dependent on several clinical factors including tumor location in the ciliary body, large tumor size, diffuse (flat) configuration, and extraocular extension as well as histopathologic and cytogenetic factors including epithelioid cell type, increased mitotic activity, infiltrating lymphocytes, tumor vascular networks, and chromosomal mutations including monosomy 3 and 8q addition.[7,8] In several articles, tumor size has been identified as one of the key clinical features predictive of metastasis.[9,10] Furthermore, increasing tumor thickness, from small to medium to large, has been correlated with increasing risk for metastasis, but the exact relationship per millimeter of tumor thickness has not been previously addressed, to our knowledge. In this analysis, we evaluate a large cohort of 8033 patients observed long-term for melanoma-related

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Table 1. Uveal Melanoma in 8033 Patients: Demographic Data

Feature	Type of Melanoma, No. of Eyes								
	Iris (n=285)	Ciliary Body (n=492)	Iris vs Ciliary Body *P* Value[a]	Choroidal (n=7256)	Iris vs Choroidal *P* Value[a]	Ciliary Body vs Choroidal *P* Value[a]	Posterior Uveal (n=7748)	Iris vs Posterior Uveal *P* Value[a]	Uveal (n=8033)
Age, mean (median) [range], y	50 (52) [3-87]	59 (61) [6-93]	<.001[b]	58 (59) [5-99]	<.001[b]	.91[b]	58 (59) [5-99]	<.001[c]	58 (59) [3-99]
Race/ethnicity, No. (%)									
White	279 (98)	473 (96)	.18	7098 (98)	.94	.02	7571 (98)	.84	7850 (98)
African American	1 (<1)	1 (<1)	.70	31 (<1)	.85	.45	32 (<1)	.87	33 (<1)
Hispanic	3 (1)	13 (3)	.13	89 (1)	.79	.008	102 (1)	.70	105 (1)
Asian	1 (<1)	3 (<1)	.63	24 (<1)	.95	.31	27 (<1)	.99	28 (<1)
Native American	0	0	NA	1 (<1)	.84	.80	1 (<1)	.85	1 (<1)
Middle Eastern	1 (<1)	2 (<1)	.90	12 (<1)	.46	.22	14 (<1)	.51	15 (<1)
Asian Indian	0 (0)	0 (0)	NA	1 (<1)	.84	.80	1 (<1)	.85	1 (<1)
Sex, No. (%)	NA		.05	NA	.29	<.001	NA	<.001	NA
Male	137 (48)	201 (41)	NA	3718 (51)	NA	NA	3919 (51)	NA	4056 (50)
Female	148 (52)	291 (59)	NA	3538 (49)	NA	NA	3829 (49)	NA	3977 (50)
Eye, No. (%)	NA	NA	.08	3	.64	.03	NA	.57	NA
Right	144 (51)	217 (44)	NA	565 (49)	NA	NA	3782 (49)	NA	3926 (49)
Left	141 (49)	275 (56)	NA	3691 (50)	NA	NA	3966 (51)	NA	4107 (51)

Abbreviation: NA, not applicable.
[a] χ^2 Test.
[b] Post hoc test using Bonferroni correction after analysis of variance.
[c] *t* Test.

metastasis and correlate metastasis on the basis of a single millimeter increase in tumor thickness.

METHODS

A retrospective medical record review was performed for all patients with the clinical diagnosis of uveal melanoma managed by the Ocular Oncology Service, Wills Eye Institute, Thomas Jefferson University, Philadelphia, Pennsylvania, from August 25, 1970, to August 27, 2008. Institutional review board approval was obtained for this retrospective study. All patients were examined by one of the senior authors (C.L.S. or J.A.S.) using techniques of slitlamp biomicroscopy of the anterior and posterior segments of the eye and indirect ophthalmoscopy of the entire fundus. Details of the uveal melanoma were recorded on large anterior segment or fundus drawings for all patients. Anterior segment or fundus photography or both were performed on patients older than 6 years.

Clinical data were collected at the initial examination for patient age, race/ethnicity, sex, and affected eye. The tumor data included site location of tumor epicenter (iris, ciliary body, choroid), quadrant location of tumor epicenter (inferior, temporal, superior, nasal, macula), clock-hour location of the tumor, anteroposterior location of tumor epicenter (macula, macula-equator, equator–ora serrata), distance of posterior tumor margin to optic disc margin and foveola (expressed in millimeters), and largest tumor basal dimension and thickness (expressed in millimeters). Tumor basal diameter was measured by indirect ophthalmoscopy and tumor thickness by standardized ocular ultrasonography using B scan and A scan measurements. The ultrasonographic examination consisted of a dynamic evaluation of the intraocular tumor with assessment of tumor configuration and acoustic qualities on B scan, internal reflectivity on A scan, and measurement of thickness from tumor apex to base of the choroid on A scan using a perpendicular to the sclera. The ultrasonogram was performed by a single ultrasonographer over the past 20 years or the senior authors (C.L.S. or J.A.S.). Other clinical tumor features included melanoma shape and pigmentation, and related subretinal fluid, Bruch membrane rupture, extraocular extension, and intraocular hemorrhage. The tumor management was recorded. The date and interval to systemic metastasis was recorded. Screening 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), once-yearly liver imaging (magnetic resonance, computed tomography, or ultrasonography), and chest radiograph.

STATISTICAL ANALYSIS

Comparisons of patient demographic features and tumor features among iris, ciliary body, and choroidal melanoma were performed using analysis of variance (ANOVA) followed by post hoc testing using Bonferroni correction for continuous variables, such as patient age at diagnosis, tumor basal dimension, tumor thickness, and distance of tumor to optic disc margin and foveola. χ^2 Testing was performed for the other categorical variables. The specific comparisons between iris melanoma and posterior uveal melanoma were performed using *t* test for continuous variables, such as patient age at manifestation, tumor basal dimension, tumor thickness, and distance of tumor to optic disc margin and foveola. χ^2 Testing was performed for the other categorical variables.

Kaplan-Meier estimates using the product-limit method were calculated for time to melanoma metastasis for iris, ciliary body, choroidal, posterior uveal, and all uveal melanomas. These estimates were provided per 2-mm tumor thickness. The 95% confidence intervals were constructed around the estimates. Log-rank tests were performed to compare the survival distributions of small, medium, and large categories of tumor thickness.

