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Impact of Tumor Pigmentation in 6934 Patients with Uveal Melanoma at a Single Center

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Purpose: To evaluate clinical features and outcomes associated with degree of tumor pigmentation in patients with uveal melanoma (UM) of the choroid and ciliary body.

Design: Retrospective observational study.

Subjects: Six thousand nine hundred thirty-four consecutive patients with choroidal or ciliary body melanoma between 1971 and 2007 from a single ocular oncology center.

Methods: Data on patient demographics, tumor characteristics, treatment approach, and clinical outcomes were collected. Comparisons between pigmented (>80% pigmentation by surface area), partially pigmented (20%−80%), and nonpigmented tumors (<20%) were performed using relevant hypothesis testing. Survival analyses for metastasis and melanoma-related death were conducted using the Kaplan−Meier method with log-rank tests for univariate comparisons. A multivariate Cox regression analysis was performed to assess the independent effects of multiple covariates on time-to-metastasis.

Main Outcome Measures: Extraocular extension, ocular melanocytosis, time to tumor recurrence, tumor location, and melanoma-related metastasis and death.

Results: There were 6934 eyes with UM and the degree of tumor pigmentation was classified as pigmented (n = 3762; 54%), partially pigmented (n = 2115; 31%), or nonpigmented (n = 1057; 15%). Pigmented UM was associated with extraocular extension ($P < 0.001$), ocular melanocytosis ($P = 0.003$), earlier tumor recurrence ($P < 0.001$), and more anterior tumor epicenter location (ciliary body, and equator to ora serrata) ($P < 0.001$). Pigmented UMs also exhibited the highest 10-year metastasis rate at 26%, compared with 19% for partially pigmented UMs and 16% for nonpigmented UMs ($P < 0.001$). Kaplan−Meier survival curves demonstrated differences among the tumor pigmentation groups for melanoma-related metastasis ($P < 0.001$) and melanoma-related death ($P < 0.001$). Multivariate Cox regression analysis for melanoma-related metastasis showed that pigmented UMs had a 29% higher relative risk of developing metastasis compared with partially pigmented UMs ($P = 0.002$) and a 54% higher relative risk of developing metastasis compared with nonpigmented UMs ($P < 0.001$).

Conclusions: Pigmented choroidal and ciliary body melanoma is more often associated with ocular melanocytosis, extraocular extension, anterior tumor epicenter, and earlier tumor recurrence. We also revealed that patients with pigmented UMs demonstrate a higher 10-year rate of metastatic disease and have decreased metastatic survival relative to partially pigmented and nonpigmented UMs.

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Uveal melanoma (UM), arising from melanocytes of the choroid, ciliary body, and iris, is the most prevalent primary intraocular malignancy in adults.[1] Despite advancements in detection and treatment, UM remains a significant clinical challenge due to its variable presentation and metastatic potential. The clinical features of UM have been studied extensively to identify tumor characteristics to guide clinical management and improve patient outcomes. Previous studies have identified large tumor dimension, ciliary body involvement, extraocular extension, epithelioid cell type, genetic abnormalities (chromosome 3 monosomy, 8q gain[s]), and lymphocytic infiltration as tumor features predictive of greater risk for metastasis and death.[1−3] Tumor pigmentation, a discernible clinical feature of UM, remains an active area of investigation with regard to its underlying pathophysiology and prognostic value.

The color of uveal melanocytic lesions via ophthalmoscopy is determined mainly by the presence and relative composition of melanin.[1,4] Pigmented and partially pigmented UMs contain varying amounts of pheomelanin (yellow to red pigment) and eumelanin (dark brown to

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black pigment), while nonpigmented UMs predominantly consist of pheomelanin.[1,4] Prior studies evaluating the importance of tumor pigmentation in UM have yielded mixed results.[5–9] Some studies have found that tumor pigmentation is an independent risk factor for mortality, with pigmented UMs having worse survival.[5–8] For instance, Shammas and Blodi found in a cohort of 293 patients that large pigmented UMs posed a greater mortality risk among a subset of tumors with Bruch's membrane rupture.[5] In addition, Markiewicz et al studied a cohort of 154 patients and found that pigmented UMs were associated with earlier development of metastases and decreased survival relative to nonpigmented UMs.[6] Furthermore, Gelmi et al showed in a cohort of 1058 patients that greater histological tumor pigmentation of UM was associated with an unfavorable prognostic genetic status (i.e., chromosome 3 monosomy or 8q gain, loss of breast cancer-associated protein 1).[3] Conversely, some studies including that by McLean et al with a cohort of 217 patients argue that further histopathological studies and statistical analysis are necessary to precisely determine the prognostic importance of pigmentation.[2,9] Design limitations in these reports that could have contributed to these contrasting findings include small cohort size, retrospective data collection, potential for incomplete follow-up, omission of relevant covariates, and lack of standardized definitions of tumor pigmentation.

The role of melanogenesis in the development of melanoma as well as the extent to which genetic and biochemical tumor characteristics are linked with pigmentation within UM remain poorly understood.[4] Furthermore, it remains unclear whether tumor pigmentation in isolation is an independent prognostic factor for mortality in UM.[5–9] In this study, we review a large cohort of >6000 eyes with choroidal and ciliary body melanoma for the clinical features and outcomes associated with varying degrees of pigmentation from a single ocular oncology center.

Methods

A retrospective review of medical records was conducted at the Ocular Oncology Service at the Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania, United States of patients with the clinical diagnosis of choroidal or ciliary body melanoma treated between February 1971 and August 2007. This study was reviewed by the Wills Eye Hospital Institutional Review Board and was rendered exempt under category 4 (secondary research for which consent is not required). This research involved retrospective data collection and analysis without identifiable private information or identifiable biospecimens. This study adhered to the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act. The authors have no conflicts of interest to disclose.

All patients were examined by an experienced ocular oncologist (C.L.S.) at each visit using slit lamp biomicroscopy and indirect ophthalmoscopy. Findings were documented in large detailed fundus drawings and with multimodal imaging. Ophthalmic imaging included external and slit lamp photography, wide-angle fundus photography, fundus autofluorescence, ultrasonography, OCT, fluorescein angiography, indocyanine green angiography, and OCT angiography, as required at initial and subsequent encounters. Upon ocular examination, the classification of UM was established by the ocular oncologist's assessment of tumor surface area pigmentation as either pigmented (>80% by surface area), partially pigmented (20%–80%), or nonpigmented (<20%).

