RISK FACTORS FOR GROWTH AND METASTASIS OF SMALL CHOROIDAL MELANOCYTIC LESIONS*

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ABSTRACT

Purpose: To investigate the clinical features that predict growth and metastasis of an unselected group of small melanocytic choroidal tumors.

Methods: A retrospective review was performed on 1329 patients with small melanocytic choroidal tumors measuring 3 mm in thickness or less. Clinical parameters of the patient and tumor were extracted and analyzed for their relationship 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, posterior tumor margin touching optic disc, symptoms of flashes, floaters, and blurred vision, orange pigment on the tumor surface, and the presence of subretinal fluid. The relative risk (rr) was greatest for initial tumor thickness > 2.0 mm (rr 5.2) and 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 as compared to continued observation without treatment.

Of 1329 patients, 35 (3%) developed metastases. The factors predictive of metastases (multivariate analysis) included: posterior tumor margin touching the optic disc, documented growth, and greater tumor thickness. The relative risk for metastases was greatest for tumor thickness 1.1-3.0 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% demonstrate growth and 3% metastasize during the period of followup. 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.

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INTRODUCTION

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] On the basis of 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 revealed 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, which is primarily attributed to earlier diagnosis and treatment.[19] Surgical treatment of cutaneous melanoma has scarcely changed during the past 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 with a diagnosis of cutaneous melanoma were at Clark level III invasion at diagnosis.[20] By contrast, in 1977, diagnosis was made in nearly half the men and women before their tumors had reached Clark level III. Survival with cutaneous melanoma is inversely related to the level of cutaneous invasion of the malignant cells, so that level III is correlated with 65% survival and level II with 92% survival.[20,21] Other factors affecting prognosis include patient age and sex; and tumor thickness, location, and 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 desirable to make an earlier diagnosis, 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, prior to the development of high-risk characteristics. With that question in mind, the present 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: we have reviewed 1,329 choroidal melanocytic tumors ranging from flat lesions to those up to 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

The records of all patients with choroidal tumors of melanocytic origin managed on the Ocular Oncology Service at Wills Eye Hospital between April 1970 and December 1990 were reviewed. 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 criterion 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 patient were evaluated using standard examination techniques for patients with intraocular tumors,[27] and all data were prospectively collected. Fundus examination was performed using indirect ophthalmoscopy; slit-lamp biomicroscopy with Hruby, 60-diopter, and 90-diopter lenses when applicable; detailed fundus drawing; and fundus photography. 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 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 closest 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, were also assessed. The record of each patient was reviewed to establish if there was documented evidence of growth or metastases at any time during follow-up. 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.

A series of univariate Cox proportional hazards regressions assessed the degree of relationship of all of the variables in Tables I and II to the outcome measures of (1) time to metastases (Table I) and (2) time to growth (Table II). Subsequent multivariate models included variables that were significant at a univariate level ($P<.05$) and sought to identify which combi-

nation of factors best related to time to metastases (Table III) and time to growth (Table IV). Finally, a multivariate model that adjusted for statistically significant tumor variables was performed to evaluate the effect of initial treatment on time to growth. Mean metastases and growth-free intervals were also calculated.[28]

RESULTS

We identified 1,547 patients with small choroidal melanocytic tumors (3 mm or less in thickness) examined on the Ocular Oncology Service during the 20 years included in this study. Of the 1,547 patients, 218 were examined only once with no available follow-up, and these were not included in this analysis; this left a total of 1,329 patients with follow-up who were included for analysis. All 1,329 patients were followed for eventual tumor metastases. In 42 cases, the initial management was enucleation; therefore, only the remaining 1,287 cases were included in the evaluation for eventual tumor growth.

The completeness of follow-up analysis revealed that follow-up time was ≤6 months in 4.7%, >6 to 12 months in 5.9%, >12 to 18 months in 8.1%, >18 to 24 months in 4.6%, > 2 to 3 years in 11.7%, >3 to 4 years in 11.7%, >4 to 5 years in 9.9%, and > 5 years in 43.5% of patients. There was no statistically significant difference in follow-up time for patients who developed metastasis versus those who did not develop metastasis, using both parametric ($F(1,1327) = .04$, $P=.85$) and nonparametric analyses (Wilcoxon, $P=.31$).

