Choroidal Nevus Transformation Into Melanoma

Analysis of 2514 Consecutive Cases

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Objective: To determine features that are predictive of growth of choroidal nevi into melanoma.

Methods: This was a retrospective medical record review of 2514 consecutive eyes; Kaplan-Meier estimates and Cox regression analyses were used.

Results: The median tumor basal diameter was 5.0 mm and thickness was 1.5 mm. Nevus growth into melanoma occurred in 2%, 9%, and 13% of eyes at 1, 5, and 10 years, respectively. Factors predictive of growth into melanoma by multivariable analysis included tumor thickness greater than 2 mm ($P<.001$), subretinal fluid ($P=.002$), symptoms ($P=.002$), orange pigment ($P<.001$), tumor margin within 3 mm of the optic disc ($P=.001$), ultrasonographic hollowness ($P<.001$), and halo absence ($P=.009$). A mnemonic device to recall risk factors of ocular melanoma is "To find small ocular melanoma using helpful hints," representing *thickness*, *fluid*, *symptoms*, *orange* pigment, *margin*, *ultrasonographic hollowness*, and *halo* absence. The median hazard ratio for those with 1 to 2 risk factors was 3; for 3 or 4 factors, 5; for 5 to 6 factors, 9; and for all 7 factors, 21.

Conclusions: In an analysis of 2514 choroidal nevi, factors predictive of growth into melanoma included greater thickness, subretinal fluid, symptoms, orange pigment, margin near disc, and 2 new features: ultrasonographic hollowness and absence of halo.

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DURING THE PAST HALF-century, advances in the early detection of cutaneous melanoma have been important for improved survival of affected patients.[1-3] Despite the increasing incidence of cutaneous melanoma, the mortality rate has gradually decreased.[2] In the 1950s, the estimated lifetime risk of a US inhabitant developing invasive cutaneous melanoma was 1 in 600,

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and that has increased to a current risk of 1 in 62, with a projected 2010 risk of 1 in 50.[1] In the face of this alarming increase, the 5-year survival in those with stage 1 cutaneous melanoma has improved from 50% in the 1950s to near 90% currently.[1]

An important factor in improved survival with cutaneous melanoma has been the development of the ABCD mnemonic device in the 1980s.[1-3] This mnemonic device, representing *asymmetry*, *border* irregularity, *color* variegation, and *diameter* larger than 6 mm, has provided objective, reproducible criteria for the early diagnosis of cutaneous melanoma. Rather than diagnosing melanoma as such simply because it looks like melanoma, clinicians have been guided by the well-defined features of the ABCD mnemonic to more objectively identify early melanoma.[1] In the 1990s, dermoscopy (epiluminescence microscopy), autofluorescence, and digital image analysis added more technologically directed methods for early tumor detection, but it was realized that these tests were not universally available. The most common method, clinical examination with the naked eye, has remained the most practical one. In 2005, further analysis identified another clinical factor for early melanoma, evolution, and the ABCD mnemonic was modified to ABCDE.[1]

In ophthalmology, there has been a similar drive toward early detection of uveal melanoma. In 1995, statistically derived clinical risk factors were identified as features of early choroidal melanoma; these included thickness greater than 2

mm, subretinal fluid, symptoms, orange pigment, and margin near the optic disc.[4] These features, remembered with the mnemonic device "To find small ocular melanoma," were all based on routine funduscopic examination, making their use practical and significant. The presence of 3 or more risk factors was associated with a more than 50% chance of tumor growth in 5 years.[5] In our practice of ocular oncology, these risk factors have been immensely valuable in early detection of choroidal melanoma. In this analysis, we further investigate clinical features in the detection of early choroidal melanoma in a larger cohort of patients with presumed choroidal nevi to further refine relevant risk factors.

METHODS

A retrospective medical record review was performed on all patients with the clinical diagnosis of choroidal nevus treated in the Ocular Oncology Service at Wills Eye Institute between April 1974 and June 2006. Institutional review board approval was obtained for this retrospective study. All patients were examined by 1 of the senior authors (C.L.S. or J.A.S.) using modern techniques of indirect ophthalmoscopy of the entire fundus and high-resolution magnification ophthalmoscopy (Goldman or 60-diopter lens with slitlamp biomicroscopy) of the nevus or macula when necessary and possible. Details of the choroidal nevus were recorded on large fundus drawings in all patients. Fundus photography was performed on patients older than 6 years. The following clinical data were collected at initial examination: patient age, race, sex, medical history (dysplastic nevus syndrome; cutaneous, choroidal, or conjunctival melanoma; and neurofibromatosis), ocular melanocytosis, symptoms, and best-corrected visual acuity using Snellen charts. Other recorded data included quadrantic location of tumor epicenter (inferior, temporal, superior, nasal, or macula), anteroposterior location of tumor epicenter (macula, macula to equator, or equator to ora serrata), distance of nearest tumor margin to optic disc margin and foveola (in millimeters), largest tumor basal dimension and thickness (in millimeters), tumor color (pigmented, mixed, or nonpigmented), and presence of amelanotic halo. If an eye had more than 1 nevus, then the largest nevus was included in the analysis. Other related data included subretinal fluid, orange pigment, drusen, retinal pigment epithelial (RPE) alterations (hyperplasia, detachment, fibrosis, or atrophy), and choroidal neovascular membrane.

