Risk Factors for Growth and Metastasis of Small Choroidal Melanocytic Lesions

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Background: The management of small melanocytic choroidal tumors is controversial. An important reason for this controversy is that the natural course and metastatic potential of these lesions are not defined clearly. Prior studies that have attempted to elucidate the natural course of these lesions have focused on selected small groups of patients with presumed small choroidal melanomas. There are no large studies investigating the growth potential and metastatic potential for the spectrum of small melanocytic choroidal tumors when considered as an unselected whole group. In addition, the clinical features of these tumors predictive of metastases have not yet been identified.

Methods: A retrospective review was performed on 1329 patients with small melanocytic choroidal tumors measuring 3 mm or less in thickness. Clinical parameters of the patient and tumor were obtained and analyzed for their relation to eventual tumor growth and metastasis using a Cox proportional hazards regression model.

Results: Tumor growth was documented in 18% of patients. The factors predictive of tumor growth (multivariate analysis) included greater tumor thickness ($P = 0.0001$), posterior tumor margin touching optic disc ($P = 0.0001$), symptoms of flashes, floaters ($P = 0.002$), and blurred vision ($P = 0.003$) relative to no symptoms, orange pigment on the tumor surface ($P = 0.004$), and the presence of subretinal fluid ($P = 0.05$). The relative risk (RR) was greatest for initial tumor thickness 2.1 to 3.0 mm (RR = 5.2) and tumor thickness 1.1 to 2.0 mm (RR = 4.3) relative to tumors 1 mm or less in thickness, as well as posterior margin touching the optic disc (RR = 2.6). After adjusting for significant tumor variables, the effect of interventional tumor treatment showed a decreasing risk for tumor growth compared with continued observation without treatment. Of 1329 patients, metastases developed in 35 (3%). The factors predictive of metastases (multivariate analysis) included posterior tumor margin touching the optic disc ($P = 0.003$), documented growth ($P = 0.003$), and greater tumor thickness ($P = 0.004$). The relative risk for metastases was greatest for tumor thickness 1.1 to 3.0 mm (RR = 8.8) and growth (RR = 3.2).

Conclusion: Of small choroidal melanocytic tumors measuring 3 mm or less in thickness at the time of initial examination, 18% demonstrated growth and 3% metastasized during the period of follow-up. Based on this analysis, the clinical features of these tumors can be used to estimate the risk for tumor growth and metastases and assist the clinician with patient management. *Ophthalmology 1995;102:1351-1361*

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The management of small choroidal melanocytic tumors is controversial.[1] An important reason for this controversy is that the natural course and malignant potential of these lesions are not well understood. It is well documented that large tumor dimension and anterior location are two of the major clinical risk factors for uveal melanoma metastases.[2–7] Based on this and other factors, many clinicians believe that small, minimally elevated melanocytic choroidal tumors are best managed by observation and that interventional treatment should be withheld until growth is documented.[1,8–17] Despite this trend in management, a recent meta-analysis of tumors classified as small choroidal melanoma showed a mortality rate of 16% over 5 years.[18]

From a different but perhaps comparative perspective, there has been improvement in the survival of patients with cutaneous melanoma and this is attributed primarily to earlier diagnosis and treatment.[19] Surgical treatment of cutaneous melanoma scarcely has changed during the last few decades and the improved "survival rates almost certainly result from earlier diagnosis."[19] In 1966, more than two thirds of the women and more than three fourths of the men who received diagnoses of cutaneous melanoma were at Clark level III invasion.[20] By contrast, in 1977, nearly half the men and women received diagnoses before their tumors had reached Clark level III. Survival with cutaneous melanoma inversely is related to the level of cutaneous invasion of the malignant cells, so that level III is correlated with a 65% survival rate, whereas level II has a 92% survival rate.[20,21] Other factors affecting prognosis include patient age and sex, tumor thickness, location, type, and lymph node involvement.[22] The increased awareness of clinical suspicious features have promoted early detection and treatment of cutaneous melanoma.

The same philosophy applies to uveal melanoma and cancer in general. In these diseases, it is likely that an earlier diagnosis will improve management and thereby increase survival. We and others have observed the natural course of small melanocytic choroidal tumors and have assessed parameters predictive of enlargement of these lesions.[23–26] However, our ultimate concern is not whether a small tumor demonstrates growth but whether it has potential to metastasize and cause death of the patient. Hence, we wondered whether the survival of patients with uveal melanoma, like the survival of patients with cutaneous melanoma, could be improved by early recognition and prompt treatment, before the development of high-risk characteristics. With that question in mind, the current study was undertaken to determine the clinical features of small melanocytic tumors predictive of metastasis. Our study represents, by far, the largest and most inclusive study of this type, in that we have reviewed 1329 choroidal melanocytic tumors ranging from flat lesions to those 3 mm in thickness, regardless of artificial classifications such as nonsuspicious or suspicious choroidal nevus, indeterminate choroidal tumor, nevoma, or active or dormant choroidal melanoma.[23–26]