A series of univariate Cox regression analyses were performed to identify the factors predictive of melanoma metastasis in the 8033 patients on the basis of clinical features at manifestation. All of the variables were analyzed as discrete variables except for patient age at manifestation, tumor basal dimension, tumor thickness, and distance of tumor to optic disc margin and foveola, which were evaluated as continuous vari-

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Table 2. Tumor Features of Uveal Melanoma in 8033 Patients

Feature	Type of Melanoma								
	Iris (n=285)	Ciliary Body (n=492)	Iris vs Ciliary Body *P* Value[a]	Choroidal (n=7256)	Iris vs Choroidal *P* Value[a]	Ciliary Body vs Choroidal *P* Value[a]	Posterior Uveal (n=7748)	Iris vs Posterior Uveal *P* Value[a]	Uveal (n=8033)
Quadrant, No. (%)									
Superior	23 (8)	135 (27)	<.001	1607 (22)	<.001	.007	1742 (22)	<.001	1765 (22)
Nasal	56 (20)	117 (24)	.18	1510 (21)	.64	.118	1627 (21)	.58	1683 (21)
Inferior	128 (45)	138 (28)	<.001	1478 (20)	<.001	<.001	1616 (21)	<.001	1744 (22)
Temporal	48 (17)	92 (19)	.52	2094 (29)	<.001	<.001	2186 (28)	<.001	2234 (28)
Macula	0	0		356 (5)	<.001	<.001	356 (5)	<.001	356 (4)
Diffuse	30 (11)	10 (2)	<.001	211 (3)	<.001	.259	221 (3)	<.001	251 (3)
Epicenter clock-hour position, No. (%)									
1	6 (2)	41 (8)	<.001	458 (6)	.004	.077	499 (6)	.003	505 (6)
2	5 (2)	32 (7)	.003	552 (8)	<.001	.370	584 (8)	<.001	589 (7)
3	17 (6)	34 (7)	.61	848 (12)	.003	.001	882 (11)	.004	899 (11)
4	40 (14)	31 (6)	<.001	537 (7)	<.001	.365	568 (7)	<.001	608 (8)
5	34 (12)	50 (10)	.45	493 (7)	.001	.005	543 (7)	.002	577 (7)
6	52 (18)	50 (10)	.001	547 (8)	<.001	.035	596 (8)	<.001	648 (8)
7	36 (13)	43 (9)	.08	492 (7)	<.001	.097	535 (7)	<.001	571 (7)
8	23 (8)	33 (7)	.48	604 (8)	.88	.206	637 (8)	.93	660 (8)
9	19 (7)	49 (10)	.12	828 (11)	.01	.32	877 (11)	.01	896 (11)
10	6 (2)	35 (7)	.003	552 (8)	<.001	.689	587 (8)	.001	593 (7)
11	7 (2)	44 (9)	<.001	507 (7)	.003	.102	552 (7)	.002	559 (7)
12	8 (3)	40 (8)	.003	641 (9)	<.001	.594	681 (9)	<.001	689 (9)
Diffuse	32 (11)	10 (2)	<.001	197 (3)	<.001	.364	207 (3)	<.001	239 (3)
Anteroposterior epicenter, No. (%)			NA		NA	NA		NA	
Iris	285 (100)	0		0			0		285 (4)
Ciliary body	0	492 (100)		0			492 (6)		492 (6)
Ora to equator	0	0		1217 (17)			1217 (16)		1217 (15)
Equator to macula	0	0		5622 (77)			5622 (73)		5622 (70)
Macula	0	0		417 (6)			417 (5)		417 (5)
Distance, mean (median) [range], mm									
To foveola	21.0 (21.0) [1.0-25.0]	13.4 (14.0) [0-25.0]	<.001[b]	3.8 (3.0) [0-25.0]	<.001[b]	<.001	4.4 (3.0) [0-25.0]	<.001[c]	4.9 (3.0) [0-25.0]
To optic disc	20.4 (20.0) [14.0-25.0]	13.5 (14.0) [0-25.0]	<.001[b]	4.0 (3.0) [0-22.0]	<.001[b]	<.001	4.6 (3.5) [0-25.0]	<.001[c]	5.1 (3.8) [0-25.0]
Tumor size, mean (median) [range], mm									
Base	6.5 (5.5) [1.0-25.0]	11.7 (11.0) [2.0-24.0]	<.001[b]	11.3 (11.0) [2.0-33.0]	<.01[b]	.116	11.3 (11.0) [2.0-33.0]	<.001[c]	11.1 (11.0) [1.0-33.0]
Thickness	2.7 (2.1) [0-24.0]	6.6 (6.0) [0.8-17.0]	<.001[b]	5.5 (4.5) [1.0-23.0]	<.01[b]	<.001	5.6 (4.5) [1.0-23.0]	<.001[c]	5.5 (4.5) [1.0-24.0]

[a] χ^2 Test.
[b] Post hoc test using Bonferroni correction after analysis of variance.
[c] *t* Test.

ables. Subsequent multivariate analyses were performed using the Cox regression forward stepwise method for the factors identified to be significant at the 5% level of significance. Hazard ratios were calculated for each risk factor. Kaplan-Meier estimates were calculated for time to melanoma metastasis for iris, ciliary body, choroidal, posterior uveal, and all uveal melanomas. Kaplan-Meier estimates for time to metastasis per millimeter tumor thickness were calculated.

RESULTS

Of 8033 patients managed on the Oncology Service at Wills Eye Institute, the mean (median) age was 58 (59) years (age range, 3-99 years) and 98% were white (**Table 1**). Patient demographic data are detailed in Table 1 and tumor features in **Table 2**. By χ^2 test, iris compared with ciliary body melanoma was located more commonly inferior (45% vs 28%, respectively; $P<.001$) and diffuse (11% vs 2%, respectively; $P<.001$) and was less often superior (8% vs 27%, respectively; $P<.001$) (Table 2). Ciliary body compared with choroidal melanoma was located more commonly inferior (28% vs 20%, respectively; $P<.001$) and less often temporal (19% vs 29%, respectively; $P<.001$). Clock-hour location of the melanoma did not significantly differ between ciliary body and choroidal tumors, but it did significantly differ between iris and posterior uveal melanoma in that iris tumors were more likely located at the 4- through 7-o'clock positions and less likely at the 9- through 3-o'clock positions. The frequency at the 8-o'clock position did not differ between iris and posterior uveal melanomas.