The nevus and related features were then analyzed with regard to transformation (growth) into melanoma. Growth into melanoma was defined as enlargement in the basal dimension or thickness of at least 0.5 mm. Statistical analysis was performed regarding time to detection of transformation into melanoma and features at presentation predictive of transformation into melanoma.

A series of univariate Cox proportional hazards regressions were used to assess the degree of relationship of all of the variables at presentation to growth into melanoma. All of the variables were analyzed as discrete variables except for patient age at presentation, tumor basal dimension, tumor thickness, and distance of tumor to optic disc margin and foveola, which were evaluated as continuous variables. Subsequent multivariate models included variables that were significant on a univariate level ($P<.05$) to identify the combination of factors most related to the outcome of growth into melanoma. Kaplan-Meier survival estimates were calculated for time to growth into melanoma. Hazard ratios (HRs) were calculated for each risk factor and each combination of risk factors.

RESULTS

Of the 2514 patients with choroidal nevus who were followed up, the median patient age at referral was 62 years (mean, 60 years; range, 4-97 years); 2487 of patients were white (99%), 12 were African American (<1%), 11 were Hispanic (<1%), and 4 were Asian (<1%). Nine hundred thirty-one patients were male (37%) and 1583 were female (63%). Medical histories revealed dysplastic nevus syndrome (n=20 [1%]), cutaneous melanoma (n=96 [4%]), choroidal melanoma in the opposite eye (n=94 [4%]), conjunctival melanoma or primary acquired melanosis (n=10 [<1%]), neurofibromatosis (n=3 [<1%]), and ocular melanocytosis (n=94 [4%]). Patient symptoms included decreased vision (n=135 [5%]), visual field defect (n=28 [1%]), and flashes/floaters (n=92 [4%]). Most cases (n=2333 [93%]) had best-corrected visual acuities (BCVAs) (by Snellen charts) of 20/20 to 20/40; 140 had BCVAs of 20/50 to 20/100 (5%); 25 had BCVAs of 20/200 to 20/400 (1%); 16 had BCVAs of counting fingers to hand motions (<1%); and none had BCVAs of light perception to no light perception.

The median basal diameter of the choroidal nevi was 5.0 mm (mean, 5.1 mm; range, 0.4-24 mm) and the median thickness was 1.5 mm (mean, 1.6 mm; range, 0.6-4.5 mm). Mean follow-up was 53 months, with a range of 6 to 434 months. The quadrant location for the nevus was inferior in 503 eyes (20%), temporal in 724 eyes (29%), superior in 465 eyes (18%), nasal in 599 eyes (24%), and in the macula in 223 eyes (9%). The anteroposterior location to the nevus was the macula in 540 eyes (21%), macular to equator in 1752 eyes (70%), and equator to ora serrata in 222 eyes (9%). The tumor was a mean of 5.6 mm to the optic disc and 5.3 mm to the foveola. Associated features included subretinal fluid (n=269 [11%]), orange pigment (n=193 [8%]), drusen (n=1356 [54%]), RPE atrophy (n=271 [11%]), RPE hyperplasia (n=208 [8%]), RPE fibrous metaplasia (n=207 [8%]), RPE detachment (n=33 [1%]), and retinal invasion (n=4 [<1%]). Ocular ultrasonography revealed acoustic solidity in 1185 eyes (64%) and hollowness in 458 eyes (25%). Other features included a surrounding amelanotic halo in 119 eyes (5%) and choroidal neovascularization in 12 (<1%).

Transformation into melanoma was diagnosed in 180 eyes (7%) (**Figure 1** and **Figure 2**). The growth measurements and rates are listed in **Table 1**. The Kaplan-Meier estimates of time to growth are listed in **Table 2**. Univariable and multivariable analyses of risk factors for growth of choroidal nevus into melanoma are listed in **Table 3** and **Table 4**. Through multivariable analysis, we found that factors predictive of growth into melanoma included tumor thickness greater than 2 mm (HR, 2.09; $P<.001$), subretinal fluid (HR, 3.16; $P=.002$), symptoms (HR, 2.34; $P=.002$), orange pigment (HR, 2.75; $P<.001$), tumor margin within 3 mm of the optic disc (HR, 1.82; $P=.001$), ultrasonographic hollowness (HR, 2.92; $P<.001$), and absence of surrounding halo (HR, 6.48; $P=.009$). When assessing tumor thickness as a continuous variable, significance was found in the multivariate model (HR, 2.75, per 1-mm increase; 95% confidence interval, 2.02-3.75; $P<.001$). When assessing