Materials and Methods

A review of the records of all patients with choroidal tumors of melanocytic origin who received therapy at the Ocular Oncology Service at Wills Eye Hospital between April 1970 and December 1990 was performed. Those tumors that were 3.0 mm or less in thickness (measured by A- and B-scan ultrasonography and/or indirect ophthalmoscopy) at the initial visit were identified and selected for analysis. To avoid subjective judgment, the only inclusion criteria from a diagnostic standpoint was the presence of a choroidal melanocytic lesion measuring 3 mm or less in thickness. Thus, our analysis represented all small choroidal melanocytic lesions, including those with a clinical diagnosis of choroidal nevus and choroidal melanoma.

All patients were evaluated using standard examination techniques for those with intraocular tumors,[27] and all data prospectively were collected. Fundus examination using indirect ophthalmoscopy, slit-lamp biomicroscopy with Hruby, 60- and 90-diopter lenses when applicable, detailed fundus drawing, and fundus photography was performed. Clinical features found on the initial examination and analyzed in this report included patient age and sex, visual symptoms, best visual acuity as measured by Snellen visual acuity charts, general tumor location (inferior, superior, temporal, nasal, or macular), anterior and posterior tumor margin as it related to the optic disc, proximity of the tumor margin to the foveola, and tumor dimensions. The tumor base dimension was estimated in millimeters from indirect ophthalmoscopy by experienced observers, and the greatest tumor thickness in millimeters was measured by ultrasonography and indirect ophthalmoscopy. Specific tumor features such as the degree of pigmentation and the presence of subretinal fluid, surface orange pigment, drusen, and retinal pigment epithelial hyperplasia also were assessed. The record of each patient was reviewed to establish whether there was documented evidence of growth or metastases at any time during the follow-up period. Growth was judged present by an increase in basal dimension of at least 0.3 mm by meticulous comparison of serial fundus photographs or by an increase in thickness of 0.5 mm by serial ultrasonograms. The interval time between the initial examination and the documentation of tumor growth and/or metastases was recorded.

Statistical Analyses

A series of univariate Cox proportional hazards regressions assessed the degree of relation of all of the variables in Tables 1 and 3 to the outcome measures of (1) time to metastases (Table 1) and (2) time to growth (Table 3). Subsequent multivariate models included variables that were significant at a univariate level ($P < 0.05$) and sought to identify which combination of factors best related to time to metastases (Table 2) and time to growth (Table 4). Finally, a multivariate model that adjusted for statis-

tically significant tumor variables was performed to evaluate the effect of initial treatment on time to growth. Mean metastases and growth-free intervals also were calculated.[28]

Results

We identified 1547 patients with small choroidal melanocytic tumors (≤3 mm in thickness) examined at the Ocular Oncology Service during the 20 years included in this study. Of the 1547 patients, 218 were only examined once with no available follow-up, and these patients were not included in this analysis. Therefore, the remaining total of 1329 patients with follow-up were included for analysis. All 1329 patients were followed for eventual tumor metastases. Of 42 patients, the initial management was enucleation; therefore only the remaining 1287 patients were included in the evaluation for eventual tumor growth.

The completeness of follow-up analysis showed that follow-up time was 6 months or less in 4.7% of patients and longer than 6 to 12 months in 5.9%, longer than 12 to 18 months in 8.1%, longer than 18 to 24 months in 4.6%, longer than 2 to 3 years in 11.7%, longer than 3 to 4 years in 11.7%, longer than 4 to 5 years in 9.9%, and longer than 5 years in 43.5%. There was no statistically significant difference in follow-up time for patients in whom metastasis developed versus those in whom it did not develop, using both parametric ($F[1,1327] = 0.04$, $P = 0.85$) and nonparametric analyses ($P = 0.31$, Wilcoxon test).

The Kaplan-Meier estimate of tumor metastasis was 0.6% at 36 months, 2% at 48 months, and 3% at 60 months. The Kaplan-Meier estimate of tumor growth was 6% at 12 months, 10% at 24 months, 14% at 36 months, 17% at 48 months, and 19% at 60 months.

Tumor Metastases

Of 1329 small, melanocytic, choroidal tumors, 35 (3%) had documented evidence of tumor metastases. The median follow-up time of the 1329 patients was 51 months (mean, 62 months; range, 1–277 months). For the 35 patients in whom metastases subsequently developed, the median time to metastases was 51 months. For the entire study sample, the mean metastasis-free interval was 182 months.