Data on patient demographics, such as age (years), race (White, African American, Hispanic, Asian, others, and unknown), sex (male, female), and affected eye (right, left), were collected. Clinical data included the presence of heterochromia, presence of ocular melanocytosis, chromosome 3 monosomy, location of tumor epicenter (choroid, ciliary body), anterior tumor margin (macula, macula to equator, equator to ora serrata, ciliary body), posterior tumor margin (macula, macula to equator, equator to ora serrata, ciliary body), distance of choroidal melanoma to the optic nerve (mm), distance of choroidal melanoma to the foveola (mm), tumor thickness at presentation (mm), diameter of the tumor (mm), physician reported iris color (blue, green, brown), and the presence of other advanced features of UM, such as subretinal fluid, Bruch's membrane rupture, extraocular extension (clinical and on imaging), and subretinal or vitreous hemorrhage.

Initial treatment methods, such as plaque radiotherapy, enucleation, partial lamellar sclerouvectomy, and transpupillary thermotherapy, were documented. Tumor outcomes at date last seen, including duration of follow-up (months), change in tumor thickness (mm, %), visual acuity (logarithm of the minimum angle of resolution, Snellen), vision loss of ≥3 lines Snellen equivalent, reason for vision loss ≥3 lines, secondary enucleation and reason(s) for secondary enucleation, local tumor recurrence, presence of UM metastasis, and location(s) of metastasis if present, were also recorded. The interval durations from the time of diagnosis to the time of vision loss ≥3 lines, recurrence, and metastasis were calculated for these outcomes when applicable.

Statistical Analysis

Statistical analysis was performed using the R Project for Statistical Computing (version 4.0.2; The R Foundation). Continuous variables were expressed as mean (median, range). Comparisons between the 3 tumor pigmentation categories (pigmented vs. partially pigmented vs. nonpigmented) were performed using the 1-way analysis of variance test for continuous variables with normal distribution and the Kruskal–Wallis H or Wilcoxon rank sum tests for continuous variables without normal distribution. The Kolmogorov–Smirnov test was used to assess for normality given the large size of the dataset.

Comparisons for categorical variables were performed using the chi-square test or Fisher exact test when indicated. Binary logistic regression was performed using generalized linear modeling to adjust for tumor thickness and diameter when comparing the prevalence of advanced clinical features and treatment modalities. Likelihood-ratio testing was used to assess group comparisons for predicted probabilities.

Kaplan–Meier analysis was performed to determine the cumulative probability of outcomes, including melanoma-related metastasis and melanoma-related death. The log-rank test was performed to assess differences in survival distribution between the tumor pigmentation categories. To create cox proportional hazard models for melanoma-related metastasis and death, univariate binary logistic regression models were performed to determine the relevant covariates. Using a significance cut-off of 0.25, select covariates underwent stepwise logistic regression to arrive at the finalized models for multivariate Cox regression. A P value <0.05 was considered statistically significant for inclusion as a relevant covariate. Hazard ratios and 95% confidence intervals (CIs) were calculated from these models to determine the risk associated with each covariate.

Results

There were 6934 patients diagnosed with melanoma of the choroid or ciliary body between 1971 and 2020 with documented tumor pigmentation. The tumors were classified as pigmented (n = 3762; 54%), partially pigmented (n = 2115; 31%), or nonpigmented (n = 1057; 15%). The order of pigmentation groups for comparisons reported in parentheses throughout the text is the following: pigmented UM versus partially pigmented UM versus nonpigmented UM.

Demographic features of the patients are listed in Table 1. A comparison of tumor pigmentation groups revealed differences in mean age at presentation (59.1 vs. 57.6 vs. 57.5 years, $P < 0.001$). Pairwise testing revealed patients with pigmented UM were generally older than patients with partially pigmented or nonpigmented UM. There was a predominance of White race among all tumor pigmentation groups (97% vs. 99% vs. 98%). The racial distribution differed significantly between pigmented and partially pigmented UM ($P = 0.030$), but there were otherwise no significant group differences for race, sex, or involved eye.

Clinical and tumor features at presentation are listed in Table 2. Ocular melanocytosis was seen in 3.7% of all patients and varied significantly with tumor pigmentation (4.4% vs. 2.9% vs. 2.7%, $P = 0.003$). A pairwise comparison showed ocular melanocytosis was more common in patients with pigmented UM than in those with partially pigmented UM ($P = 0.005$) or nonpigmented UM ($P = 0.018$). Similarly, heterochromia was also more common among those with pigmented UM (3.2% vs. 1.8% vs. 1.8%, $P < 0.001$).

Tumor epicenter was in the ciliary body in 458 patients (6.6%), ora serrata to equator in 1106 patients (16%), equator to macula in 5001 patients (72%), and the macula in 365 patients (5.3%). Pigmented tumors showed a greater tendency to be located anteriorly (equator to ora serrata, ciliary body) ($P < 0.001$), whereas partially pigmented and nonpigmented tumors occurred more often in the macula to equator region relative to pigmented tumors ($P < 0.001$). There was no significant difference in tumor pigmentation rates among UMs found in the macula. Pigmented tumors were also located further from the optic nerve (4.9 vs. 3.8 vs. 3.9 mm, $P < 0.001$) and foveola (4.7 vs. 3.5 vs. 3.6 mm, $P < 0.001$).

Tumor pigmentation revealed differences in mean tumor thickness (5.9 vs. 5.0 vs. 5.8 mm, $P < 0.001$) and mean largest basal diameter (11.6 vs. 11.0 vs. 11.1 mm, $P < 0.001$). Pairwise comparisons for tumor thickness indicated that partially pigmented UM was overall less thick than both pigmented and nonpigmented UM. For tumor largest basal diameter, pigmented UM was significantly greater in diameter than both partially pigmented and nonpigmented UM. Eyes with pigmented UM were more likely to have brown irides (33% vs. 27% vs. 20%, $P < 0.001$).

Analysis of advanced clinical features showed that partially pigmented UM, which was smallest in terms of tumor thickness, had a significantly lower rate of Bruch's membrane rupture at 19% compared with pigmented UM at 24% ($P < 0.001$). Pigmented UM demonstrated higher rates of extraocular extension overall, with figures at 3.0% for pigmented UM, compared with 2.5% for partially pigmented and 2.7% for nonpigmented UM ($P < 0.001$ for both pairwise comparisons). Additionally, the rate of subretinal/vitreous hemorrhage was higher in pigmented UM (11%) compared with partially pigmented UM (9.2%) and nonpigmented UM (11%). Significant pairwise comparisons were observed between pigmented and nonpigmented UM ($P = 0.0228$), as well as between pigmented and partially pigmented UM ($P < 0.001$).