Of all eyes with uveal melanoma, tumor shape was described in 8012 cases as dome (n=6044 [75%]), mushroom (n=1490 [19%]), flat or plateau (n=463 [6%]), and tapioca (iris tumors) (n=15 [<1%]). The melanoma was pigmented (n=4389 [55%]), nonpigmented (n=1219 [15%]), or mixed pigmentation (n=2425 [30%]). Other features included subretinal fluid (n=5667 [71%]), Bruch membrane rupture (n=1669 [21%]), extraocular extension (n=222 [3%]), and intraocular hemorrhage (vitreous or subretinal) (n=821 [10%]). Initial melanoma management included plaque radiotherapy (n=5048 [63%]), enucleation (n=2261 [28%]), transpupillary thermo-

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Table 3. Kaplan-Meier Estimates of Probability for Systemic Metastasis From Iris Melanoma Based on Millimeter Increments in Tumor Thickness in 267 Patients

Tumor Thickness, mm	Iris Melanoma		Kaplan-Meier Estimate (95% Confidence Interval), %		
	No. of Patients	No. (%) of Patients With Systemic Metastasis	3 y	5 y	10 y
Using 1-mm increments					
0-1.0	45	2 (4.4)	0	5.6 (0-16)	11.1 (0-26)
1.1-2.0	87	2 (2.3)	0	4.7 (0-11)	4.7 (0-11)
2.1-3.0	72	2 (2.8)	1.9 (0-5)	1.9 (0-5)	8.4 (0-21)
3.1-4.0	36	1 (2.8)	0	0	25.0 (0-67)
>4.0	27	1 (3.7)	0	12.5 (0-35)	12.5 (0-35)
Using 2-mm increments					
0-2.0	132	4 (3.0)	0	4.9 (0-10)	6.6 (0-13)
2.1-4.0	108	3 (2.8)	1.3 (0-4)	1.3 (0-4)	6.0 (0-15)
>4.0	27	1 (3.7)	0	12.5 (0-35)	12.5 (0-35)
Using small, medium, and large					
Small, 0-3.0	204	6 (2.9)	0.7 (0-2)	3.8 (0-8)	7.1 (1-13)
Medium, 3.1-8.0	60	2 (3.3)	0	6.7 (0-19)	6.7 (0-19)
Large, >8.0	3	0			
Total	**267**	**8** (3.0)	0.5 (0-2)	4.1 (1-8)	6.9 (2-12)

therapy (n=1775 [22%]), laser photocoagulation (n=418 [5%]), surgical excision (n=396 [5%]), external beam radiotherapy (n=39 [<1%]), particle beam radiotherapy (n=31 [<1%]), cryotherapy (n=19 [<1%]), orbital exenteration (n=16 [<1%]), and observation (n=494 [6%]).

Tumor size significantly differed depending on tumor location (Table 2). The median tumor base was significantly smaller for iris (5.5 mm) compared with ciliary body (11.0 mm) ($P<.001$) melanoma, whereas ciliary body (11.0 mm) compared with choroidal (11.0 mm) melanoma base did not differ. The median tumor thickness was significantly less for iris (2.1 mm) compared with ciliary body (6.0 mm) ($P<.001$) melanoma and for choroidal (4.5 mm) compared with ciliary body (6.0 mm) ($P<.001$) melanoma.

During the mean (median) follow-up of 52 (35) months (range, 0-436 months), melanoma-related metastasis was found in 957 patients (12%), including iris (8 of 285 [2.8%]), ciliary body (70 of 492 [14.2%]), ora serrata–equator (226 of 1217 [18.6%]), equator-macula (632 of 5622 [11.2%]), and macula (21 of 417 [5.0%]).

Of the 285 eyes with iris melanoma, the mean tumor base was 6.5 mm and thickness was 2.7 mm (Table 2). At 3, 5, and 10 years follow-up, metastasis was found in 0.5%, 4.1%, and 6.9%, respectively. At 10 years follow-up, metastasis occurred in 11.1% (0-1.0 mm thickness), 4.7% (1.1-2.0 mm), 8.4% (2.1-3.0 mm), 25% (3.1-4.0 mm), and 12.5% (>4.0 mm), respectively (**Table 3**).

Of the 492 eyes with ciliary body melanoma, the mean tumor base was 11.7 mm and thickness was 6.6 mm (Table 2). At 3, 5, and 10 years follow-up, metastasis was found in 12%, 19%, and 33%, respectively. At 10 years follow-up, metastasis occurred in 25% (0-1.0 mm thickness), 24% (1.1-2.0 mm), 15% (2.1-3.0 mm), 19% (3.1-4.0 mm), 32% (4.1-5.0 mm), 22% (5.1-6.0 mm), 35% (6.1-7.0 mm), 46% (7.1-8.0 mm), 82% (8.1-9.0 mm), 32% (9.1-10.0 mm), and 43% (>10.0 mm). (**Table 4**)

Of the 7256 eyes with choroidal melanoma, the mean tumor base was 11.3 mm and thickness was 5.5 mm (Table 2). At 3, 5, and 10 years follow-up, metastasis was found in 8%, 15%, and 25%, respectively. At 10 years follow-up, metastasis occurred in 5% (0-1.0 mm thickness), 12% (1.1-2.0 mm), 12% (2.1-3.0 mm), 16% (3.1-4.0 mm), 26% (4.1-5.0 mm), 28% (5.1-6.0 mm), 28% (6.1-7.0 mm), 41% (7.1-8.0 mm), 48% (8.1-9.0 mm), 44% (9.1-10.0 mm), and 52% (>10.0 mm) (**Table 5**). Results for posterior uveal melanoma (ciliary body and choroidal) are listed in **Table 6**.

Of all eyes with uveal (iris, ciliary body, and choroidal) melanoma, metastasis was found in 8%, 15%, and 25% at 3, 5, and 10 years follow-up, respectively. At 10 years follow-up, metastasis occurred in 6% (0-1.0 mm thickness), 12% (1.1-2.0 mm), 12% (2.1-3.0 mm), 16% (3.1-4.0 mm), 27% (4.1-5.0 mm), 28% (5.1-6.0 mm), 29% (6.1-7.0 mm), 41% (7.1-8.0 mm), 50% (8.1-9.0 mm), 44% (9.1-10.0 mm), and 51% (>10.0 mm) (**Table 7**). At 10 years follow-up, metastasis occurred in 12% of small melanoma (0-3.0 mm thickness), 26% of medium melanoma (3.1-8.0 mm thickness), and 49% of large melanoma (>8.0 mm) (**Figure**). At 20 years follow-up, metastasis occurred in 20% of small melanoma, 37% of medium melanoma, and 67% of large melanoma. (Figure)

By multivariate analysis, factors predictive of metastasis from uveal melanoma include increasing patient age, ciliary body location, increasing tumor diameter, increasing tumor thickness, brown tumor, and the presence of subretinal fluid, intraocular hemorrhage, or extraocular extension (**Table 8**). Each millimeter increase in thickness showed a 1.06 hazard ratio.