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 1,329 small melanocytic choroidal tumors, 35 (3%) had documented evidence of tumor metastases. The median follow-up time of the 1,329 patients was 51 months (mean, 62; range, 1 to 277). For the 35 patients who subsequently developed metastases, 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 I), the significant clinical features predictive of metastases included: symptoms of blurred vision ($P=.0001$); decreased visual acuity of 20/50 to 20/80 ($P=.0001$) compared with 20/20 to 20/40; posterior tumor margin touching the the optic disc ($P=.0001$) compared with >3 mm from the disc; increased largest basal dimension of 5.1 to 10.0 mm ($P=.01$) and 10.1 to 15.0 mm ($P=.0001$) compared with ≤ 5 mm; increased tumor thickness 1.1 to 2.0 mm ($P=.0004$) and tumor thickness 2.1

TABLE I: UNIVARIATE ANALYSES OF THE PREDICTIVE VALUE OF CLINICAL FEATURES ON METASTASIS IN SERIES OF 1,329 SMALL MELANOCYTIC CHOROIDAL TUMORS

CLINICAL FEATURE	NO METASTASIS N=1,294	METASTASIS N=35	*P* VALUE	RELATIVE RISK	95% CONFIDENCE INTERVAL
Age (yr) (n=1,329)					
0-30	59	3	.61	1.4	(0.4,4.7)
31-60	656	13	.05	0.5	(0.2,1.0)
>61*	579	19			
Sex (n=1,329)					
Female*	779	18			
Male	515	17	.35	1.4	(0.7,2.7)
Symptoms (n=1,329)					
None*	856	13			
Blurred vision	285	16	.0001	3.8	(1.8,7.9)
Floaters/flashes	152	6	.06	2.6	(1.0,6.8)
Visual acuity (n=1,329)					
20/20-20/40*	1,046	17			
20/50-20./80	132	13	.0001	6.5	(3.2,13.6)
20/100 or worse	116	5	.07	2.5	(0.9,6.8)
Location (n=1,329)					
Inferior*	224	8			
Superior	277	8	.69	0.8	(0.3,2.2)
Temporal	393	9	.35	0.6	(0.3,1.7)
Nasal	196	2	.08	0.3	(0.1,1.2)
Macular	204	8	.89	1.1	(0.4,2.9)
Anterior margin (n=1,329)					
0.1-3.0 mm from optic disc	44	1	.69	0.7	(0.1,5.3)
>3.0 mm from disc to equator	986	26	.49	0.8	(0.3,1.7)
Between equator and ora serrata*	264	8			
Posterior margin (n=1,329)					
Touching optic disc	167	16	.0001	5.1	(2.5,10.3)
0.1 to 3.0 mm from optic disc	185	4	.52	1.4	(0.5,4.3)
>3.0 mm from disc to equator*	904	14			
Between equator and ora serrata*	38	1			
Relationship to foveola (n =1,329)					
Subfoveal	199	8	.15	1.9	(0.8,4.2)
0.1 to 3.0 mm from foveola	213	8	.18	1.8	(0.8,4.0)
>3.0 mm from foveola*	882	19			
Largest basal dimension (n=1,329)					
0-5.0 mm*	587	7			
5.1-10.0 mm	631	21	.01	3.1	(1.3,7.3)
10.1-15.0 mm	76	7	.0001	8.1	(2.8,23.1)
Thickness (n=1,328)					
0-1.0 mm*	620	2			
1.1-2.0 mm	363	14	.0004	14.8	(3.4,65.3)
2.1-3.0 mm	310	19	.0001	19.7	(4.6,84.7)
Color (n=1,329)					
Brown*	956	25			
Yellow	338	10	.77	1.1	(0.5,2.3)