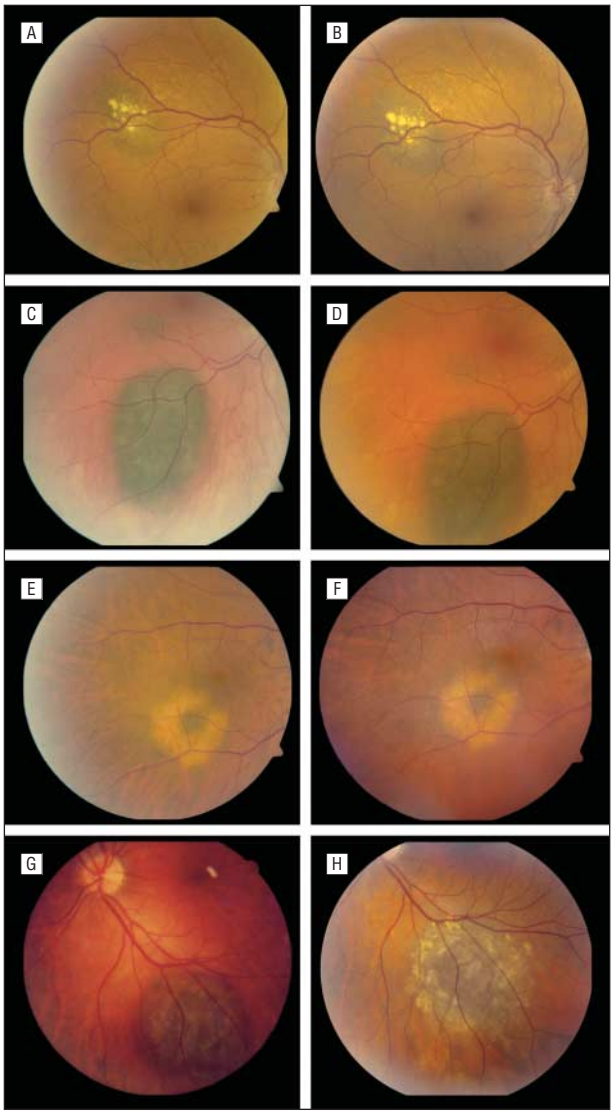

Figure 1. Choroidal nevus remaining stable over time. Choroidal nevus with drusen (A) remained stable during 3 years of follow-up, and the drusen became slightly more confluent (B). Choroidal nevus without drusen but with overlying retinal pigment epithelial atrophy (C) remained stable at 4-year follow-up (D). Halo choroidal nevus (E) remained stable at 3-year follow-up (F). Choroidal nevus with subtle drusen and retinal pigment epithelial atrophy (G) remained stable at 23-year follow-up (H).