COMMENT

One of the most important clinical features for estimation of uveal melanoma prognosis is tumor size.[2,7,9-11] Tumor size is most often measured in chord or arc length of largest basal diameter and greatest tumor thickness. The basal diameter is estimated through ophthalmoscopic judgment or measured with ultrasonography, transillumination, or digital photography calipers. Tumor

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Table 4. Kaplan-Meier Estimates of Probability for Systemic Metastasis From Ciliary Body Melanoma Based on Millimeter Increments in Tumor Thickness in 465 Patients

Tumor Thickness, mm	Ciliary Body Melanoma		Kaplan-Meier Estimate (95% Confidence Interval), %		
	No. of Patients	No. (%) of Patients With Systemic Metastasis	3 y	5 y	10 y
Using 1-mm increments					
0-1.0	6	1 (16.7)	25.0 (0-67)	25.0 (0-67)	25.0 (0-67)
1.1-2.0	27	4 (14.8)	4.8 (0-14)	24.3 (3-45)	24.3 (3-45)
2.1-3.0	45	3 (6.7)	7.0 (0-16)	7.0 (0-16)	14.7 (0-32)
3.1-4.0	59	3 (5.1)	0	8.4 (0-19)	18.5 (0-40)
4.1-5.0	51	7 (13.7)	2.7 (0-8)	17.4 (3-31)	32.2 (9-55)
5.1-6.0	51	5 (9.8)	3.4 (0-11)	7.6 (0-18)	21.8 (1-42)
6.1-7.0	39	9 (23.1)	17.6 (4-32)	22.8 (6-39)	34.6 (14-55)
7.1-8.0	41	7 (17.1)	20.8 (4-38)	20.8 (4-38)	45.7 (15-77)
8.1-9.0	42	9 (21.4)	11.1 (0-23)	11.1 (0-23)	82.0 (53-100)
9.1-10.0	25	4 (16.0)	12.5 (0-29)	32.0 (5-59)	32.0 (5-59)
>10.0	79	17 (21.5)	39.0 (23-56)	43.1 (26-60)	43.1 (26-60)
Using 2-mm increments					
0-2.0	33	5 (15.2)	8.0 (0-19)	24.6 (5-44)	24.6 (5-44)
2.1-4.0	104	6 (5.8)	2.9 (0-7)	7.4 (0-15)	17.2 (3-32)
4.1-6.0	102	12 (11.8)	3.1 (0-7)	13.0 (4-22)	28.1 (12-44)
6.1-8.0	80	16 (20.0)	19.0 (8-30)	22.1 (10-34)	38.5 (21-56)
8.1-10.0	67	13 (19.4)	11.6 (2-21)	18.7 (6-32)	67.1 (40-94)
>10.0	79	17 (21.5)	39.0 (23-56)	43.1 (26-60)	43.1 (26-60)
Using small, medium, and large					
Small, 0-3.0	78	8 (10.3)	7.7 (0-15)	15.0 (5-25)	19.0 (6-32)
Medium, 3.1-8.0	241	31 (12.9)	7.5 (3-12)	14.8 (9-21)	29.5 (19-40)
Large, >8.0	146	30 (20.5)	24.5 (15-34)	30.2 (19-41)	41.0 (26-56)
Total	**465**	**69** (14.8)	11.9 (8-16)	18.8 (14-24)	33.4 (25-41)

Table 5. Kaplan-Meier Estimates of Probability for Systemic Metastasis From Choroidal Melanoma Based on Millimeter Increments in Tumor Thickness in 6889 Patients

Tumor Thickness, mm	Choroidal Melanoma		Kaplan-Meier Estimate (95% Confidence Interval), %		
	No. of Patients	No. (%) of Patients With Systemic Metastasis	3 y	5 y	10 y
Using 1-mm increments					
0-1.0	62	3 (4.8)	2.0 (0-6)	4.5 (0-11)	4.5 (0-11)
1.1-2.0	508	37 (7.3)	2.5 (1-4)	7.5 (5-11)	12.5 (8-17)
2.1-3.0	1422	78 (5.5)	1.9 (1-3)	4.7 (3-6)	11.9 (9-15)
3.1-4.0	1189	97 (8.2)	3.3 (2-5)	8.2 (6-10)	16.5 (13-20)
4.1-5.0	757	98 (12.9)	8.0 (6-10)	15.0 (11-18)	26.4 (21-32)
5.1-6.0	560	82 (14.6)	9.0 (6-12)	18.1 (14-22)	28.4 (22-35)
6.1-7.0	474	62 (13.1)	8.8 (6-12)	14.5 (10-19)	28.2 (21-36)
7.1-8.0	471	96 (20.4)	12.5 (9-16)	21.3 (16-26)	40.6 (33-49)
8.1-9.0	361	90 (24.9)	18.3 (13-23)	33.0 (26-40)	47.5 (39-56)
9.1-10.0	356	75 (21.1)	18.6 (13-24)	30.7 (24-38)	44.5 (35-54)
>10.0	729	153 (21.0)	26.8 (23-32)	40.0 (34-46)	51.6 (44-59)
Using 2-mm increments					
0-2.0	570	40 (7.0)	2.4 (1-4)	7.2 (4-10)	11.4 (7-15)
2.1-4.0	2611	175 (6.7)	2.5 (2-3)	6.3 (5-8)	14.0 (12-16)
4.1-6.0	1317	180 (13.7)	8.4 (7-10)	16.3 (14-19)	27.2 (23-31)
6.1-8.0	945	158 (16.7)	10.7 (8-13)	18.0 (15-21)	34.6 (29-40)
8.1-10.0	717	165 (23.0)	18.5 (15-22)	31.9 (27-37)	46.2 (40-53)
>10.0	729	153 (21.0)	26.8 (22-31)	40.0 (34-46)	51.6 (44-59)
Using small, medium, and large					
Small, 0-3.0	1992	118 (5.9)	2.0 (1-3)	5.4 (4-7)	11.6 (9-14)
Medium, 3.1-8.0	3451	435 (12.6)	7.2 (6-8)	13.9 (12-15)	25.4 (23-28)
Large, >8.0	1446	318 (22.0)	22.2 (19-25)	35.5 (32-39)	48.7 (44-54)
Total	**6889**	**871** (12.6)	8.3 (7-9)	15.0 (14-16)	25.0 (23-27)

thickness is measured by ultrasonographic calipers. According to the Collaborative Ocular Melanoma Study, ultrasonography measurement of tumor thickness is relatively accurate and was within 2 mm of histopathologic measurement of thickness in 90% of eyes.[12] However, basal diameter estimates by ultrasonography showed poorer