From a univariate analysis (Table 1), the significant clinical features predictive of metastases included symptoms of blurred vision ($P = 0.0001$); decreased visual acuity of 20/50 to 20/80 ($P = 0.0001$) compared with 20/20 to 20/40; posterior tumor margin touching the optic disc ($P = 0.0001$) compared with more than 3 mm from the disc; increased largest basal dimension of 5.1 to 10.0 mm ($P = 0.01$) and 10.1 to 15.0 mm ($P = 0.0001$) compared with 5 mm or less; increased tumor thickness of 1.1 to 2.0 mm ($P = 0.0004$) and tumor thickness of 2.1 to 3.0 mm ($P = 0.0001$) compared with a thickness of 1 mm or less; documented tumor growth ($P = 0.0001$); presence of subretinal fluid ($P = 0.0002$); and surface orange pigment ($P = 0.009$). The relative risk (RR) for tumor metastases was greatest for the variables of tumor thickness (1.1–2.0 mm [RR = 14.8] and 2.1–3.0 mm [RR = 19.7] relative to a thickness of ≤1 mm), largest tumor basal dimension (10.1–15.0 mm [RR = 8.1] relative to a base dimension of ≤5 mm), and documented tumor growth (RR = 7.6). Of the 622 tumors measuring 1 mm or less in thickness, 179 were flat, 189 were 0.2 mm or less, and 425 were 0.5 mm or less.

From a multivariate model (Table 2), the best subset of independent predictors of metastases included tumor thickness, documented growth, posterior margin touching the optic disc, and symptoms of blurred vision. The relative risk for tumor thicknesses of 1.1 to 3.0 mm (relative to thicknesses ≤1 mm) was 8.8, and the relative risk for documented tumor growth was 3.2. It should be noted that in the multivariate model, the measures of tumor thickness and largest basal dimension virtually were interchangeable, both being indices of tumor size.

An attempt to analyze the effect of tumor treatment on eventual metastases, while simultaneously controlling for significant tumor variables highlighted in the initial analyses, was precluded by the small number of metastatic events.

Tumor Growth

There were 1287 patients with small choroidal melanocytic tumors who had adequate ophthalmologic follow-up for this study. Of this group, 235 (18%) had documented evidence of tumor growth either by an increase in base or thickness. The median follow-up time was 51 months (range, 1–277 months). For the 235 patients who had tumor growth, the median time to growth was 25 months. The mean growth-free interval for the entire sample of 1287 patients was 111 months.

From a univariate model (Table 3), the most significant predictive factors for growth included symptoms of blurred vision ($P = 0.0001$) and flashes/floaters ($P = 0.0001$) compared with no symptoms; visual acuity of 20/50 to 20/80 ($P = 0.0001$) and 20/100 or worse ($P = 0.0001$) compared with 20/20 to 20/40; posterior margin touching the the optic disc ($P = 0.0001$) and 0.1 to 3.0 mm from the optic disc ($P = 0.0001$) compared with tumors more than 3 mm from the disc; subfoveal location ($P = 0.0001$) and 0.1 to 3.0 mm from the foveola ($P = 0.0005$) compared with more than 3 mm from the foveola; increased largest basal dimension of 5.1 to 10.0 mm ($P = 0.0001$) and 10.1 to 15.0 mm ($P = 0.0001$) compared with 5 mm or less; increased tumor thickness of 1.1 to 2.0 mm ($P = 0.0001$) and 2.1 to 3.0 mm ($P = 0.0001$) compared with a thickness of 1 mm or less; subretinal fluid ($P = 0.0001$); and orange pigment ($P = 0.0001$). The relative risk for tumor growth was greatest for measures of tumor thickness (1.1–2.0 mm [RR = 5.5] and 2.1–3.0 mm [RR = 7.9] relative to a thickness of 1 mm or less), posterior

Table 1. Univariate Analyses of the Predictive Value of Clinical Features on Metastasis in a Series of 1329 Small Melanocytic Choroidal Tumors