TABLE I: UNIVARIATE ANALYSES OF THE PREDICTIVE VALUE OF CLINICAL FEATURES ON METASTASIS IN SERIES OF 1,329 SMALL MELANOCYTIC CHOROIDAL TUMORS (CONTINUED)

CLINICAL FEATURE	NO METASTASIS N=1,294	METASTASIS N=35	*P* VALUE	RELATIVE RISK	95% CONFIDENCE INTERVAL
Subretinal fluid (n=1,329)					
Absent*	974	16			
Present	320	19	.0002	3.6	(1.8,7.0)
Orange pigment (n=1,329)					
Absent*	945	19			
Present	349	16	.009	2.4	(1.3,4.7)
Drusen (n=1,329)					
Absent*	619	15			
Present	675	20	.22	1.5	(0.8,3.0)
Retinal pigment epithelial hyperplasia (n=1,329)					
Absent*	1,093	31			
Present	201	4	.73	0.8	(0.3,2.4)
Growth (n=1,329)					
Absent*	1,084	10			
Present	210	25	.0001	7.6	(3.7,16.1)

*Reference variable.

to 3.0 mm (P=.0001) compared with thickness ≤1 mm; documented tumor growth (P=.0001); presence of subretinal fluid (P=.0002); and surface orange pigment (P=.009). The relative risk (rr) for tumor metastases was greatest for the variables of tumor thickness (1.1 to 2.0 mm [rr 14.8] and 2.1 to 3.0 mm [rr 19.7] relative to thickness ≤1 mm), largest tumor basal dimension (10.1 to 15.0 mm [rr 8.1] relative to base ≤5 mm), and documented tumor growth (rr 7.6). Of the 622 tumors measuring ≤1 mm thickness, 179 were flat, 189 were ≤.2 mm, and 425 tumors were ≤.5 mm.

From a multivariate model (Table III), 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 thickness 1.1 to 3.0 mm (relative to thickness ≤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 were virtually interchangable, 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.

TABLE II: UNIVARIATE ANALYSES OF PREDICTIVE VALUE OF CLINICAL FEATURES ON GROWTH IN SERIES OF 1,287 SMALL MELANOCYTIC CHOROIDAL TUMORS

CLINICAL FEATURE	NO GROWTH N=1,052	GROWTH N=235	*P* VALUE	RELATIVE RISK	95% CONFIDENCE INTERVAL
Age (yr) (n=1,287)					
0-30	42	16	.02	1.9	(1.1,3.3)
31-60	512	138	.02	1.4	(1.1,1.8)
>61°	498	81			
Sex (n=1,287)					
Female°	660	120			
Male	392	115	.002	1.5	(1.2,1.9)
Symptoms (n=1,287)					
None°	752	105			
Blurred Vision	189	87	.0001	3.1	(2.4,4.2)
Floaters/flashes	110	43	.0001	2.7	(1.9,3.8)
Visual acuity (n=1,287)					
20/20-20/40°	885	160			
20/50-20./80	96	42	.0001	2.5	(1.8,3.5)
20/100 or worse	71	33	.0001	2.5	(1.7,3.6)
Location (n=1,287)					
Inferior°	192	32			
Superior	217	57	.008	1.8	(1.2,2.9)
Temporal	330	61	.49	1.2	(0.7,1.9)
Nasal	159	35	.07	1.5	(1.0,2.3)
Macular	154	50	.68	1.1	(0.7,1.7)
Anterior margin (n=1,287)					
0-3.0 mm from optic disc	31	11	.03	2.1	(1.1,4.2)
>3.0 mm from disc to equator	788	190	.04	1.5	(1.0,2.1)
Between equator and ora serrata°	233	34			
Posterior margin (n=1,287)					
Touching optic disc	96	67	.0001	3.6	(2.7,4.8)
0.1 to 3.0 mm from optic disc	136	42	.0001	2.0	(1.4,2.9)
>3.0 mm from disc to equator°	787	120			
Between equator and ora serrata°	33	6			
Relationship to foveola (n=1,287)					
Subfoveal	132	58	.0001	2.5	(1.8,3.4)
0.1 to 3.0 mm from foveola	157	50	.0005	1.8	(1.3,2.5)
>3.0 mm from foveola°	763	127			
Largest basal dimension (n=1,287)					
0-5.0 mm°	511	66			
5.1-10.0 mm	486	148	.0001	2.4	(1.8,3.2)
10.1-15.0 mm	55	21	.0001	2.9	(1.8,4.7)
Thickness (n=1,287)					
0-1.0 mm°	582	37			
1.1-2.0 mm	277	90	.0001	5.5	(3.8,8.1)
2.1-3.0 mm	192	108	.0001	7.9	(5.4,11.5)
Color (n=1,287)					
Brown°	784	170			
Yellow	268	65	.32	1.2	(0.9,1.5)