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Table 6. Kaplan-Meier Estimates of Probability for Systemic Metastasis From Posterior Uveal Melanoma (Involving Ciliary Body and/or Choroid) Based on Millimeter Increments in Tumor Thickness in 7354 Patients

Tumor Thickness, mm	Posterior Uveal Melanoma		Kaplan-Meier Estimate (95% Confidence Interval), %		
	No. of Patients	No. (%) of Patients With Systemic Metastasis	3 y	5 y	10 y
Using 1-mm increments					
0-1.0	68	4 (5.9)	3.6 (0-9)	5.9 (0-12)	5.9 (0-12)
1.1-2.0	535	41 (7.7)	2.6 (1-4)	8.4 (5-11)	13.1 (9-17)
2.1-3.0	1467	81 (5.5)	2.0 (1-3)	4.7 (3-6)	12.0 (9-15)
3.1-4.0	1248	100 (8.0)	3.2 (2-4)	8.2 (6-10)	16.6 (13-20)
4.1-5.0	808	105 (13.0)	7.8 (6-10)	15.1 (12-18)	26.8 (22-32)
5.1-6.0	611	87 (14.2)	8.6 (6-11)	17.3 (13-21)	28.0 (22-34)
6.1-7.0	513	71 (13.8)	9.5 (6-13)	15.2 (11-19)	28.9 (22-36)
7.1-8.0	512	103 (20.1)	13.1 (10-17)	21.4 (17-26)	40.8 (33-48)
8.1-9.0	403	99 (24.6)	17.6 (13-22)	31.1 (25-37)	50.2 (41-59)
9.1-10.0	381	79 (20.7)	18.3 (13-23)	30.8 (24-38)	44.0 (35-53)
>10.0	808	170 (21.0)	27.9 (23-32)	40.2 (35-46)	51.1 (44-58)
Using 2-mm increments					
0-2.0	603	45 (7.5)	2.7 (1-4)	8.1 (5-11)	12.1 (8-16)
2.1-4.0	2715	181 (6.7)	2.5 (2-3)	6.3 (5-8)	14.1 (12-16)
4.1-6.0	1419	192 (13.5)	8.0 (6-10)	16.1 (14-19)	27.3 (23-31)
6.1-8.0	1025	174 (17.0)	11.3 (9-14)	18.3 (15-21)	35.0 (30-40)
8.1-10.0	784	178 (22.7)	18.0 (15-21)	31.0 (26-36)	47.8 (41-54)
>10.0	808	170 (21.0)	27.8 (23-32)	40.3 (35-46)	51.1 (44-58)
Using small, medium, and large					
Small, 0-3.0	2070	126 (6.1)	2.2 (1-3)	5.8 (4-7)	11.9 (9-14)
Medium, 3.1-8.0	3692	466 (12.6)	7.3 (6-8)	14.0 (12-15)	25.7 (23-28)
Large, >8.0	1592	348 (21.9)	22.4 (20-25)	35.1 (32-39)	49.4 (45-54)
Total	**7354**	**940** (12.8)	8.5 (8-9)	15.2 (14-16)	25.4 (24-27)

Table 7. Kaplan-Meier Estimates of Probability for Systemic Metastasis From Uveal Melanoma Based on Millimeter Increments in Tumor Thickness in 7621 Patients

Tumor Thickness, mm	Uveal Melanoma		Kaplan-Meier Estimate (95% Confidence Interval), %		
	No. of Patients	No. (%) of Patients With Systemic Metastasis	3 y	5 y	10 y
Using 2-mm increments					
0-1.0	113	6 (5.3)	2.4 (0-6)	5.7 (0-11)	5.7 (0-11)
1.1-2.0	622	43 (6.9)	2.3 (1-4)	7.9 (5-11)	12.0 (8-16)
2.1-3.0	1539	83 (5.4)	2.0 (1-3)	4.6 (3-6)	11.8 (9-15)
3.1-4.0	1284	101 (7.9)	3.1 (2-4)	8.1 (6-10)	16.3 (13-20)
4.1-5.0	820	106 (12.9)	7.5 (5-10)	15.2 (12-18)	26.8 (22-32)
5.1-6.0	617	87 (14.1)	8.6 (6-11)	17.3 (13-21)	27.9 (22-34)
6.1-7.0	516	71 (13.8)	9.5 (6-13)	15.2 (12-20)	28.8 (22-36)
7.1-8.0	515	103 (20.0)	13.0 (10-17)	21.3 (17-26)	40.8 (33-48)
8.1-9.0	404	99 (24.5)	17.6 (13-22)	31.1 (25-37)	50.2 (41-59)
9.1-10.0	382	79 (20.7)	18.2 (13-23)	30.7 (24-37)	43.7 (34-53)
>10.0	809	170 (21.0)	27.8 (23-32)	40.2 (35-46)	51.0 (44-58)
Using 2-mm increments					
0-2.0	735	49 (6.7)	2.3 (1-4)	7.6 (5-10)	11.3 (8-15)
2.1-4.0	2823	184 (6.5)	2.5 (2-3)	6.2 (5-7)	13.9 (12-16)
4.1-6.0	1437	193 (13.4)	8.0 (6-10)	16.1 (14-19)	27.2 (23-31)
6.1-8.0	1031	174 (16.9)	11.3 (9-14)	18.3 (15-21)	35.0 (30-40)
8.1-10.0	786	178 (22.6)	17.9 (15-21)	30.9 (26-35)	47.6 (41-54)
>10.0	809	170 (21.0)	27.8 (23-32)	40.2 (35-46)	51.0 (44-58)
Using small, medium, and large					
Small, 0-3.0	2274	132 (5.8)	2.1 (1-3)	5.6 (4-7)	11.5 (9-14)
Medium, 3.1-8.0	3752	468 (12.5)	7.2 (6-8)	13.9 (12-15)	25.5 (23-28)
Large, >8.0	1595	348 (21.8)	22.3 (20-25)	35.0 (32-39)	49.2 (44-54)
Total	**7621**	**948** (12.4)	8.2 (7-9)	14.9 (14-16)	24.8 (23-26)

accuracy, as correlation within 2 mm of histopathology measurements was noted in only 58% of cases. Most studies on prognosis have used either basal diameter or thickness as the basis for estimating prognosis. For accuracy and reproducibility reasons, we have historically preferred thickness measurements.