Clinical Feature	No Metastasis (n = 1294)	Metastasis (n = 35)	P	Relative Risk	95% Confidence Interval
Age (yrs)					
0-30	59	3	0.61	1.4	0.4, 4.7
31-60	656	13	0.05	0.5	0.2, 1.0
>61*	579	19			
Sex					
F*	779	18			
M	515	17	0.35	1.4	0.7, 2.7
Symptoms					
None*	856	13			
Blurred vision	285	16	0.0001	3.8	1.8, 7.9
Floaters/flashes	152	6	0.06	2.6	1.0, 6.8
Visual acuity					
20/20-20/40*	1046	17			
20/50-20/80	132	13	0.0001	6.5	3.2, 13.6
20/100 or worse	116	5	0.07	2.5	0.9, 6.8
Location					
Inferior*	224	8			
Superior	277	8	0.69	0.8	0.3, 2.2
Temporal	393	9	0.35	0.6	0.3, 1.7
Nasal	196	2	0.08	0.3	0.1, 1.2
Macular	204	8	0.89	1.1	0.4, 2.9
Anterior margin					
0.1-3.0 mm from optic disc	44	1	0.69	0.7	0.1, 5.3
>3.0 mm from disc to the equator	986	26	0.49	0.8	0.3, 1.7
Between equator and ora serrata*	264	8			
Posterior margin					
Touching the optic disc	167	16	0.0001	5.1	2.5, 10.3
0.1-3.0 mm from optic disc	185	4	0.52	1.4	0.5, 4.3
>3.0 mm from disc to the equator*	904	14			
Between equator and ora serrata*	38	1			
Relationship to foveola					
Subfoveal	199	8	0.15	1.9	0.8, 4.2
0.1-3.0 mm from foveola	213	8	0.18	1.8	0.8, 4.0
>3.0 mm from foveola*	882	19			
Largest basal dimension (mm)					
0-5.0*	587	7			
5.1-10.0	631	21	0.01	3.1	1.3, 7.3
10.1-15.0	76	7	0.0001	8.1	2.8, 23.1
Thickness† (mm)					
0-1.0*	620	2			
1.1-2.0	363	14	0.0004	14.8	3.4, 65.3
2.1-3.0	310	19	0.0001	19.7	4.6, 84.7
Color					
Brown*	956	25			
Yellow	338	10	0.77	1.1	0.5, 2.3
Subretinal fluid					
Absent*	974	16			
Present	320	19	0.0002	3.6	1.8, 7.0
Orange pigment					
Absent*	945	19			
Present	349	16	0.009	2.4	1.3, 4.7

(continues)

Table 1 (*continued*). Univariate Analyses of the Predictive Value of Clinical Features on Metastasis in a Series of 1329 Small Melanocytic Choroidal Tumors

Clinical Feature	No Metastasis (n = 1294)	Metastasis (n = 35)	P	Relative Risk	95% Confidence Interval
Drusen					
Absent*	619	15			
Present	675	20	0.22	1.5	0.8, 3.0
Retinal pigment epithelial hyperplasia					
Absent*	1093	31			
Present	201	4	0.73	0.8	0.3, 2.4
Growth					
Absent*	1084	10			
Present	210	25	0.0001	7.6	3.7, 16.1

* Reference variable.

† N = 1328 tumors.

margin (touching the optic disc [RR = 3.6] relative to tumors not touching the disc), subretinal fluid [RR = 3.6], orange pigment [RR = 3.4], and blurred vision relative to no symptoms [RR = 3.1].

From a multivariate model (Table 4), the most important factors for tumor growth included greater tumor thickness, posterior margin touching the optic disc, symptoms of flashes/floaters and blurred vision, orange pigment, and subretinal fluid. The relative risk for tumor thicknesses of 2.1 to 3.0 mm relative to thicknesses 1 mm or less was 5.2, and the relative risk for the posterior margin touching the optic disc relative to more than 3.0 mm from the disc was 2.6. Again, the largest basal dimension of the tumor was equivalent to tumor thickness and could be used interchangeably in the multivariate model. Although sex was a significant factor ($P = 0.002$) in the univariate analysis for tumor growth, it became a nonsignificant factor ($P = 0.22$) in the multivariate analysis.

After adjusting for statistically significant clinical tumor variables identified in the aforementioned multivariate model, the effect of initial interventional treatment (plaque radiotherapy or laser photocoagulation versus observation) showed a significant decreasing risk for ultimate growth ($P = 0.0001$; RR = 0.20, 95% confidence interval = 0.13–0.31). The individual treatment modalities were not analyzed due to the small sample size of each treatment type.

The combined relative risk for metastases from small choroidal melanocytic lesions based on the multivariate results was calculated.[28] The relative risk for combinations of features was compared with the absence of the feature(s) (e.g., a tumor measuring >1.1 mm in thickness with the posterior margin touching the optic disc and with documented growth carried a risk 81 times greater for metastasis to develop than a tumor measuring less than 1.0 mm in thickness with a margin that did not touch the disc and showed no evidence of growth). The percentage of patients in whom metastases developed (Table 5) with various combinations of risk features also was tabulated. For example, using the same features as mentioned above, metastasis developed in 17% of patients with a tumor measuring 2.0 mm in thickness, posterior margin touching the disc, and with documented growth.

Discussion

There is a continuing evolution in medicine toward early detection and management of a variety of cancers. Self-

Table 2. Multivariate Analysis of Clinical Factors Predictive of Metastases of Small Melanocytic Choroidal Tumors (N = 1329)*

Clinical Feature	P	Relative Risk	95% Confidence Interval
Symptoms (none versus blurred vision)	0.060	1.9	1.0, 3.7
Posterior margin (not touching the optic disc versus touching the disc)	0.003	2.9	1.4, 5.7
Growth (absent versus present)	0.003	3.2	1.5, 7.0
Thickness† (0–1.0 versus 1.1–3.0 mm)	0.004	8.8	2.0, 38.1

* Values in parentheses reflect reference variable versus significant variable.