Primary treatment modality comparisons adjusted for tumor dimensions with binary logistic regression are listed in Table 3. Plaque radiotherapy was performed in 4482 (65%), enucleation in 1919 (28%), partial lamellar sclerouvectomy in 105 (23%), and transpupillary thermotherapy in 316 (4.9%) patients. There were no differences in rates of plaque radiotherapy, enucleation, partial lamellar sclerouvectomy, or transpupillary thermotherapy.

Treatment outcomes are listed in Table 4. The mean follow-up duration was 74.8 months (median 48.1 months, range 0.23−537.9 months). Mean follow-up duration differed by pigmentation group (69.6 vs. 81.9 vs. 78.9 months, $P < 0.001$). Pairwise comparisons revealed mean follow-up duration was shorter for pigmented UMs compared with nonpigmented UMs (69.6 vs. 78.9 months, $P = 0.004$) and partially pigmented UMs (69.6 vs. 81.9 months, $P < 0.001$). Mean visual acuity (mean Snellen equivalent) at date last seen for all patients was 20/300 (median 20/200, range 20/20-no light perception) and pigmented UM demonstrated the best mean visual acuity at date last seen (20/280 vs. 20/300 vs. 20/380, $P = 0.026$). Visual acuity loss ≥3 lines Snellen equivalent was seen in 3062 (63%) patients at their most recent follow-up visit and did not differ significantly by tumor pigmentation group. Local recurrence of UM was seen in 8.5% of patients and did not vary by tumor pigmentation via Pearson chi-square testing. However, pigmented UM was associated with a significantly shorter average duration from the date first seen to the date of recurrence (47.0 vs. 67.2 vs. 70.2 months, $P < 0.001$). There were no differences in rates of secondary enucleation among the groups (7.9% vs. 7.6% vs. 7.5%, $P = 0.88$).

Melanoma-related metastasis developed in 997 (14%) patients with 225 (4.6%) developing metastasis within 2 years, 548 (13%) within 5 years, and 747 (22%) within 10 years. Metastasis varied significantly by tumor pigmentation ($P < 0.001$). Pigmented tumors demonstrated greater 10-year Kaplan−Meier metastatic rate (26% vs. 19% vs. 16%, $P < 0.001$) (Fig 1). Pairwise testing revealed that patients with pigmented UMs were more likely to have metastasis compared with patients with partially pigmented ($P < 0.001$) and nonpigmented ($P < 0.001$) UMs. While not displayed in Table 4, patients with pigmented UM had higher rates of liver metastasis (14% vs. 11% vs. 9.7%, $P < 0.001$) and lung metastasis (2.9% vs. 2.4% vs. 1.2%, $P = 0.010$). Melanoma-related death occurred in 544 (7.9%) patients and differed significantly overall by tumor pigmentation (8.6% vs. 7.4% vs. 6.4%, $P = 0.030$).

Kaplan−Meier survival curves demonstrating differences among the tumor pigmentation groups for melanoma-related metastasis ($P < 0.001$) (Fig 1) and melanoma-related death

Table 1. Impact of Tumor Pigmentation on Outcomes in 6934 Patients with Uveal Melanoma at a Single Center: Demographic Features

Demographic Features	Tumor Pigmentation			Overall *P* Value	Pigmented vs. Nonpigmented *P*-Value	Pigmented vs. Partially Pigmented *P* Value	Partially Pigmented vs. Nonpigmented *P* Value	Total (N = 6934 Patients) [N (%)]
	Pigmented (n = 3762 Patients) [n (%)]	*Partially Pigmented (n = 2115 Patients) [n (%)]*	*Nonpigmented (n = 1057 Patients) [n (%)]*					
Age (yrs)								
Mean (median, range)	59.1 (60.0, 8.0-99.0)	57.6 (58.0, 7.0-99.0)	57.5 (58.0, 7.0-95.0)	**<0.001***	**<0.001**§	**<0.001**§	0.81§	58.4 (59.0, 7.0-99.0)
Race								
White	3654 (97)	2084 (99)	1032 (98)	0.17†	0.93†	**0.030**†	0.39†	6770 (98)
African American	20 (0.5)	5 (0.2)	5 (0.5)					30 (0.4)
Hispanic	61 (1.6)	19 (0.9)	14 (1.3)					94 (1.4)
Asian	17 (0.5)	5 (0.2)	5 (0.5)					27 (0.4)
Middle Eastern	9.0 (0.2)	2.0 (0.1)	1.0 (0.1)					12 (0.2)
American Indian	1 (<0.1)	0 (0)	0 (0)					1 (<0.1)
Sex								
Male	1929 (51)	1078 (51)	519 (49)	0.45‡	0.21‡	0.82‡	0.32‡	3526 (51)
Female	1833 (49)	1037 (49)	538 (51)					3408 (49)
Affected eye								
Right	1863 (50)	1022 (48)	502 (48)	0.43‡	0.24‡	0.38‡	0.66‡	3387 (49)
Left	1899 (50)	1093 (52)	555 (52)					3547 (51)

P-values that are statistically significant ($P < 0.05$) are indicated in bold.
*Kruskal–Wallis rank sum test.
†Fisher exact test for count data with simulated *P* value (based on 2000 replicates).
‡Pearson chi-squared test.
§Wilcox rank sum test.

Table 2. Impact of Tumor Pigmentation on Outcomes in 6934 Patients with Uveal Melanoma at a Single Center: Clinical Features