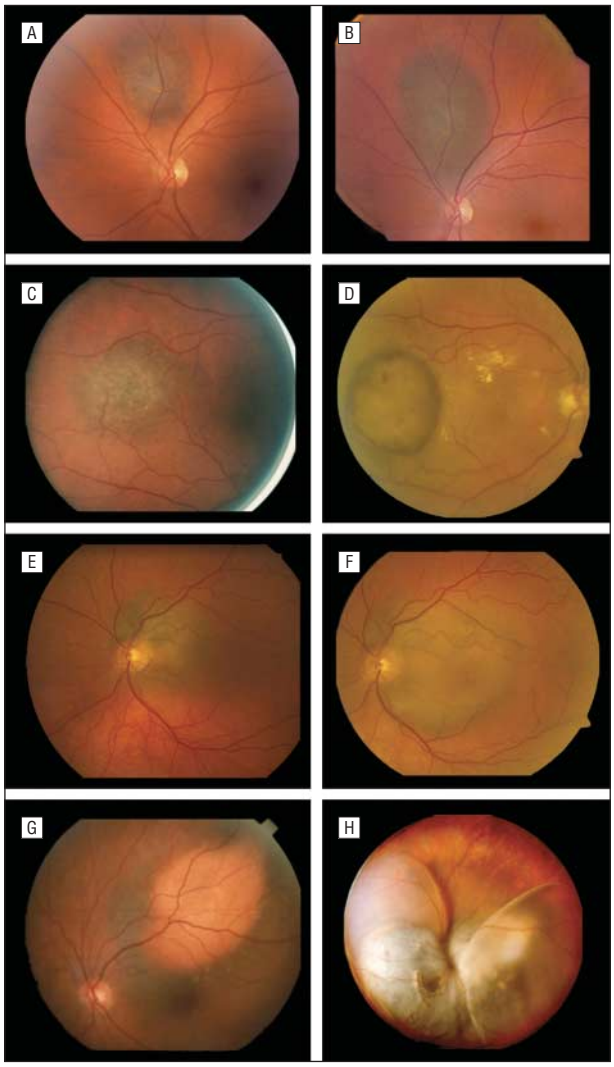

Figure 2. Choroidal nevus transforming into melanoma over time. Suspicious choroidal nevus with orange pigment and overlying subretinal fluid (A) showed enlargement in basal dimension during 6 years (B). Choroidal nevus with overlying retinal pigment epithelial atrophy (C) showed marked enlargement with flat basal growth, development of a central nodule, and retinal invasion over several years (D). Suspicious choroidal nevus with overlying orange pigment and subtle subretinal fluid (E) showed enlargement during 2 years (F). Suspicious choroidal nevus with variable pigmentation and lacking drusen (G) remained stable for 14 years and at year 15 showed marked enlargement with prominent retinal detachment (H).

distance to the optic nerve as a continuous variable, significance was found in the multivariate model (HR, 0.90, per 1-mm increase; 95% confidence interval, 0.85-0.95; $P<.001$). The percentage of nevi to show growth into melanoma and HR with and without each risk factor is listed in **Table 5**. The risks for various combinations of factors are listed in the eTable (http://www.archophthalmol.com). The median HR for growth of nevus into melanoma with 1 or 2 risk factors was 3; for those with 3 or 4 factors, 5; for 5 to 6 factors, 9; and for all 7 factors, 21.

COMMENT

Choroidal melanoma is a dangerous ophthalmic malignancy. Using cumulative incidence analysis, Kujala and colleagues[6] reported the following rates of melanoma-related mortality in 289 patients with uveal melanoma: 31% by 5 years, 45% by 15 years, 49% by 25 years, and 52% by 35 years. After risks regression analysis, the HR was 1.08 ($P=.001$) for each millimeter increase in tumor diameter. Melanoma-related mortality at 10, 20, and 30 years, respectively, was 10%, 15%, and 20% for tumors classified as small (<10-mm diameter), 38%, 50%, and 52% for medium-sized melanoma (10- to 15-mm diameter); and 57%, 58%, and 61% for large melanoma (>16-mm diameter). Diener-West et al[7] reviewed mortality in a meta-analysis of 8 articles based on tumor thickness rather than tumor diameter. They found 5-year all-cause mortality from uveal melanoma to be 16% for small melanoma (<3-mm thickness), 32% for medium-sized melanoma (3- to 8-mm thickness), and 53% for large melanoma (>8-mm thickness).

Table 1. Choroidal Nevus Growth Into Melanoma in 180 of 2514 Eyes With Follow-up

Measurement of Choroidal Nevus	Mean (Median, Range)
Overall growth, mm	
Basal diameter	1.85 (1.25, 0-14.50)
Thickness	1.45 (1.30, 0-10.10)
Growth rate, mm/y	
Basal diameter	0.96 (0.35, 0-12.22)
Thickness	1.12 (0.21, 0-13.50)

Table 2. Time to Growth of Choroidal Nevus Into Melanoma Using Kaplan-Meier Estimates

Year	Kaplan-Meier Estimates, %	No. Failed/Left
1	1.9	44/1943
2	4.4	86/1459
3	6.2	111/1195
4	7.2	123/973
5	8.6	136/790
6	9.9	146/621
7	10.7	151/503
10	12.8	160/309
15	17.3	171/129

In 2007, the Ocular Oncology Service at Wills Eye Institute reviewed a large cohort of 8033 patients with uveal melanoma using Kaplan-Meier analysis and found a similar increasing risk for metastasis with increasing tumor thickness (Thangappan A, Shields CL, Nagori S, et al. Posterior uveal melanoma thickness at diagnosis correlates with tumor location. Paper presented at: American Academy of Ophthalmology Meeting; New Orleans, LA; November 12-13, 2007). Melanoma metastasis at 10 years was 10% for small melanoma (<3-mm thickness), 23% for medium-sized melanoma (3.1- to 8-mm thickness), and 52% for large melanoma (>8-mm thickness). More specifically, metastasis (per millimeter of thickness) at 10 years was found in 7% (0-1 mm), 13% (1-2 mm), 10% (2-3 mm), 16% (3-4 mm), 24% (4-5 mm), 27% (5-6 mm), 27% (6-7 mm), 39% (7-8 mm), 49% (8-9 mm), 53% (9-10 mm), and 58% (>10 mm) of cases. It is thus evident from these studies that tumor size strongly correlates with patient prognosis. Early detection of uveal melanoma at a time when the malignancy is small is critical in improving patients' survival.