† Largest tumor base could be substituted for tumor thickness yielding similar results in the multivariate analysis.

Table 3. Univariate Analyses of the Predictive Value of Clinical Features on Growth in a Series of 1287 Small Melanocytic Choroidal Tumors

Clinical Feature	No Growth (n = 1052)	Growth (n = 235)	P	Relative Risk	95% Confidence Interval
Age (yrs)					
0–30	42	16	0.02	1.9	1.1, 3.3
31–60	512	138	0.02	1.4	1.1, 1.8
>61*	498	81			
Sex					
F*	660	120			
M	392	115	0.002	1.5	1.2, 1.9
Symptoms†					
None*	752	105			
Blurred vision	189	87	0.0001	3.1	2.4, 4.2
Floaters/flashes	110	43	0.0001	2.7	1.9, 3.8
Visual acuity					
20/20–20/40*	885	160			
20/50–20/80	96	42	0.0001	2.5	1.8, 3.5
20/100 or worse	71	33	0.0001	2.5	1.7, 3.6
Location					
Inferior*	192	32			
Superior	217	57	0.008	1.8	1.2, 2.9
Temporal	330	61	0.49	1.2	0.7, 1.9
Nasal	159	35	0.07	1.5	1.0, 2.3
Macular	154	50	0.68	1.1	0.7, 1.7
Anterior margin					
0–3.0 mm from optic disc	31	11	0.03	2.1	1.1, 4.2
>3.0 mm from disc to the equator	788	190	0.04	1.5	1.0, 2.1
Between equator and ora serrata*	233	34			
Posterior margin					
Touching the optic disc	96	67	0.0001	3.6	2.7, 4.8
0.1–3.0 mm from optic disc	136	42	0.0001	2.0	1.4, 2.9
>3.0 mm from disc to the equator*	787	120			
Between equator and ora serrata*	33	6			
Relationship to foveola					
Subfoveal	132	58	0.0001	2.5	1.8, 3.4
0.1–3.0 mm from foveola	157	50	0.0005	1.8	1.3, 2.5
>3.0 mm from foveola*	763	127			
Largest basal dimension (mm)					
0–5.0*	511	66			
5.1–10.0	486	148	0.0001	2.4	1.8, 3.2
10.1–15.0	55	21	0.0001	2.9	1.8, 4.7
Thickness† (mm)					
0–1.0*	582	37			
1.1–2.0	277	90	0.0001	5.5	3.8, 8.1
2.1–3.0	192	108	0.0001	7.9	5.4, 11.5
Color					
Brown*	784	170			
Yellow	268	65	0.32	1.2	0.9, 1.5
Subretinal fluid					
Absent*	858	121			
Present	194	114	0.0001	3.6	2.8, 4.7
Orange pigment					
Absent*	830	120			
Present	222	115	0.0001	3.4	2.6, 4.3

(continues)

Table 3 (*continued*). Univariate Analyses of the Predictive Value of Clinical Features on Growth in a Series of 1287 Small Melanocytic Choroidal Tumors

Clinical Feature	No Growth (n = 1052)	Growth (n = 235)	P	Relative Risk	95% Confidence Interval
Drusen					
Absent*	513	102			
Present	539	133	0.01	1.4	1.1, 1.8
Retinal pigment epithelial hyperplasia					
Absent*	896	193			
Present	156	42	0.09	1.4	1.0, 1.9

* Reference variable.

† N = 1286 tumors.

examination and early detection of breast cancers are examples of increased awareness and improved management in oncologic disease.[29,30] Colonic evaluation for premalignant polyps is important in preventing colonic cancer.[31-33] The evidence is overwhelming that the detection and removal of small adenomatous and pre-invasive adenocarcinomas prevent death caused by colorectal cancer.[33] Polyps measuring 1 cm in size are targeted for detection and removal. In addition, early identification and treatment of patients with precancerous cutaneous melanocytic lesions such as dysplastic nevi (familial atypical mole, melanoma syndrome) have been shown to prevent eventual cancer formation.[34-38] Although the incidence of cutaneous melanoma has been increasing in recent decades, the survival rate has improved largely because of increased awareness and early diagnosis and treatment.[19]