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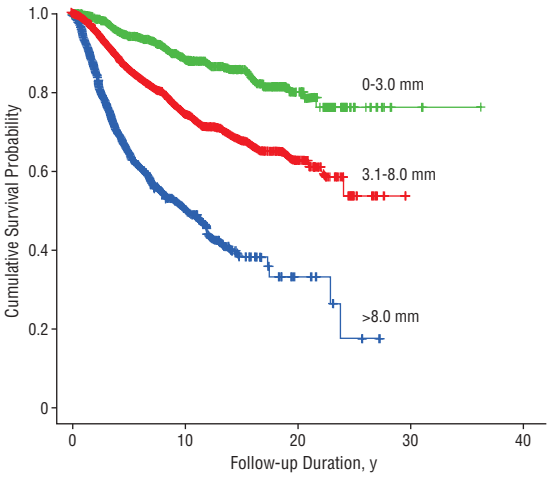
In 1980, McLean et al[13] analyzed the natural history of uveal melanoma in 2055 cases managed with enucleation between 1940 and 1960 and filed in the Registry of Ophthalmic Pathology. The tumor size was measured on gross examination of the globe and classified into small (<11 mm diameter), medium (11-15 mm diameter), or large (>15 mm diameter). At 10 years follow-up, actuarial survival was 81% for small melanoma, 60% for medium melanoma, and 35% for large melanoma.

In 2003, Kujala et al[9] evaluated long-term prognosis of 289 patients with uveal melanoma who were observed for a median of 28 years. By Kaplan-Meier analysis, they found melanoma metastasis at 32% by 5 years, 50% by 15 years, 56% by 25 years, and 62% by 35 years. Of those who died of uveal melanoma, death occurred within 15 years in 90% and 25 years in 98%. Tumor size was graded by diameter (without thickness measurement) and Kaplan-Meier estimates for melanoma-related mortality for 5, 15, 25, and 35 years at 8%, 12%, 18%, and 42%, respectively, for small tumors (<10 mm basal diameter), 32%, 48%, 60%, and 60%, respectively, for medium tumors (10-15 mm basal diameter), and 50%, 63%, 66%, and 75%, respectively, for large tumors (>15 mm basal diameter). Each millimeter increase in tumor diameter showed a 1.08 hazard ratio.

Diener-West et al[2] performed a meta-analysis of published articles about uveal melanoma prognosis based on tumor size graded as small, medium, or large. As this was a meta-analysis, there were numerous individual definitions for each size category. The tumor size definition varied per article with small tumors defined as one of the following: less than 3 mm thickness and less than 10 mm diameter, less than 10 mm diameter, less than or equal to 10 mm diameter, less than 11 mm diameter, less than 11 mm diameter or less than or equal to 2 mm high, or less than 300 mm^3. Medium tumors were defined as 10 to 15 mm diameter, 11 to 15 mm diameter, 11 to 15 mm diameter or 3 to 5 mm high, or less than or equal to 15 mm diameter. Large tumors were defined as greater than 15 mm diameter or greater than 15 mm diameter or greater than 5 mm high. They found 5-year all-cause mortality to be 16% for small melanoma, 32% for medium melanoma, and 53% for large melanoma. They recognized the difficulties in conducting their meta-analysis for mortality rates from the few published articles, heterogeneous populations and treatments, different methods of reporting mortality, and, importantly, difference in definitions of tumor size.

The Collaborative Ocular Melanoma Study (COMS) conducted 2 multicenter trials regarding therapy for uveal melanoma. In the medium-sized tumor trial (2.5-10 mm thickness and basal diameter <16 mm), eyes were randomized to iodine I 125 brachytherapy or enucleation. In this trial, melanoma-related mortality at 5, 10, and 12 years was 10%, 18%, and 21%, respectively, for patients in the ^{125}I brachytherapy treatment arm and 11%, 17%, and 17%, respectively, for those in the enucleation treatment arm.[3,4] In the large tumor trial (>10 mm thickness or >2 mm thickness and >16 mm basal diameter), eyes were randomized to enucleation or external beam radiotherapy preceding enucleation. In that trial, melanoma-related mortality at 5 and 10 years was 28% and 40%, respectively, for patients in the enucleation treatment arm and 26% and 45% in the external beam radiotherapy preceding enucleation treatment arm.[5,6]



Tumor thickness, mm	1 y	3 y	5 y	10 y	15 y	20 y	*P* value
0-3.0	0.5 (10/1782)	2.1 (34/1338)	5.6 (77/949)	11.5 (114/386)	14.1 (122/158)	19.7 (130/52)	
3.1-8.0	1.1 (37/2983)	7.2 (191/2030)	13.9 (318/1362)	25.5 (432/449)	32.3 (458/152)	37.3 (465/49)	<.001
>8.0	5.3 (61/988)	22.3 (207/546)	35.0 (284/318)	49.2 (330/83)	61.7 (344/24)	66.9 (346/7)	<.001

Figure. Kaplan-Meier analysis of time to systemic metastasis from uveal melanoma based on tumor thickness in 7621 patients. The values in the table are given as the percentage with the event (number failed/number left) at each increasing increment. *P* values were determined by comparing values with the 0- to 3-mm group using the log-rank test.

In our analysis, we attempted to maintain simplicity, accuracy, and reproducibility of tumor measurement for the ample cohort of 8033 eyes with melanomas. The tumor dimensions were described as basal diameter by clinical estimation by 2 experienced observers (C.L.S. and J.A.S.) and tumor thickness by ultrasonographic measurement in every case. Thickness measurement by ocular ultrasonography was believed to represent a relatively nonarbitrary measurement of tumor size. Tumor thickness at diagnosis was a mean of 2.7 mm for iris melanoma, 6.6 mm for ciliary body melanoma, and 5.5 mm for choroidal melanoma. In our analysis, melanoma size was not artificially classified into small, medium, or large, but instead was based on exact millimeter thickness. The multivariate analysis revealed tumor thickness as a significant factor predictive of metastasis and each millimeter increase imparted a 1.06 hazard ratio. The rate of melanoma-related metastasis at 10 years based on exact tumor thickness was 6% (0-1.0 mm thickness), 12% (1.1-2.0 mm), 12% (2.1-3.0 mm), 16% (3.1-4.0 mm), 27% (4.1-5.0 mm), 28% (5.1-6.0 mm), 29% (6.1-7.0 mm), 41% (7.1-8.0 mm), 50% (8.1-9.0 mm), 44% (9.1-10.0 mm), and 51% (>10.0 mm) (Table 7).