Clinical Features	Tumor Pigmentation			Overall P Value	Pigmented vs. Nonpigmented P Value	Pigmented vs. Partially Pigmented P Value	Partially Pigmented vs. Nonpigmented P Value	Total (N = 6934 Patients) [N (%)]
	Pigmented (n = 3762 Patients) [n (%)]	*Partially Pigmented (n = 2115 Patients) [n (%)]*	*Nonpigmented (n = 1057 Patients) [n (%)]*					
Globe features								
Heterochromia	120 (3.2)	38 (1.8)	19 (1.8)	**0.001**[*]	**0.017**[*]	**0.002**[*]	>0.99[*]	177 (2.6)
Melanocytosis	164 (4.4)	61 (2.9)	29 (2.7)	**0.003**[*]	**0.018**[*]	**0.005**[*]	0.82[*]	254 (3.7)
Chromosome 3 analysis	n = 169	n = 83	n = 40					N = 292
Chromosome 3 monosomy	58 (34)	19 (23)	8 (20)	0.068[*]	0.080[*]	0.064[*]	0.72[*]	85 (29)
Tumor epicenter	n = 3759	n = 2115	n = 1056					N = 6930
Choroid macula	199 (5.3)	104 (4.9)	62 (5.9)	0.52[*]	0.46[*]	0.53[*]	0.26[*]	365 (5.3)
Choroid macula to equator	2402 (64)	1741 (82)	858 (81)	**<0.001**[*]	**<0.001**[*]	**<0.001**[*]	0.46[*]	5001 (72)
Choroid equator to ora serrata	776 (21)	223 (10)	107 (10)	**<0.001**[*]	**<0.001**[*]	**<0.001**[*]	0.72[*]	1106 (16)
Ciliary body	382 (10)	47 (2.2)	29 (2.8)	**<0.001**[*]	**<0.001**[*]	**<0.001**[*]	0.36[*]	458 (6.6)
Tumor thickness (mm)	n = 3751	n = 2113	n = 1054					N = 6918
Mean (median, range)	5.9 (5.0, 0.25-23.0)	5.0 (4.0, 0.50-20.0)	5.8 (5.0, 0.50-19.5)	**<0.001**[†]	0.36[§]	**<0.001**[§]	**<0.001**[§]	5.6 (4.5, 0.25-23.0)
Largest basal diameter (mm)	n = 3759	n = 2114	n = 1056					N = 6929
Mean (median, range)	11.6 (11.5, 2.0-33.0)	11.0 (11.0, 2.4-24.0)	11.1 (11.0, 3.0-24.0)	**<0.001**[†]	**0.001**[§]	**<0.001**[§]	0.78[§]	11.4 (11.0, 2.0-33.0)
Distance of choroidal melanoma to nerve (mm)	n = 3663	n = 2109	n = 1048					N = 6820
Mean (median, range)	4.9 (4.0, 0.0-23.0)	3.8 (3.0, 0.0-19.0)	3.9 (3.0, 0.0-22.0)	**<0.001**[†]	**<0.001**[§]	**<0.001**[§]	0.77[§]	4.4 (3.5, 0.0-23.0)
Distance of choroidal melanoma to foveola (mm)	n = 3663	n = 2109	n = 1048					N = 6820
Mean (median, range)	4.7 (3.1, 0.0-25.0)	3.5 (3.0, 0.0-18.0)	3.6 (3.0, 0.0-20.0)	**<0.001**[†]	**<0.001**[§]	**<0.001**[§]	0.92[§]	4.2 (3.0, 0.0-25.0)
Iris color								
Blue	1746 (46)	1119 (53)	637 (60)	**<0.001**[*]	**<0.001**[§]	**<0.001**[§]	**<0.001**[§]	3702 (51)
Green	773 (21)	422 (20)	204 (19)					1458 (20)
Brown	1243 (33)	574 (27)	216 (20)					2085 (29)
Advanced features[‖]	n = 3377	n = 2068	n = 1027					N = 6472
Subretinal fluid	2501 (77)	1639 (77)	839 (77)	**<0.001**[‡]	**<0.001**[‡]	**<0.001**[‡]	0.228[‡]	4979 (77)
Bruch's membrane rupture	693 (24)	446 (19)	272 (24)	**<0.001**[‡]	**<0.001**[‡]	**<0.001**[‡]	0.281[‡]	1411 (22)
	n = 3762	n = 2115	n = 1057					N = 6934
Extraocular extension	144 (3.0)	36 (2.5)	15 (2.7)	**<0.001**[‡]	**0.00015**[‡]	**0.0003**[‡]	0.409[‡]	195 (2.8)
Subretinal or vitreous hemorrhage	365 (11)	239 (9.2)	123 (11)	**<0.001**[‡]	**0.0228**[‡]	**<0.001**[‡]	0.100[‡]	727 (11)

mm = millimeter.
P-values that are statistically significant ($P < 0.05$) are indicated in bold.
*Pearson chi-squared test.
[†]Kruskal–Wallis rank sum test.
[‡]Likelihood-ratio test.
[§]Wilcox rank sum test.
[‖]Patients with ciliary body melanoma were excluded from subretinal fluid and Bruch's membrane rupture analysis. Percentages for all features were adjusted for tumor size and thickness.

Table 3. Impact of Tumor Pigmentation on Outcomes in 6934 Patients with Uveal Melanoma at a Single Center: Treatment

Treatment	Tumor Pigmentation: *Pigmented (n = 3762 Patients) [n (%)]*	*Partially Pigmented (n = 2115 Patients) [n (%)]*	*Nonpigmented (n = 1057 Patients) [n (%)]*	Overall *P* Value	Pigmented vs. Nonpigmented *P* Value	Pigmented vs. Partially Pigmented *P* Value	Partially Pigmented vs. Nonpigmented *P* Value	Total (N = 6934 Patients) [N (%)]
Initial treatment†								
Plaque radiotherapy	2368 (63)	1439 (68)	675 (64)	0.459*	0.623*	0.1935*	0.410*	4482 (65)
Enucleation	1098 (29)	508 (24)	313 (20)	0.312*	0.168*	0.986*	0.175*	1919 (28)
	n = 382	n = 47	n = 29					N = 458
PLSU	86 (23)	10 (21)	9 (31)	0.382*	0.217*	0.421*	0.609*	105 (23)
	n = 3377	n = 2068	n = 1027					N = 6472
TTT	166 (4.9)	115 (5.6)	35 (3.4)	0.159*	0.117*	0.547*	0.0441*	316 (4.9)

PLSU = partial lamellar sclerouvectomy; TTT = transpupillary thermotherapy.
*Likelihood-ratio test.
†Patients with choroidal melanoma were excluded from PLSU treatment analysis. Patients with ciliary body melanoma were excluded from TTT treatment analysis. Percentages for all treatments were adjusted for tumor diameter and thickness.

($P < 0.001$) (Fig 2) were created. The Kaplan−Meier (2-year/5-year/10-year) probability of metastasis for patients with pigmented UM was 5.7%/16%/26%, for patients with partially pigmented UM was 3.8%/11%/19%, and for patients with nonpigmented UM was 2.5%/9.1%/16% ($P < 0.001$). The Kaplan−Meier (2-year/5-year/10-year) probability of melanoma-related death for patients with pigmented UM was 3.2%/10%/16%, for patients with partially pigmented UM was 2.2%/7.5%/12%, and for patient with nonpigmented UM was 1.4%/5.8%/10% ($P < 0.001$).