In contrast to improved survival rates with these nonocular tumors, the survival rate with uveal melanoma has changed little over the last few decades.[15,18] Zimmerman and McLean[15] reported 2627 cases of choroidal melanoma treated by enucleation and submitted to the Armed Forces Institute of Pathology over a 40-year period (1936–1975). The authors found that the survival rate practically was unchanged, despite an increasing proportion of smaller tumors. The authors stated that in contrast with the improvement in survival achieved by earlier diagnosis and better management of retinoblastoma, there has not been a clinically significant improvement in survival of patients treated for uveal melanoma by enucleation.[15] Diener-West and co-workers[18] found that small choroidal melanomas carried a 16% mortality rate over 5 years. Individuals with a small choroidal melanoma had a 1.3 times greater risk for death within 5 years compared with the general population of similar age and sex.[18] They recommended treatment as early as possible to provide the best chance for a normal lifespan.[18] Increased survival with choroidal melanoma, similar to other cancers, depends on improvements in early detection of malignant or pre-

Table 4. Multivariate Analysis of Clinical Factors Predictive of Growth of 1287 Small Melanocytic Choroidal Tumors*

Clinical Feature	P	Relative Risk	95% Confidence Interval
Subretinal fluid			
Absent versus present	0.05	1.4	1.0, 1.8
Orange pigment			
Absent versus present	0.004	1.5	1.2, 2.0
Symptoms			
None versus blurred vision	0.003	1.6	1.2, 2.2
None versus flashes/floaters	0.002	1.8	1.2, 2.6
Posterior margin			
>3.0 mm from optic disc versus touching the disc	0.0001	2.6	1.9, 3.6
>3.0 mm from optic disc versus 0.1 to 3.0 mm from disc	0.08	1.4	1.0, 2.0
Thickness†			
0–1.0 versus 1.1–2.0 mm	0.0001	4.3	2.9, 6.4
0–1.0 versus 2.1–3.0 mm	0.0001	5.2	3.5, 7.8

* Values reflect reference variable versus significant variable.

† Largest tumor base could be substituted for tumor thickness yielding similar results in the multivariate analysis.

Table 5. Percentage of Patients with Metastases from Small Choroidal Melanocytic Lesions with Various Combinations of Risk Factors

Risk Features	No. Metastasis/ No. with Feature(s)	(%)	No. Metastasis/ No. without Feature(s)	(%)
1 feature				
Thickness > 1 mm (T)*	33/707	(5)	2/622	(<1)
Growth (G)†	25/235	(11)	10/1084	(<1)
Posterior margin touching disc (PM)‡	16/183	(9)	19/1146	(2)
Symptoms (S)§	16/301	(5)	19/1027	(2)
2 features				
T + G	24/198	(12)	11/1131	(<1)
T + PM	16/119	(13)	19/1210	(2)
T + S	16/213	(8)	19/1115	(2)
G + PM	10/67	(15)	25/1262	(2)
G + S	11/87	(13)	24/1241	(2)
PM + S	9/68	(13)	26/1260	(2)
3 features				
T + G + PM	10/58	(17)	25/1270	(2)
T + G + S	11/73	(15)	24/1255	(2)
T + PM + S	9/57	(16)	26/1271	(2)
G + PM + S	6/29	(21)	29/1299	(2)
4 features				
T + G + PM + S	6/24	(25)	29/1304	(2)

* Thickness refers to ultrasound thickness measuring 1.1–3.0 mm.

† Growth refers to documented tumor enlargement.

‡ Posterior margin refers to the posterior edge of the tumor touching the disc.

§ Symptoms refer to blurred vision.

malignant lesions and/or advancements in treatment methods.

Because it appears well documented that earlier recognition and treatment of other cancers offer the patient a better prognosis, it seems uncomfortable that ophthalmologists have adopted a philosophy that small pigmented choroidal lesions should be observed indefinitely until growth is documented. The relaxed attitude is due to the unclear delineation between a choroidal nevus and choroidal melanoma, the longstanding teaching that one should wait until appearance of documented growth before suspecting a choroidal melanoma, and importantly that there is no current evidence that early treatment is beneficial.[1,12,13,25]

This study has shown that documented growth of a small melanocytic choroidal tumor increases the risk for metastases almost eight times more than a tumor that does not grow. In addition, if we assume each clinical feature is truly independent, then the risk for metastases multiplies when two or more risk factors are found with a single choroidal lesion.[39] For example, a melanocytic choroidal tumor measuring more than 1 mm in thickness with documented growth has a 28 times greater risk for metastasis than a tumor measuring less than 1.0 mm in thickness with no evidence of growth. These estimates would represent a worst-case scenario, given the assumption of complete independence among the clinical features, and caution should be taken with the interpretation of these risk estimates. Based on these important findings, it is possible that we are waiting too long in the overall course of the patient's disease by watching for gross clinical evidence of tumor enlargement.

To understand better the impact of each clinical risk factor, we extracted the percentage of patients in whom metastases developed with various combinations of risk factors (Table 5). For example, metastases developed in 14% of patients with a melanocytic choroidal tumor that measured more than 1.0 mm in thickness and touched the optic disc, whereas a similar lesion with the same features but with documented growth resulted in metastases in 17% of the patients. Finally, a combination of all four risk factors showed that metastases developed in 25% of patients who had symptoms of blurred vision and a tumor measuring at least 1.0 mm in thickness that abutted the optic disc and had documented growth.