The metastatic potential was further refined based on tumor location in the iris, ciliary body, choroid, and entire posterior uvea (ciliary body and choroid) (Tables 3-6). The 10-year rate of metastasis for a 3.5- mm-thick melanoma in the ciliary body was 19%, choroid was 17%, and

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Table 8. Univariate and Multivariate Analyses of Factors Predictive of Melanoma Metastasis in 8033 Patients Based on Clinical Features at Presentation

Feature	*P* Value	Hazard Ratio (95% Confidence Interval)
Univariate Analysis		
Age[a]	<.001	1.18 (1.13-1.23)
Uveal melanoma		
Ciliary body vs iris[b]	<.001	6.25 (3.01-12.98)
Choroidal vs iris[b]	<.001	4.38 (2.19-8.80)
Uveal melanoma location		
Posterior uvea vs iris[b]	<.001	4.48 (2.23-8.99)
Epicenter quadrantic		
Superior vs macula[b]	<.001	2.94 (1.77-4.90)
Nasal vs macula[b]	<.001	3.13 (1.88-5.21)
Inferior vs macula[b]	<.001	3.15 (1.89-5.23)
Temporal vs macula[b]	<.001	2.81 (1.69-4.66)
Diffuse vs macula[b]	<.001	10.86 (6.26-18.85)
Epicenter clock-hour position[c]		
Diffuse vs 1[b]	<.001	4.14 (2.88-5.97)
Diffuse vs 2[b]	<.001	4.76 (3.29-6.89)
Diffuse vs 3[b]	<.001	4.03 (2.92-5.56)
Diffuse vs 4[b]	<.001	4.52 (3.16-6.47)
Diffuse vs 5[b]	<.001	3.50 (2.47-4.95)
Diffuse vs 6[b]	<.001	3.87 (2.74-5.47)
Diffuse vs 7[b]	<.001	3.50 (2.49-4.93)
Diffuse vs 8[b]	<.001	3.49 (2.49-4.89)
Diffuse vs 9[b]	<.001	4.03 (2.92-5.56)
Diffuse vs 10[b]	<.001	3.29 (2.34-4.61)
Diffuse vs 11[b]	<.001	3.26 (2.31-4.60)
Diffuse vs 12[b]	<.001	3.98 (2.83-5.58)
Diffuse vs not diffuse[b]	<.001	3.84 (2.95-5.00)
Epicenter anteroposterior		
Ciliary body vs iris melanoma[b]	<.001	6.26 (3.01-13.02)
Ora serrata–equator vs iris melanoma[b]	<.001	7.76 (3.84-15.71)
Equator-macula vs iris melanoma[b]	<.001	3.99 (1.99-8.01)
Ciliary body vs equator-macula melanoma[b]	<.001	1.57 (1.23-2.01)
Ora serrata–equator vs equator-macula melanoma[b]	<.001	1.95 (1.67-2.27)
Ciliary body vs macula melanoma[b]	<.001	3.75 (2.30-6.11)
Ora serrata–equator vs macula melanoma[b]	<.001	4.64 (2.97-7.26)
Equator-macula vs macula melanoma[b]	<.001	2.39 (1.55-3.69)
Anterior margin		
Ciliary body vs iris melanoma[b]	<.001	2.08 (1.64-2.62)
Iris vs equator-macula melanoma[b]	<.001	2.00 (1.57-2.54)
Ciliary body vs equator-macula melanoma[b]	<.001	4.14 (3.51-4.89)
Ora serrata–equator vs equator-macula melanoma[b]	<.001	2.04 (1.73-2.42)
Posterior margin		
Ora serrata–equator vs iris melanoma[b]	<.001	3.70 (1.72-7.98)
Equator-macula vs iris melanoma[b]	<.001	3.71 (1.85-7.47)
Macula vs iris melanoma[b]	<.001	3.57 (1.77-7.19)
Diameter[d]	<.001	1.21 (1.20-1.23)
Thickness[d]	<.001	1.22 (1.20-1.24)
Shape		
Mushroom vs dome[b]	.001	1.33 (1.13-1.57)
Diffuse vs dome[b]	.004	1.45 (1.12-1.87)
Color		
Brown vs yellow[b]	<.001	1.57 (1.29-1.92)
Subretinal fluid		
Present vs absent[b]	<.001	1.52 (1.31-1.77)
Bruch membrane		
Present vs absent[b]	<.001	1.38 (1.19-1.61)
Extraocular extension		
Present vs absent[b]	<.001	2.68 (1.97-3.64)
Hemorrhage intraocular		
Present vs absent[b]	<.001	1.76 (1.47-2.11)

(continued)

Table 8. Univariate and Multivariate Analyses of Factors Predictive of Melanoma Metastasis in 8033 Patients Based on Clinical Features at Presentation (continued)

Feature	*P* Value	Hazard Ratio (95% Confidence Interval)
Multivariate Analysis		
Age[a]	<.001	1.13 (1.08-1.18)
Uveal melanoma location		
Posterior uvea vs iris[b]	.026	2.30 (1.10-4.80)
Anterior margin		
Iris vs equator melanoma[b]	.009	1.46 (1.10-1.94)
Ciliary body vs equator melanoma[b]	<.001	1.68 (1.38-2.06)
Diameter[d]	<.001	1.14 (1.11-1.16)
Thickness[d]	<.001	1.06 (1.03-1.09)
Color[d]		
Brown vs yellow[b]	.001	1.41 (1.15-1.73)
Subretinal fluid		
Present vs absent[b]	.002	1.28 (1.09-1.51)
Extraocular extension		
Present vs absent[b]	.039	1.41 (1.02-1.95)
Hemorrhage intraocular		
Present vs absent[b]	.043	1.22 (1.01-1.47)

[a] Per 10-year increase.
[b] Reference variable.
[c] A comparison of every clock hour vs the 12- or 6-o'clock position showed no significant statistical difference. A comparison of every clock-hour increase (without considering the diffuse option) showed no significant difference.
[d] Per 1-mm increase.

posterior uvea was 17%. A comparison of metastatic potential at different sites with different sizes can quickly be understood using the data in the tables. For example, a melanoma measuring 2, 5, or 8 mm thickness developed metastasis at 10 years in 24%, 32%, and 46%, respectively, if in the ciliary body compared with 13%, 26%, and 41%, respectively, if in the choroid (Tables 4 and 5).