Variables considered for inclusion in the Cox regression analysis for melanoma-related metastasis and melanoma-related death include age, sex, melanocytosis, tumor epicenter, largest basal diameter, thickness, tumor pigmentation, extraocular extension, and local tumor recurrence. For the stepwise logistic model focusing on metastasis, covariates selected included melanocytosis, tumor epicenter, largest basal diameter, thickness, tumor pigmentation, extraocular extension, and local tumor recurrence. Ultimately, stepwise logistic regression identified melanocytosis, largest basal diameter, thickness, tumor pigmentation, extraocular extension, and local tumor recurrence as the final set of covariates associated with metastasis. Similarly, in the stepwise logistic model for melanoma-related death, covariates considered included age, melanocytosis, tumor epicenter, largest basal diameter, thickness, tumor pigmentation, extraocular extension, and local tumor recurrence. The final selection process identified largest basal diameter, thickness, and local tumor recurrence as the covariates most strongly associated with melanoma-related death. Importantly, the inflation factors of all covariates in the final models were not indicative of multicollinearity. Although the univariate binary logistic regression for chromosome 3 monosomy in relation to melanoma-related metastasis and death produced a statistically significant odds ratio, chromosome 3 monosomy was not considered for inclusion in the Cox regression analysis because of the limited proportion of patients with tumor genetic analysis (4%) and the large number of patients who were treated before the advent of tumor genetic testing. Furthermore, the comparison of chromosome 3 monosomy by tumor pigmentation status was not significant ($P = 0.068$).

These finalized multivariate regression models were then used to calculate Cox proportional hazards for metastasis and melanoma-related death (Table 5). The hazard ratios for varying levels of tumor pigmentation showed that pigmented UMs had a 29% higher relative risk of developing metastasis compared with partially pigmented UMs ($P = 0.002$) and a 54% higher relative risk of developing metastasis compared with nonpigmented UMs ($P < 0.001$). No hazard rations could be calculated for melanoma-related death because tumor pigmentation did not meet the criteria to be included as a relevant covariate in the finalized Cox regression model.

Discussion

The results of this study demonstrate that increased tumor pigmentation in UM is associated with an increased risk for melanoma-related metastasis and death. This relationship was most pronounced when comparing pigmented UMs with nonpigmented UMs rather than with partially pigmented UMs, indicating a trend of increasing risk with degree of pigmentation. However, it is important to note that tumor pigmentation was not selected as a relevant covariate in the Cox regression models analyzing for melanoma-related death. The length of follow-up and loss to follow-up are important factors to consider with regards to patient death data in this long-term retrospective review. Among patients who underwent chromosome 3 genetic analysis of their tumor (n = 292), pigmented UMs were not significantly more likely to demonstrate chromosome 3 monosomy. Although UMs in the macula did not differ significantly by tumor pigmentation, pigmented UMs

Table 4. Impact of Tumor Pigmentation on Outcomes in 6934 Patients with Uveal Melanoma at a Single Center: Outcomes at Date Last Seen

Outcomes	Tumor Pigmentation			Overall *P* Value	Pigmented vs. Nonpigmented *P* Value	Pigmented vs. Partially Pigmented *P* Value	Partially Pigmented vs. Nonpigmented *P* Value	Total (N = 6934 Patients) [N (%)]
	Pigmented (n = 3762 Patients) [n (%)]	*Partially Pigmented (n = 2115 Patients) [n (%)]*	*Nonpigmented (n = 1057 Patients) [n (%)]*					
Follow-up duration (mos)	n = 3164	n = 1807	n = 880					N = 5851
Mean (median, range)	69.6 (44.3, 0.80-537.9)	81.9 (53.2, 0.23-495.2)	78.9 (49.4, 1.0-403.4)	**<0.001***	**0.004‡**	**<0.001‡**	0.36‡	74.8 (48.1, 0.23-537.9)
Change in thickness (mm)	n = 2402	n = 1504	n = 664					N = 4570
Mean (median, range)	−1.9 (−1.5, −14.6-11.4)	−1.7 (−1.4, −18.6-11.3)	−2.0 (−1.6, −11.3-6.2)	**0.015***	0.17‡	**0.037‡**	**0.007‡**	−1.8 (−1.5, −18.6-11.4)
Visual acuity at DLS (logMAR)	n = 2596	n = 1565	n = 702					N = 4863
Mean logMAR (median, range)	1.2 (0.88, 0.0-3.0)	1.2 (1.0, 0.0-3.0)	1.3 (1.0, 0.0-3.0)	**0.026***	**0.007‡**	0.35‡	0.058‡	1.2 (1.0, 0.0-3.0)
Mean Snellen equivalent (median, range)	20/280 (20/150, 20/20-NLP)	20/300 (20/200, 20/20-NLP)	20/380 (20/200, 20/20-NLP)					20/300 (20/200, 20/20-NLP)
Vision loss ≥3 lines	n = 2601	n = 1566	n = 702					N = 4869
n (%)	1631 (63)	991 (63)	440 (63)	0.93†	0.99†	0.71†	0.78†	3062 (63)
	n = 1636	n = 995	n = 443					N = 3074
Mean months from DFS to vision loss ≥3 lines (median, range)	28.7 (16.4, 0.10-373.1)	36.0 (19.9, 0.07-385.2)	33.7 (18.1, 0.17-332.0)	**<0.001***	0.055‡	**<0.001‡**	0.24‡	31.8 (17.5, 0.07-385.2)
Secondary enucleation	n = 3164	n = 1807	n = 880					N = 5851
n (%)	250 (7.9)	137 (7.6)	66 (7.5)	0.88†	0.69†	0.69†	0.94†	453 (7.7)
	n = 244	n = 134	n = 65					N = 443
Mean mos from DFS to secondary enucleation (median, range)	46.6 (28.6, 0.63-298.0)	66.10 (39.2, 0.10-387.6)	59.1 (44.5, 0.50-187.2)	**0.030***	**0.023‡**	**0.046‡**	0.69‡	54.3 (33.4, 0.10-387.6)
Local tumor recurrence	n = 3164	n = 1807	n = 880					N = 5851
n (%)	267 (8.4)	161 (8.9)	71 (8.1)	0.74†	0.73†	0.57†	0.47†	499 (8.5)
	n = 264	n = 157	n = 69					N = 490
Mean mos from DFS to recurrence (median, range)	47.0 (32.0, 1.2-266.3)	67.2 (41.8, 0.73-387.3)	70.2 (58.0, 2.4-261.1)	**<0.001***	**<0.001‡**	**0.005‡**	0.19‡	56.7 (37.8, 0.73-387.3)
Melanoma-related metastasis								
n (%)	602 (16)	271 (13)	124 (12)	**<0.001†**	**<0.001†**	**<0.001†**	0.38†	997 (14)
	n = 538	n = 235	n = 102					N = 875
Mean mos from DFS to metastasis (median, range)	55.7 (40.4, 0.03-303.1)	64.4 (42.9, 0.07-359.1)	73.8 (49.6, 0.93-357.7)	**0.044***	**0.016‡**	0.23‡	0.17‡	60.1 (41.8, 0.03-359.1)
Death								
n (%)	573 (15)	295 (14)	129 (12)	**0.037†**	**0.014†**	0.18†	0.17†	997 (14)
	n = 525	n = 251	n = 111					N = 887
Mean mos from DFS to death (median, range)	83.5 (51.9, 0.07-574.9)	94.0 (55.2, 0.13-474.0)	94.8 (64.5, 0.33-337.2)	0.061*	**0.029‡**	0.15‡	0.34‡	87.9 (53.9, 0.07-574.9)