Early detection of cancer, in general, has been found to be increasingly important for patient prognosis.[8-11] Gastric cancer used to be the main cause of cancer death in Japan, but nationwide screening for this tumor has resulted in earlier detection and a concurrent improved survival rate of more than 90% at 5 years.[8] Likewise, hepatocellular carcinoma has shown improvement in survival, from death typically within 1 year to 60% to 70% survival at 5 years if the malignancy is discovered early.[9] Finally, it is well recognized that Breslow tumor thickness is the most important prognostic factor for skin melanoma. Melanomas with less than a 0.76-mm thickness show nearly 100% 10-year survival.[10,11] The importance of early cutaneous melanoma detection was emphasized by Ackerman[12] in his bold 1985 editorial entitled "No One Should Die of Malignant Melanoma." In that piece, he stated that this goal could be achieved with education and commitment by all physicians to recognize flat melanoma.

There is strong interest for early detection of choroidal melanoma, and its differentiation from nevus continues to be the major impediment. Choroidal nevus and small choroidal melanoma can show several overlapping features, including tumor size, color, location, and related fundus changes, such as subretinal fluid and orange pigment. The challenge is to identify the single small melanoma among the thousands of choroidal nevi. It has been estimated that 6% of the white population harbors a choroidal nevus[13] and that 1 in approximately 8000 of these nevi transform into melanoma.[14,15] Further thought into age-adjusted lifetime risk revealed that by age 80 years, the risk for transformation is 0.78% and the risk would thereafter approach 1%.[16] It has been stated that a prospective study to observe malignant transformation would be cumbersome and costly, requiring almost 1000 cases of nevus followed up for 10 years to observe 1 occurrence[15]; hence, retrospective analysis, such as that performed in this study, is more practical.

In an analysis of 188 patients with small choroidal lesions of 1 to 3 mm of thickness with a 5- to 16-mm base, the Collaborative Ocular Melanoma Study (COMS) found factors that were predictive of growth to include greater initial tumor thickness and diameter, orange pigment, absence of drusen, and absence of RPE changes.[17] In an analysis of 240 patients with small choroidal melanocytic lesions, Singh et al[18] found factors predictive of growth to include thickness greater than 2 mm, a proximity within 3 mm of the foveola, male sex, symptoms, and orange pigment. In our current study of 2514 patients with small choroidal melanocytic lesions, factors predictive of growth included thickness greater than 2 mm, subretinal fluid, symptoms, orange pigment, tumor margin less than 3 mm to disc, ultrasonographic hollowness, and lack of surrounding halo. Most authorities agree that documentation of growth is a strong feature of an active melanoma, especially if growth occurs within a short period. However, it should be realized that slow growth of 0.5 mm throughout many years or decades could simply represent the natural evolution of a benign choroidal nevus. In our cohort, the growth rate was approximately 1 mm per year in basal diameter and thickness and the overall growth was 1.85 mm in basal diameter.

In 1995, a publication from our department[4] revealed 5 factors that are statistically predictive of growth of choroidal melanocytic tumors: thickness greater than 2 mm, subretinal fluid, symptoms, orange pigment, and tumor margin within 3 mm of the disc. These factors were remembered with the mnemonic TFSOM—"To find small ocular melanoma." The presence of 3 risk factors imparted a greater than 50% chance for growth.[5] The most dangerous combination of factors with 69% risk for growth was thickness greater than 2 mm, symptoms, and tumor margin at disc. Our current data analysis has contributed 2 additional risk factors, ultrasonographic hollowness and lack of halo. The previous studies did not evaluate acoustic qualities on ultrasonography. We have revised

Table 3. Univariable Analysis of Factors at Initial Presentation Predicting Growth of Choroidal Nevus Into Melanoma