In the entire group of 8033 patients, a gradual increasing risk for metastasis was noted with increasing thickness with the exception of the relatively thin (diffuse) melanomas, measuring 2 mm or less in thickness. Iris melanoma from 0 to 1.0 mm and ciliary body or choroidal melanoma from 1.1 to 2.0 mm imparted a slightly higher metastatic rate than those slightly thicker, believed to be caused by the inclusion of a subset of melanoma termed *diffuse melanoma*. Diffuse melanoma is a variant of melanoma that exhibits horizontal growth pattern in a relatively flat configuration and displays a more aggressive course with invasion of the sclera, extrascleral extension, epithelioid cell type, and higher rate of metastasis.[14] In this analysis, diffuse melanoma represented 3% of all uveal melanoma, and specifically included 3% of choroidal, 2% of ciliary body, and 11% of iris melanomas. Diffuse melanoma imparted a 3.84 relative risk for metastasis compared with a nondiffuse melanoma and specifically a 3.26 to 4.76 relative risk for metastasis compared with nondiffuse melanoma at any specific clock hour (Table 8). It is recognized in the literature that this thin variant of melanoma imparts greater metastatic risk when in the choroid or in the iris.[14,15]

The most important factor for metastasis from cutaneous melanoma remains tumor thickness.[16-20] The standard method for measuring cutaneous melanoma thickness is by histologic Breslow depth as measured from the granular layer of the epidermis down to the deepest point of invasion. The TNM classification of melanoma uses Breslow thickness as the main indicator of "T," representing tumor size. In an analysis of 5702 patients with cutaneous

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melanoma in Germany, comparing results from melanoma in the head/neck region to other sites, it was found that the variable with the highest prognostic effect was tumor thickness.[16] An analysis of Medicare patients in the United States showed that those with cutaneous melanoma detected by dermatologists (compared with nondermatologists) had better survival primarily because of earlier tumor stage ($P<.01$) and thinner tumor (0.86 mm vs 1.0 mm, $P<.05$).[17] Comparing patient survival with cutaneous melanoma in the United Kingdom vs Australia, it was found again that tumor thickness was the most important factor.[18] Sartore et al[19] reported that sentinel lymph node metastasis from cutaneous melanoma was minimized in thin tumors (<1.19 mm thickness) and those that lacked ulceration and lymphovascular invasion. Recent developments for measurement of exact in vivo thickness of cutaneous melanoma using 75-MHz ultrasonography has been explored and found to show reliable correlation with pathologic Breslow thickness.[20]

Uveal melanoma size is not the only factor related to prognosis. There are numerous factors to consider, but tumor size continues to be one of the most important clinical factors. Coupland et al[21] evaluated 847 patients with uveal melanoma for metastatic death and found clinical and histopathologic predictive factors of largest basal tumor diameter, closed loops, epithelioid cells, mitotic rate, and extraocular spread. Damato et al[22] included genetic testing in their analysis for factors predictive of metastatic death and found the most important independent predictors to be basal tumor diameter, chromosome 3 loss, and epithelioid cell histopathology. Eskelin et al[23] explored tumor doubling times and speculated that most metastases initiate 5 years before primary treatment. Further theoretical analysis revealed estimates that metastases occur at an approximate tumor volume of 7 mm^3, when the tumor is clinically visible at roughly 3 mm diameter and 1.5 mm thickness.[24]

Screening for metastasis from choroidal melanoma generally includes twice-yearly liver function tests (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, or bilirubin levels) and physical examination and once-yearly liver and lung imaging. However, there remains debate on which tests have the highest yield and most beneficial cost-effectiveness.[25,26] Eskelin et al[25] evaluated 46 consecutive patients with metastatic uveal melanoma who were screened with liver function tests, chest radiograph, and abdominal ultrasonography. They found that the lactate dehydrogenase level was the most sensitive liver function test. In addition, they noted that semiannual screening with liver function tests and abdominal ultrasonography detected disease in more than 95% of patients while they were still asymptomatic. Chest radiography was found to be insensitive. Our protocol is similar to that used by Eskelin et al. A different approach was used in the COMS, in which 2320 patients were screened annually with liver function tests. If the test results were elevated, a diagnostic or imaging test was performed. They found that the sensitivity, specificity, and positive and negative predictive values associated with one abnormal liver function test for metastasis was 15%, 92%, 46%, and 71%, respectively.[26] They concluded that their approach showed high specificity but low sensitivity and advised better tests to detect metastatic disease.[26]

In this analysis, we correlated long-term prognosis in a refined and practical millimeter-by-millimeter fashion, using ultrasonography for accurate measurements. These data are applicable for the practicing clinician in that they are simple and useful in the clinic setting. This is especially practical for those patients who do not undergo genetic sampling or those who do not have histopathologic assessment owing to treatment with nonenucleation methods. Knowledge of the approximate risk for melanoma-related metastasis based on accurate measurement of thickness and the added risk of each millimeter of thickness could ultimately affect the therapeutic decision.

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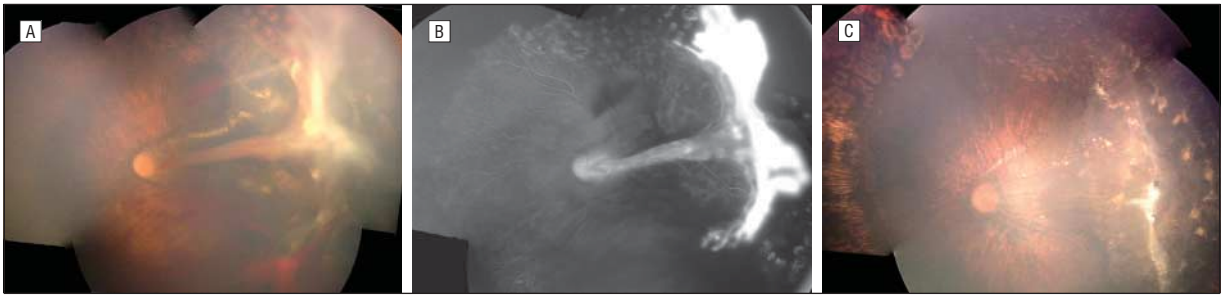
Archives Web Quiz Winner

Congratulations to the winner of our March quiz, Theodore K. Lin, MD, Vitreoretinal Fellow, Department of Surgery, Section of Ophthalmology and Visual Sciences, University of Chicago, Chicago, Illinois. The correct answer to our March challenge was Norrie disease. For a complete discussion of this case, see the Letters: Research Letters section in the April *Archives* (Shima C, Kusaka S, Kondo H, Hasebe H, Fujikado T, Tano Y. Lens-sparing vitrectomy effective for reattachment of newly developed falciform retinal detachment in patient with Norrie disease. *Arch Ophthalmol*. 2009;127[4]:579-580).



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