(*Continued*)

Table 4. (Continued.)

Outcomes	Tumor Pigmentation			Overall P Value	Pigmented vs. Nonpigmented P Value	Pigmented vs. Partially Pigmented P Value	Partially Pigmented vs. Nonpigmented P Value	Total (N = 6934 Patients) [N (%)]
	Pigmented (n = 3762 Patients) [n (%)]	*Partially Pigmented (n = 2115 Patients) [n (%)]*	*Nonpigmented (n = 1057 Patients) [n (%)]*					
Melanoma-related death n (%)	n = 3739 323 (8.6)	n = 2096 154 (7.4)	n = 1050 67 (6.4)	**0.030**†	**0.018**†	0.084†	0.32†	N = 6885 544 (7.9)
	n = 312	n = 143	n = 59					N = 514
Mean mos from DFS to death from uveal melanoma (median, range)	59.9 (42.9, 4.5-386.8)	67.94 (45.3, 1.4-474.0)	71.9 (52.3, 2.1-230.1)	0.13*	0.060‡	0.25‡	0.34‡	63.5 (44.3, 1.4-474.0)

DFS = date first seen; DLS = date last seen; mm = millimeter; logMAR = logarithm of the minimum angle of resolution; NLP = no light perception.
P-values that are statistically significant ($P < 0.05$) are indicated in bold.
*Kruskal–Wallis rank sum test.
†Pearson chi-squared test.
‡Wilcox rank sum test.

showed a significantly greater tendency to occur anterior to the equator (equator to ora serrata, and ciliary body) with a greater average distance from the optic nerve and foveola compared with partially and nonpigmented UMs.

Pigmented tumors also demonstrated other notable associations including older patient age at diagnosis and greater rates of ocular melanocytosis, heterochromia, and brown irides, while nonpigmented UMs were more strongly associated with blue irides. In terms of advanced clinical features, partially pigmented UMs appeared to show the most favorable profile compared with pigmented UM, with lower rates of Bruch's membrane rupture and subretinal/vitreous hemorrhage. Partially pigmented UMs were also the smallest in terms of thickness (5.9 mm for pigmented UMs vs. 5.0 mm for partially pigmented UMs vs. 5.8 mm for nonpigmented UMs, $P < 0.001$). In contrast, extraocular extension was most often observed with pigmented UM ($P < 0.001$). The relative association and significance of extraocular extension and pigmented tumor status remained when excluding ciliary body melanomas as they are known to more often display extraocular extension and are disproportionately more pigmented.[1]

The breakdown of tumor pigmentation in this large study cohort (54% pigmented, 31% partially pigmented, and 15% nonpigmented) is consistent with the distribution of tumor pigmentation found in the literature.[5,10] While prior studies have claimed that pigmentation in UM may be unrelated to metastasis and mortality, our study further supports existing studies from more recent years that show a direct relationship.[5,9,11] By virtue of our study's large sample size, we were able to include partially pigmented UM as a separate group in the Kaplan–Meier and Cox regression analysis. This distinction allowed us to identify partially pigmented UM as having a lower risk of metastasis compared with pigmented UM. Specifically, the hazard ratio for pigmented versus nonpigmented UMs is 1.54 (CI: 1.24, 1.91), indicating a significant increase in risk. The comparison between pigmented and partially pigmented UMs yields a hazard ratio of 1.29 (CI: 1.10, 1.52). The partial overlap between these 2 CIs indicates that while both pigmented and partially pigmented UMs carry higher risks than nonpigmented UMs, the incremental increase from partially pigmented to pigmented may not be as pronounced. Finally, the hazard ratio comparing partially pigmented to nonpigmented UMs is 1.17 (CI: 0.92, 1.49), reflecting a nonsignificant difference. This overlap of this estimate's CI further suggests a more gradual trend across the spectrum of pigmentation rather than a stepwise association. In addition to tumor pigmentation, our study showed that tumor size, local tumor recurrence, melanocytosis, and extraocular extension are factors that increase the odds of metastasis and death, which is concordant with prior studies.[1,2]

Our findings confirm that increased tumor pigmentation is associated with older age at diagnosis, darker iris color, extraocular extension, ocular melanocytosis, and anterior location, as reported previously.[1,5,10,12–16] Nonpigmented tumors had the greatest rate of Bruch's membrane rupture in our study (24%) followed by pigmented (24%) and then partially pigmented (19%) tumors.[5] In terms of tumor thickness and diameter, there were significant differences