Variable	No. (%)		HR (95% CI)	*P* Value
	Growth Into Melanoma (n=180)	No Growth Into Melanoma (n=2334)		
Sex, male vs female[a]	82 (45.6)	849 (36.4)	1.55 (1.16-2.08)	.003
Total No. of nevi/patient, mean	1.13	1.28	0.58[b] (0.39-0.85)	.005
Symptoms				
Decreased vision vs none[a]	45 (25.0)	124 (5.3)	5.21 (3.67-7.38)	<.001
Visual field defect vs none[a]	4 (2.2)	24 (1.0)	3.86 (1.42-10.47)	.008
Flashes/floaters vs none[a]	20 (11.1)	87 (3.7)	3.71 (2.30-5.98)	<.001
Visual acuity				
20/50 or worse vs better[a]	19 (10.6)	109 (4.7)	2.51 (1.56-4.04)	<.001
Decreased vs not decreased[a]	47 (26.1)	108 (4.6)	5.20 (3.72-7.27)	<.001
Quadratic location of nevus				
Macula vs inferior[a]	27 (15.0)	196 (8.4)	2.39 (1.41-4.05)	.001
Macula vs temporal[a]	27 (15.0)	196 (8.4)	2.34 (1.44-3.80)	.001
Macula vs superior	27 (15.0)	196 (8.4)	2.02 (1.21-3.39)	.007
Anteroposterior location of nevus epicenter				
Macula vs macula to equator[a]	61 (33.9)	479 (20.5)	1.86 (1.35-2.54)	<.001
Macula vs equator to ora[a]	61 (33.9)	479 (20.5)	2.38 (1.28-4.42)	.006
Distance of nevus to optic nerve				
Mean, mm	3.64	5.61	0.87[c] (0.83-0.91)	<.001
0 mm vs >0 mm[a]	44 (24.4)	187 (8.0)	3.07 (2.19-4.33)	<.001
≤3 mm vs >3 mm[a]	105 (58.3)	712 (30.5)	2.94 (2.18-3.95)	<.001
Distance of nevus to foveola				
Mean, mm	3.43	5.25	0.87[c] (0.83-0.92)	<.001
≤3 mm vs >3 mm[a]	40 (22.2)	183 (7.8)	2.87 (2.02-4.08)	<.001
Largest basal dimension				
Mean, mm	6.72	5.05	1.16[c] (1.12-1.21)	<.001
>5 mm vs ≤5 mm[a]	124 (68.9)	986 (42.2)	2.67 (1.95-3.66)	<.001
Thickness				
Mean, mm	2.09	1.55	4.48[c] (3.62-5.53)	<.001
>2 mm vs ≤2 mm[a]	82 (45.6)	360 (15.4)	5.15 (3.82-6.95)	<.001
Color				
Mixed vs pigmented[a]	37 (20.6)	288 (12.3)	1.79 (1.23-2.60)	.002
Nonpigmented vs pigmented[a]	33 (18.3)	242 (10.4)	2.60 (1.76-3.83)	<.001
Subretinal fluid				
Trace vs none[a]	21 (11.7)	96 (4.1)	4.52 (2.83-7.22)	<.001
Moderate vs none[a]	39 (21.7)	89 (3.8)	7.24 (5.02-10.45)	<.001
Severe vs none[a]	11 (6.1)	10 (0.4)	12.87 (6.89-24.04)	<.001
Orange pigment, present vs absent[a]	58 (32.2)	135 (5.8)	6.16 (4.51-8.43)	<.001
RPE hyperplasia, present vs absent[a]	25 (13.9)	183 (7.8)	1.82 (1.19-2.78)	.005
Halo, absent vs present[a]	177 (98.3)	2218 (95.0)	3.58 (1.14-11.23)	.03
Retinal invasion, present vs absent[a]	2 (1.1)	2 (0.1)	8.80 (2.18-35.57)	.002
Foveolar status				
Subfoveal fluid vs no subfoveal fluid[a]	29 (16.1)	43 (1.8)	6.20 (4.15-9.26)	<.001
Subfoveal nevus vs extrafoveal nevus[a]	29 (16.1)	127 (5.4)	2.88 (1.94-4.29)	<.001
Ultrasonographic acoustic quality				
Hollow vs flat[a]	103 (62.8)	355 (21.0)	21.00 (5.18-85.13)	<.001
Solid vs flat[a]	59 (36.0)	1126 (66.7)	5.14 (1.26-21.04)	.02
Hollow vs solid/flat[a]	103 (62.8)	355 (21.0)	4.64 (3.38-6.37)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio; RPE, retinal pigment epithelium.
[a] Reference variable.
[b] Per increase of 1.
[c] Per increase of 1 mm.

our mnemonic, adding UHH to the end—"To find small ocular melanoma using helpful hints"—which represents *thickness* greater than 2 mm, subretinal *fluid*, *symptoms, margin* within 3 mm of the disc, *ultrasonographic hollowness*, and absence of *halo*. In Table 5, the individual risk factors are listed in the order in which they impact tumor growth, and in the eTable, the combinations of risk factors with relative risks (HRs) for growth are listed. The median HR for growth of nevus into melanoma with 1 or 2 risk factors was 3; for those with 3 or 4 factors, 5; for 5 to 6 factors, 9; and for all 7 factors, 21 (eTable). The highest HR found was 31 for the combination of the following factors: symptoms (flashing and floaters), orange pigment, margin near disc, ultrasonographic hollowness, and no halo.