It seems reasonable that a preventative approach to this disease would be to treat high-risk lesions before documented growth to prevent malignant transformation and improve overall patient survival. However, two major difficulties with this approach are the reliable identification of a precursor lesion and the most effective treatment for it. This study was designed to identify clinical factors of choroidal melanocytic lesions statistically predictive of growth and metastasis. As an adjunct to the analysis, an

evaluation of the effects of treatment on metastasis was attempted but not feasible due to the small number of metastatic events and nonrandomized retrospective approach.

A review of the literature shows that attempts have been made using various analytic methods to investigate the risk of precursor lesions to evolve into choroidal melanoma.[23–26] Most recently, Butler and co-workers[26] studied "indeterminate" pigmented choroidal tumors and identified risk factors for tumor enlargement, including greater tumor thickness, symptoms, orange pigment, internal quiet zone on B-scan ultrasonography, and hot spots of fluorescein angiography. Of the 195 tumors in their series without documented growth, there were no metastases, and of the 98 tumors demonstrating growth, metastases developed in 5%. The elegant statistical analysis was somewhat lessened[40] by the limited inclusion criteria stated as "masses between 1.5 mm and 4.0 mm thick and/or more than 6 mm in diameter."[26] Other studies investigating the malignant potential of small choroidal melanomas found mortality rates between 7% and 15% over a 5- to 6-year follow-up period.[3,17,41,42] To our knowledge, there are no reports, before the current study, evaluating the malignant potential of all small melanocytic choroidal tumors, including those that were diagnosed initially as malignant melanoma as well as those diagnosed clinically as benign nevus.

A problem in the management of small choroidal melanocytic lesions is the artificial and often subjective clinical classification of choroidal melanocytic tumors into choroidal nevus and melanoma.[23–26] The above studies on mortality focused on those lesions subjectively classified as small choroidal melanomas or "indeterminate" lesions. The purpose of our study was to define, in a more generalized, less-biased fashion, the overall malignant potential of all melanocytic choroidal tumors objectively found to be 3 mm or less in thickness, regardless of the clinician's original diagnosis or classification.

The clinical features that predicted metastases from small choroidal melanocytic tumors in our study included posterior tumor location touching the optic disc, increased tumor thickness, symptoms of blurred vision, and documented tumor enlargement. Factors such as increased tumor thickness and documented tumor growth seem to be associated logically with increased tumor activity and risk for development of metastases. It is more difficult to explain the correlation of posterior location with increased metastases. Prior studies have correlated ciliary body location of uveal melanoma with increased metastases,[6,7] but our study was limited to choroidal tumors and did not include ciliary body tumors. A prior study from our department found that tumors located closer to the optic disc had a greater tendency to demonstrate growth; however, metastases were not included as an outcome measure.[24]

Choroidal melanomas that show clinical evidence of growth have an increased mitotic activity histopathologically compared with nongrowing tumors.[41] Mitotic activity has long been associated with malignant potential.[3] In our study, we found that documented tumor growth carried a substantial relative risk of 7.6 for development of metastases compared with nongrowing lesions. Because of the prominent risk for metastases in growing tumors, we sought to identify the factors that predicted tumor growth. The factors that were identified as predictive of future growth included posterior tumor location, increased tumor thickness, symptoms, presence of orange pigment, and subretinal fluid. These are similar to the clinical parameters that were recognized in a prior, less-comprehensive report from our department.[24] Identification of those patients at greatest risk for tumor growth raises the suspicion for potential malignancy; thus, a decision for preventative treatment should be considered.

Deductive reasoning from this analysis might suggest that early treatment of high-risk lesions before growth may eliminate "growth" as a risk for metastases and perhaps improve overall survival. Conservative reasoning would argue that the risk for metastases is low at approximately 3% overall and interventional treatment of the high-risk group would induce poor vision in a great proportion of patients, most of whom would not have had eventual melanoma metastases. Although small melanocytic lesions have a 3% overall metastatic rate over the short term (approximately 5 years), they may have a worse survival over the long term, as is seen with uveal melanoma in general. In addition, of those patients with all of the high-risk factors, the risk is 154 times greater for metastases to develop than those patients without the risk factors. Certainly, the best method to answer this delicate question would be a randomized prospective trial evaluating observation versus interventional treatment for patients with small melanocytic lesions identified to be at high risk for tumor growth or metastases. Our study indicated that treatment correlated with a decreased risk for tumor growth but we were unable to analyze the impact of treatment on metastases due to the low number of metastases.