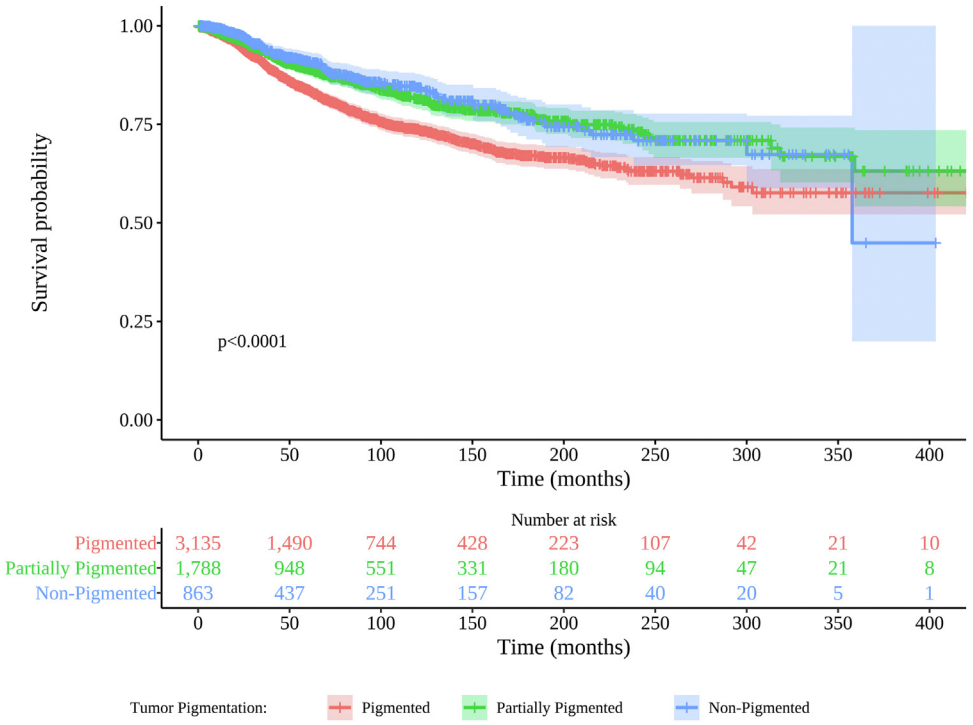

Figure 1. Kaplan–Meier analysis of uveal melanoma-related metastasis based on tumor pigmentation (pigmented vs. partially pigmented vs. nonpigmented).

in pairwise comparisons between pigmentation groups which showed that pigmented tumors were overall thicker (5.9 vs. 4.0 vs. 5.8, $P < 0.001$) and had greater diameters (11.6 vs. 11.0 vs. 11.1, $P < 0.001$). These findings align with research suggesting that heavily pigmented UM is associated with larger tumor size,[17] implying an accelerated growth rate in such tumors.

Increasing tumor pigmentation in UM has been proposed to be a potentiating factor for metastasis and death due to associated features on histopathology,[2,17] tumor characteristics at

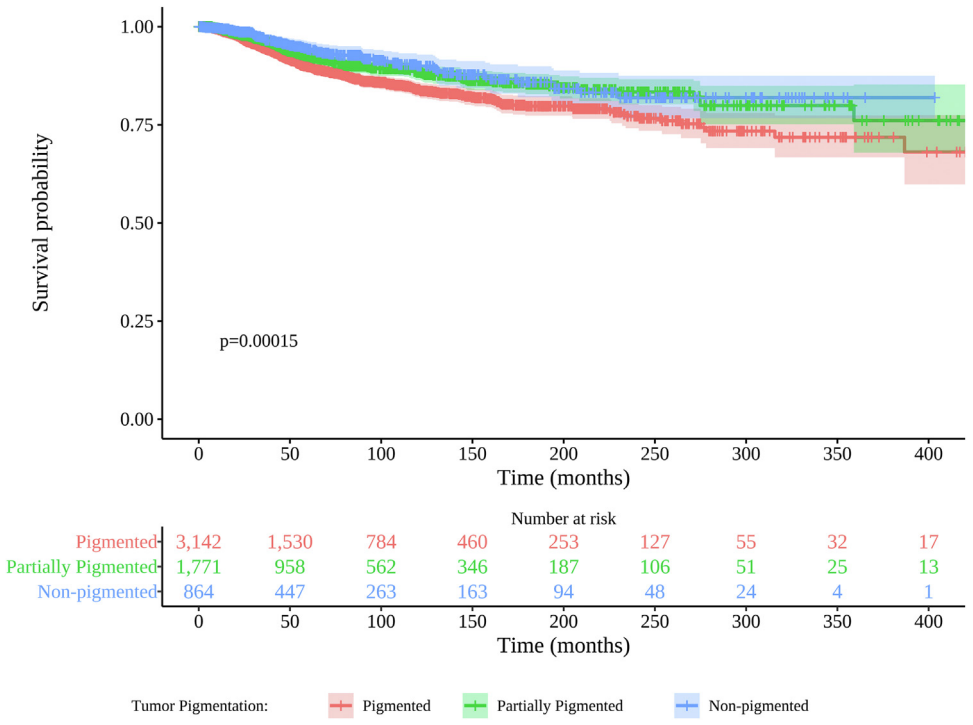

Figure 2. Kaplan–Meier analysis of uveal melanoma-related death based on tumor pigmentation (pigmented vs. partially pigmented vs. nonpigmented).

Table 5. Impact of Tumor Pigmentation on Outcomes in 6934 Patients with Uveal Melanoma at a Single Center: Multivariate Cox Proportional Hazard Results

Relevant covariates[†]	Melanoma-Related Metastasis (n = 812 Patients)		Melanoma-Related Death (n = 475 Patients)	
	Hazard ratio (95% CI)	P *value**	*Hazard ratio (95% CI)*	P *value**
Tumor pigmentation				
Pigmented vs. nonpigmented	1.54 (1.24, 1.91)	**<0.001**	—	—
Pigmented vs. partially pigmented	1.29 (1.10, 1.52)	**0.002**	—	—
Partially pigmented vs. nonpigmented	1.17 (0.92, 1.49)	0.20	—	—
Largest basal diameter	1.16 (1.13, 1.18)	**<0.001**	1.18 (1.15, 1.22)	**<0.001**
Thickness	1.09 (1.06, 1.12)	**<0.001**	1.08 (1.04, 1.11)	**<0.001**
Local recurrence	1.63 (1.33, 1.99)	**<0.001**	1.63 (1.25, 2.12)	**<0.001**
Melanocytosis	1.44 (1.06, 1.97)	**0.021**	—	—
Extraocular extension	1.42 (1.01, 1.98)	**0.042**	—	—

CI = confidence interval.
P-values that are statistically significant ($P < 0.05$) are indicated in bold.
*Wald test.
[†]Relevant covariates for the outcomes of melanoma-related metastasis and melanoma-related death were selected via stepwise logistic regression.

presentation,[11,18] and genomic profiles.[3] The Collaborative Ocular Melanoma Study report No. 6 found that heavily pigmented tumors were more likely to be epithelioid cell rich and contain tumor necrosis and lymphocytic infiltration on histopathology.[17] Uveal melanomas with a greater proportion of epithelioid cells are known to show more aggressive growth and increased potential for metastasis.[1] The proposed mechanism is perhaps by their ability to interfere with the immune system's ability to identify and target tumor cells, enabling them to evade detection and facilitate easier spread. Thus, the improved clinical outcomes observed in nonpigmented UMs may be attributed, in part, to the cellular type and pattern of nonpigmented UMs. These tumors are less frequently associated with significant inflammatory infiltrate or epithelioid cell types, which may result in greater immune recognition and subsequent control through cellular and humoral responses.[1,3]