There was apparent overlap in the risk factors found in this current study, our previous study from 1995,[4,5] and in the COMS.[17] The COMS found that lack of dru-

Table 4. Multivariable Analysis of Factors at Initial Presentation Predicting Growth of Choroidal Nevus Into Melanoma

Variable	HR (95% CI)	*P* Value
Thickness, No. of tumors >2 mm vs ≤2 mm[a,b]	2.09 (1.48-2.94)	<.001
Subretinal fluid, present vs absent[a]	3.16 (1.53-6.57)	.002
Symptoms		
1, Decreased vision vs none[a]	1.67 (1.08-2.57)	.02
2, Flashes/floaters vs none[a]	2.34 (1.37-4.00)	.002
Orange pigment, present vs absent[a]	2.75 (1.88-4.01)	<.001
Distance to optic nerve, ≤3 mm vs >3 mm[a]	1.82 (1.26-2.62)	.001
Ultrasonography acoustic quality, hollow vs solid[a]	2.92 (2.05-4.14)	<.001
Halo, absent vs present[a]	6.48 (1.59-26.34)	.009

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Reference variable.
[b] When assessing tumor thickness as a continuous variable, significance was found in the multivariate model (HR, 2.75, per 1-mm increase; 95% CI, 2.02-3.75; $P<.001$). When assessing distance to the optic nerve as a continuous variable, significance was found in the multivariate model (HR, 0.90, per 1-mm increase; 95% CI, 0.85-0.95; $P<.001$).

Table 5. Percentage Growth of Choroidal Nevus Into Melanoma With and Without Risk Factors

			Nevus Growth Into Melanoma, No. (%)		
Mnemonic	Initial	Features	Feature Present	Feature Absent	HR[a]
To	T	Thickness >2 mm	82 (19)	98 (5)	2
Find	F	Fluid	71 (27)	109 (5)	3
Small	S	Symptoms	69 (23)	111 (5)	2
Ocular	O	Orange pigment	58 (30)	122 (5)	3
Melanoma	M	Margin ≤3 mm to disc	105 (13)	75 (4)	2
Using helpful	UH	Ultrasonographic hollowness	103 (25)	77 (4)	3
Hints	H	Halo absence	177 (7)	3 (2)	6

Abbreviation: HR, hazard ratio.
[a] Rounded. Compared with eye without feature using multivariable analysis.

sen was a risk factor for growth, whereas this did not achieve significance in our results. To accommodate this relevant finding, we slightly modified the meaning of our mnemonic further to include all 3 studies, in particular the lack of drusen. In the mnemonic, TFSOM UHH—"To find small ocular melanoma using helpful hints"—the word *daily* at the end would represent *drusen absent*; so, the full reminder would be "To find small ocular melanoma using helpful hints daily." Mnemonics and acronyms are most effective if they are easily remembered and they can carry a profound impact. Some criticize the multiple modifications of the ABCD acronym for skin melanoma, but the important role this has played in the early detection of the disease cannot be overlooked.[19] One critic of the ABCD modifications admitted to the need for such devices and wrote "All have some justification, but lead to a more complex primary message."[19] He further clarified that the message for the general public should be simple, and for the practicing clinician, a complex algorithm can be effective.[19]

The importance of hollowness on ultrasonography is a feature that has not been particularly emphasized for detection of early choroidal melanoma. Of the 408 nevi with ultrasonographic hollowness, 25% showed growth into melanoma compared with 4% growth in those without hollowness. In the COMS, low to medium internal reflectivity, often compatible with acoustic hollowness on B scans, was found in 88% of choroidal melanomas[20]; so the importance of this finding in our analysis is not surprising.

The relevance of halo nevi has not been previously recognized. The halo nevus is a pigmented choroidal nevus surrounded by a halo or circular band of depigmentation. Halo nevi have been recognized on the skin and the halo has been described microscopically as a lymphohistiocytic infiltrate with absence or diminution of melanin pigment.[21] The halo phenomenon can be found with dysplastic nevus and even with melanoma. In this current study, the presence of halo suggested nevus stability. Of the 2395 nevi without halo, 7% showed growth to melanoma compared with 2% of the 119 with halo (Table 5).

Until systemic therapies for metastatic uveal melanoma improve,[22] our focus should be on early detection to minimize metastatic disease. All ophthalmologists should participate in this effort and patients with risk factors can be referred for evaluation at centers familiar with the nuances in the diagnosis and management of early melanoma. In this analysis, we did not include the results of optical coherence tomography, autofluorescence, fluorescein angiography, or other tests, as these are not universally available and might not be practical for assessment of all lesions. However, in our practice of ocular oncology, optical coherence tomography and autofluorescence have proven useful for detection of subtle subretinal fluid related to the mass as well as subtle lipofuscin (orange pigment) over the mass.[23-27]

In conclusion, *thickness* greater than 2 mm, *fluid*, *symptoms*, *orange* pigment, *margin* near disc, *ultrasono-*

graphic hollowness, *halo* absence, and *drusen absence*—remembered through the mnemonic "To find small ocular melanoma using helpful hints daily"—are profoundly important risk factors for the detection of early choroidal melanoma. Patients with choroidal nevi showing no features of the disease should be initially monitored twice yearly and followed up annually thereafter if their condition is stable. Those with 1 or 2 features should be monitored every 4 to 6 months. Nevi with 3 or more features should be evaluated at an experienced center for management alternatives and possible treatment owing to the high risk of ultimate growth. Detection of a uveal melanoma at an early point, when the tumor is 2.1-mm thick and at a 10% risk for metastasis, is far better than detection at 4.5-mm thickness, with 24% risk for metastasis (Thangappan A, Shields CL, Nagori S, et al. Posterior uveal melanoma thickness at diagnosis correlates with tumor location. Paper presented at: American Academy of Ophthalmology Meeting; New Orleans, LA; November 12-13, 2007). As confidently stated by Ackerman, "With big enough hopes and serious enough convictions, no human being need die of malignant melanoma."[12]