There are several reasons to view our results with caution. First, although the data were collected prospectively, this study was a retrospective one, without randomization. The main goal was to identify risk factors for growth and metastases; not to evaluate the impact of treatment of the high-risk group. Second, the median follow-up was relatively short (51 months). Longer follow-up likely would increase the percent metastasis and possibly provide more insight into the impact of risk factors. Third, the eyes treated with enucleation at the first visit were excluded from the analysis for tumor growth. Because they were presumably suspicious enough to warrant enucleation at the initial examination, they likely possessed features that may have contributed valuable data for the analysis, especially the impact of tumor growth in the analysis. Most likely, these tumors would have increased the percent growth and perhaps even increased the percent metastases if they were not treated initially. Fourth, even though the analysis determined that treatment was correlated with a decreased risk for tumor growth, this should not be extrapolated to mean a decreased risk for metastases. Treatment was an associated factor but not necessarily causal. It is possible that some other factor(s) associated

with both growth and lack of treatment could cause metastases.

On the other hand, the positive points of this study also should be recognized. These include the large number of patients included in the analysis, the complete, uniform follow-up at one institution, and the objective inclusion criteria, including all small choroidal melanocytic tumors.

In summary, the results of our investigation allow us to identify risk factors for metastases of small melanocytic choroidal lesions. These features may serve as a guide for the ocular oncologist when faced with the decision of management of these difficult cases. Although there has been a trend toward simple observation of small melanocytic choroidal tumors in recent years, our study has suggested that waiting for growth may be associated with a greater risk of metastasis. Hence, there may be a valid argument for active treatment, rather than observation, for those precursor lesions with high-risk clinical features, as identified in this study. Hopefully, in the future there will be more evidence that treatment of precursor melanocytic choroidal lesions will prevent choroidal melanoma and its associated mortality, as we have witnessed with other precursor lesions seen in other suspecialities of oncology.

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Discussion
by
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I would like to focus on the important question that Shields et al have raised, "Are we waiting too long?" in treating patients with uveal melanoma. Although there is no definitive answer to this question, I believe that their data interpreted, in light of a new theory of cancer,[1] does suggest that we are not waiting too long.

Shields et al found no metastasis with thin nongrowing tumors, even though many of them were not treated. Similarly, Butler et al[2] studying small choroidal tumors (<10 mm in diameter and 3 mm in height) found no mortality with nongrowing tumors. Based on their data, let us assume that all thin (defined as <1 mm in thickness) nongrowing tumors are benign, all growing tumors are malignant, and all thick-growing tumors arise from thin-growing tumors. By comparing the difference in metastasis rates between thin- and thick-growing tumors, we have an estimate of the effect of delaying treatment of thin tumors until they become thick. They found that the thin-growing tumors had a metastasis rate of 11%, whereas the thicker tumors had a metastasis rate of 12%. The 1% difference in metastasis rates indicates that there is little benefit from early treatment.

To get a significant effect of earlier treatment, one would have assume that a significant proportion of the growing tumors arose from nongrowing benign nevi and that the earlier treatment occurred while the tumor was still a benign nevus. Because there is a high prevalence of uveal nevi (5% of eyes) and the low incidence of uveal melanoma (7 per million annually), approximately 1 in 15,000 nevi becomes a melanoma each year. Therefore, treatment of uveal nevi would be practical only if we can identify nevi that are at high risk of becoming melanomas. Unfortunately, there is probably no way of identifying "high-risk nevi."

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The risk factors for growth that Shields et al found (subretinal fluid, orange pigment, symptoms, touching the optic disc and thickness >1 mm) are most certainly the result, not the cause, of growth. Therefore, they identify malignant tumors that are growing not benign tumors that will in the future undergo malignant transformation and begin to grow.

Schachat,[3] in discussing the article by Butler et al at the 1993 AAO Annual Meeting, arrived at the conclusion that we are waiting too long. His analysis differed from mine regarding two key points. First, Schachat had to guesstimate the effect of delayed treatment, which he assumed was a 2.5% increase in mortality. This is greater than the 1% increase in mortality I estimated based on data presented by Shields et al. Second, because these studies are from oncology centers, I suspect that the proportion of benign nongrowing tumors is greater than what is reported in either study. Schachat stated that he was willing enucleate 300 eyes, to save two or three lives over a 5-year period, but would he feel as strongly if the savings in lives were a fraction of a life not two or three.

The theory of cancer[1] that I have used to explain the behavior of uveal melanoma can be applied to a variety of neoplasms. The main conclusion derived from this theory is that much of the improvement in survival rates that has been associated with early detection is due to the treatment of a higher proportion of benign tumors, not to the curing of malignancies. If this theory is correct regarding uveal melanoma, then we must face the fact that modifications of local treatment will not result in any significant improvement in survival, and research must be directed toward treatment of metastatic disease.

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