Perhaps the most revealing explanation for these differences currently lies in genetic factors strongly associated with tumor pigmentary status. Genomic profiling of UMs has shown that chromosome 3 monosomy is an independent risk factor for shorter survival time and organ metastasis.[2,3] In fact, tumors with monosomy 3 and 8q gain mutations demonstrate an 11−123 times higher risk of metastatic disease than those with normal chromosomes 3, 6, and 8.[3] As previously stated, Gelmi et al recently showed that deleterious mutations such as chromosome 3 monosomy or 8q gain and breast cancer-associated protein 1 mutations were associated with tumors that had greater histological tumor pigmentation.[3] In our study's analysis of the subset of patients with chromosome 3 status (n = 292, 4%), chromosome 3 monosomy did not vary significantly by tumor pigmentation status determined via ophthalmoscopy ($P = 0.068$). Although this finding was not statistically significant, only a minority of patients had tumor genetic testing results in our study and this finding may warrant further examination in subsequent studies with more chromosomal data.

It is not completely understood why rates of chromosome 3 monosomy are greater in patients with pigmented UMs, but it may be related to oxidative damage from localized inflammation and macrophage recruitment (more common in pigmented UMs on histopathology) promoting mutagenesis in pigmented UMs.[3] Other authors have suggested that there may be genes located on chromosome 3 influencing melanin synthesis that lead to the association of chromosome 3 monosomy with greater pigmentation.[3]

The strong relationship between iris color and tumor pigmentation suggests that iris color may play a critical role in UM pigmentation and pathophysiology. Similar to prior studies, our findings show an association between pigmented UM and patients with brown irides, whereas nonpigmented UM appears to be more prevalent among patients with blue irides.[10,16] While exposure to ultraviolet light is a known risk factor for skin melanoma, the role of ultraviolet light exposure in the development of UM is less clear with no link firmly established.[1,10] Studies have shown that individuals with lighter-colored irides have increased susceptibility to ultraviolet-related cellular damage from early-life and intermittent high-burden ultraviolet exposure.[10,16] This may predispose uveal cells to undergo ultraviolet-related oncogenic changes and increase the risk for UM in patients with lighter-colored irides, even in the absence of direct ultraviolet penetration into deeper structures such as the choroid.[10,16] However, this idea is not supported by studies indicating that UM lacks genetic ultraviolet signature.[19,20] While there is some evidence suggesting a potential association between lighter-colored irides and an increased risk of UM metastasis,[10] they were also more likely to develop nonpigmented UM in this study, which is conflictingly associated with a lower risk for UM metastasis.[5–8] This discrepancy highlights the lack of a clear consensus on how ultraviolet susceptibility and other inherent biochemical properties of the uvea may vary among different iris colors. Some authors speculate that genetic factors related to iris color may impact UM susceptibility and that the clinical assessment of tumor pigment might be influenced secondarily by iris color.[10,16]

The disproportionate anatomic location of pigmented UMs and nonpigmented UMs may be due to the distribution of uveal melanocytes and the types of melanin produced. Uveal

melanocyte concentrations of the iris and ciliary body are greater than the choroid and contain relatively less pheomelanin, consistent with the greater proportion of nonpigmented choroidal tumors in our study.[21,22] While the distribution of choroidal melanomas specifically in the macular region did not differ significantly among the pigmentation groups in our study ($P = 0.52$), heavily pigmented UMs were significantly more commonly located anterior to the equator and significantly less common in the choroid macula-to-equator region ($P < 0.001$). The relationship between UM pigmentation and location requires further investigation with regard to UM pathogenesis and prognosis.

The results of this study have important clinical implications for the management of patients with UM. Our findings suggest that tumor pigmentation evaluation by indirect ophthalmoscopy is a potentially valuable method for identifying patients at higher risk of metastasis, even before the results of genetic testing are available. Future studies are needed to elucidate the different oncogenic mechanisms that influence tumor pigmentation in UM.

Our study has several key strengths including a relatively large number of patients from a single ocular oncology center, with standardized ocular examination, classification, data management, and treatment protocols. Data collection techniques were standardized and there was a relatively even distribution of patient demographics in the groups of varying tumor pigmentation.

However, this study also has several limitations such as its retrospective design. While relevant prevalence estimates and logistic regression models were adjusted for using clinical knowledge and systematic model selection, it is possible that additional confounding variables that were not included or collected could introduce bias into our results. For example, chromosome 3 monosomy data was not available for approximately 96% of patients as it was not routinely performed for patients who were treated before the advent of routine genetic testing for UMs and thus chromosome 3 monosomy was not included as a covariate in our Cox regression analysis. Moreover, our analysis often revealed no significant difference between nonpigmented and partially pigmented UMs, suggesting a nuanced relationship between tumor pigmentation and clinical outcomes. Furthermore, it's important to consider potential confounding factors that may influence the evaluation of tumor pigmentation. Factors such as media opacity, vitreous hemorrhage, retinal detachment, or choroidal pigmentation could impact the accuracy of assessing tumor pigmentation and should be taken into account in future studies. Lastly, future studies would benefit from the incorporation of cell-type and histopathological findings.

In conclusion, in this study we observed that patients with pigmented UM exhibit a more aggressive tumor profile, characterized by a higher risk for melanoma-related metastasis and death as well as greater rates of extraocular extension, ocular melanocytosis, and earlier tumor recurrence. We also revealed that pigmented tumors had a propensity to occur anterior to the equator whereas nonpigmented tumors tended to occur in the macula to equator region. These results indicate that tumor pigmentation could serve as a valuable and readily available prognostic tool in the clinical management of UM.

Footnotes and Disclosures

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HUMAN SUBJECTS: No human subjects were included in this study. This study was reviewed by the Wills Eye Hospital Institutional Review Board and was rendered exempt under category 4 (secondary research for which consent is not required). This research involved retrospective data collection and analysis without identifiable private information or identifiable biospecimens. This study adhered to the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act.

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Author Contributions:

Conception and design: Goldstein, Bayasi, Thomas, Shields

Data collection: Goldstein, Bayasi, Barke, Nguyen, Pastore, Shields

Analysis and interpretation: Goldstein, Bayasi, Thomas, Shields

Obtained funding: N/A

Overall responsibility: Goldstein, Bayasi, Thomas, Barke, Nguyen, Pastore, Shields

Abbreviations and Acronyms:
CI = confidence interval; **UM** = uveal melanoma.

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Choroid, Ciliary body, Melanoma, Metastasis, Pigmentation.

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