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REFERENCES

1. Rigel DS, Friedman RJ, Kopf AW, Polsky D. ABCDE: an evolving concept in the early detection of melanoma. *Arch Dermatol*. 2005;141(8):1032-1034.
2. Schaffer JV, Rigel DS, Kopf AW, Bolognia JL. Cutaneous melanoma: past, present, and future. *J Am Acad Dermatol*. 2004;51(1)(suppl):S65-S69.
3. Weinstock MA. Progress and prospects on melanoma: the way forward for early detection and reduced mortality. *Clin Cancer Res*. 2006;12(7, pt 2):2297s-2300s.
4. 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.
5. Shields CL, Cater JC, Shields JA, Singh AD, Santos MC, Carvalho C. Combination of clinical factors predictive of growth of small choroidal melanocytic tumors. *Arch Ophthalmol*. 2000;118(3):360-364.
6. Kujala E, Makitie T, Kivela T. Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci*. 2003;44(11):4651-4659.
7. 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.
8. Katai H, Sano T. Early gastric cancer: concepts, diagnosis, and management. *Int J Clin Oncol*. 2005;10(6):375-383.
9. Yoshida H, Yoshida H, Shiina S, Omata M. Early liver cancer: concepts, diagnosis, and management. *Int J Clin Oncol*. 2005;10(6):384-390.
10. Takata M, Saida T. Early cancers of the skin: clinical, histopathological, and molecular characteristics. *Int J Clin Oncol*. 2005;10(6):391-397.
11. Saida T. Lessons learned from studies of the development of early melanoma. *Int J Clin Oncol*. 2005;10(6):371-374.
12. Ackerman AB. No one should die of malignant melanoma. *J Am Acad Dermatol*. 1985;12(1, pt 1):115-116.
13. Sumich P, Mitchell P, Wang JJ. Choroidal nevi in a white population: the Blue Mountains Eye Study. *Arch Ophthalmol*. 1998;116(5):645-650.
14. Ganley JP, Comstock GW. Benign nevi and malignant melanomas of the choroid. *Am J Ophthalmol*. 1973;76(1):19-25.
15. Singh AD, Kalyani P, Topham A. Estimating the risk of malignant transformation of a choroidal nevus. *Ophthalmology*. 2005;112(10):1784-1789.
16. Kivelä T, Eskelin S. Transformation of nevus to melanoma. *Ophthalmology*. 2006;113(5):887-888, e1.
17. 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.
18. 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.
19. Weinstock MA. ABDC, ABCDE, and ABCCCDEEEEFNU. *Arch Dermatol*. 2006;142(4):528.
20. Boldt HC, Byrne SF, Gilson MM, et al; Collaborative Ocular Melanoma Study Group. Baseline echographic characteristics of tumors in eyes of patients enrolled in the Collaborative Ocular Melanoma Study: COMS report No. 29. *Ophthalmology*. 2008;115(8):1390-1397, 1397, e1-e2.
21. Mooney MA, Barr RJ, Buxton MG. Halo nevus or halo phenomenon? a study of 142 cases. *J Cutan Pathol*. 1995;22(4):342-348.
22. Shields JA, Shields CL, Materin MA, Sato T, Ganguly A. Role of cytogenetics in management of uveal melanoma. *Arch Ophthalmol*. 2008;126(3):416-419.
23. Shields CL, Mashayekhi A, Materin MA, et al. Optical coherence tomography of choroidal nevus in 120 patients. *Retina*. 2005;25(3):243-252.
24. Espinoza G, Rosenblatt B, Harbour JW. Optical coherence tomography in the evaluation of retinal changes associated with suspicious choroidal melanocytic tumors. *Am J Ophthalmol*. 2004;137(1):90-95.
25. Shields CL, Bianciotto C, Pirondini C, Materin MA, Harmon SA, Shields JA. Autofluorescence of orange pigment overlying small choroidal melanoma. *Retina*. 2007;27(8):1107-1111.
26. Shields CL, Bianciotto C, Pirondini C, Materin MA, Harmon SA, Shields JA. Autofluorescence of choroidal melanoma in 51 cases. *Br J Ophthalmol*. 2008;92(5):617-622.
27. Shields CL, Pirondini C, Bianciotto C, Materin MA, Harmon SA, Shields JA. Autofluorescence of choroidal nevus in 64 cases. *Retina*. 2008;28(8):1035-1043.