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 ² 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, 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 ² 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.³ 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.³

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...
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 nevus 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 33 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 340 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, 2.73; 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, 2.73, per 1-mm increase; 95% confidence interval, 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% confidence interval, 0.85-0.95; \( P < 0.001 \)). 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 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 (\( P = 0.001 \)) 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. 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).

**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).
show nearly 100% 10-year survival.10,11 The importance

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nancy of Ophthalmology Meeting; New Orleans, LA; No-

10 12.8 160/309

7 10.7 151/503

6 9.9 146/621

5 8.6 136/790

4 7.2 123/973

3 6.2 111/1195

2 4.4 86/1459

1 1.9 44/1943

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

<table>
<thead>
<tr>
<th>Measurement of Choroidal Nevus</th>
<th>Mean (Median, Range)</th>
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<tbody>
<tr>
<td>Overall growth, mm</td>
<td>1.85 (1.25, 0-14.50)</td>
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<tr>
<td>Thickness</td>
<td>1.45 (1.30, 0-10.10)</td>
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<tr>
<td>Growth rate, mm/yr</td>
<td>0.96 (0.35, 0-12.22)</td>
</tr>
<tr>
<td>Basal diameter</td>
<td>1.12 (0.21, 0-13.50)</td>
</tr>
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</table>

In 2007, the Ocular Oncology Service at Wills Eye Inst-

stitute reviewed a large cohort of 8033 patients with uveal melanoma using Kaplan-Meier analysis and found a si-

milar increasing risk for metastasis with increasing tumor thickness (Thangappan A, Shields CL, Nagori S, et al. Pos-

terior uveal melanoma thickness at diagnosis correlates with tumor location. Paper presented at: American Acad-

emy of Ophthalmology Meeting; New Orleans, LA; No-

vember 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 improv-

ing patients’ survival.

Early detection of cancer, in general, has been found to be increasingly important for patient prognosis.8,11 Ga-

stric cancer used to be the main cause of cancer death in Japan, but nationwide screening for this tumor has re-

sulted in earlier detection and a concurrent improved sur-

vival rate of more than 90% at 5 years.8 Likewise, hepa-

tocellular carcinoma has shown improvement in survival, from death typically within 1 year to 60% to 70% sur-

vival at 5 years if the malignancy is discovered early.8 Fi-

nally, it is well recognized that Breslow tumor thickness is the most important prognostic factor for skin mela-

noma. 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 empha-

sized by Ackerman12 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 edu-

cation and commitment by all physicians to recognize flat melanoma.

There is strong interest for early detection of chorio-

dal melanoma, and its differentiation from nevus con-

tinues 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 or-

ange 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 nevus13 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 occurrence15; hence, retrospective analysis, such as that performed in this study, is more practical.

In an analysis of 188 patients with small choroidal les-

ions 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, ab-

sence of drusen, and absence of RPE changes.22 In an anal-

ysis of 240 patients with small choroidal melanocytic les-

ions, Singh et al18 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 pig-

ment. In our current study of 2514 patients with small cho-

roidal melanocytic lesions, factors predictive of growth in-

cluded thickness greater than 2 mm, subretinal fluid, sym-

ptoms, 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, espe-

cially if growth occurs within a short period. However, it

should be realized that slow growth of 0.5 mm through-

out many years or decades could simply represent the natu-

ral 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 department4 re-

vealed 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 uveal melanoma.” The presence of 3 risk factors im-

parted a greater than 50% chance for growth.2 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 contrib-

uted 2 additional risk factors, ultrasonographic hollowness and lack of halo. The previous studies did not evalu-

ate acoustic qualities on ultrasonography. We have revised

<table>
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<th>Year</th>
<th>Kaplan-Meier Estimates, %</th>
<th>No. Failed/Left</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1.9</td>
<td>44/1943</td>
</tr>
<tr>
<td>2</td>
<td>4.4</td>
<td>86/1459</td>
</tr>
<tr>
<td>3</td>
<td>6.2</td>
<td>111/1195</td>
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<tr>
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<tr>
<td>10</td>
<td>12.8</td>
<td>160/309</td>
</tr>
<tr>
<td>15</td>
<td>17.3</td>
<td>171/129</td>
</tr>
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Table 2. Time to Growth of Choroidal Nevus Into Melanoma Using Kaplan-Meier Estimates

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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-
The importance of hollowness on ultrasonography is a feature that has not been particularly emphasized for detection of early choroidal melanoma. Of 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; 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. 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, 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.

In conclusion, thickness greater than 2 mm, fluid, symptoms, orange pigment, margin near disc, ultrasonographic hollowness, and, of course, halo were strong predictors of growth to melanoma.
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 (Thanagapan 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.”

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Author Contributions: Dr C. L. Shields had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Additional Information: The eTable is available at http://www.archophthalmol.com.

Additional Contributions: Rishita Nutheti, Hyderabad, India, provided statistical analysis.

REFERENCES