TABLE II: UNIVARIATE ANALYSES OF PREDICTIVE VALUE OF CLINICAL FEATURES ON GROWTH IN SERIES OF 1,287 SMALL MELANOCYTIC CHOROIDAL TUMORS (CONTINUED)

CLINICAL FEATURE	NO GROWTH N=1,052	GROWTH N=235	*P* VALUE	RELATIVE RISK	95% CONFIDENCE INTERVAL
Subretinal fluid (n=1,287)					
Absent*	858	121			
Present	194	114	.0001	3.6	(2.8,4.7)
Orange pigment (n=1,287)					
Absent*	830	120			
Present	222	115	.0001	3.4	(2.6,4.3)
Drusen (n=1,287)					
Absent*	513	102			
Present	539	133	.01	1.4	(1.1,1.8)
Retinal pigment epithelial hyperplasia (n=1,287)					
Absent*	896	193			
Present	156	42	.09	1.4	(1.0,1.9)

*Reference variable.

TABLE III: MULTIVARIATE ANALYSIS OF CLINICAL FACTORS PREDICTIVE OF METASTASES OF SMALL MELANOCYTIC CHOROIDAL TUMORS (N=1,329)

CLINICAL FEATURE*	*P* VALUE	RELATIVE RISK	95% CONFIDENCE INTERVAL
Symptoms (none versus blurred vision)	.060	1.9	(1.0,3.7)
Posterior margin (not touching optic disc versus touching disc)	.003	2.9	(1.4,5.7)
Growth (absent versus present)	.003	3.2	(1.5,7.0)
Thickness† (0-1.0 versus 1.1-3.0 mm)	.004	8.8	(2.0,38.1)

*(Reference variable versus significant variable).
†Largest tumor base could be substituted for tumor thickness yielding similar results in multivariate analysis.

TABLE IV: MULTIVARIATE ANALYSIS OF CLINICAL FACTORS PREDICTIVE OF GROWTH OF SMALL MELANOCYTIC CHOROIDAL TUMORS (N=1,287)

CLINICAL FEATURE*	*P* VALUE	RELATIVE RISK	95% CONFIDENCE INTERVAL
Subretinal fluid			
(absent versus present)	.05	1.4	(1.0,1.8)
Orange pitment			
(absent versus present)	.004	1.5	(1.2,2.0)
Symptoms			
(none versus blurred vision)	.003	1.6	(1.2,2.2)
(none versus flashes/floaters)	.002	1.8	(1.2,2.6)
Posterior margin			
(>3.0 mm from optic disc versus touching the disc)	.0001	2.6	(1.9,3.6)
(>3.0 mm from optic disc versus 0.1 to 3.0 mm from disc)	.08	1.4	(1.0,2.0)
Thickness†			
(0-1.0 mm versus 1.1-2.0 mm)	.0001	4.3	(2.9,6.4)
(0-1.0 mm versus 2.1-3.0 mm)	.0001	5.2	(3.5,7.8)

*(Reference variable versus significant variable).
†Largest tumor base could be substituted for tumor thickness yielding similar results in multivariate analysis.

TUMOR GROWTH

There were 1,287 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 by an increase in either base or thickness. The median follow-up time was 51 months (range, 1 to 277). For the 235 patients who experienced tumor growth, the median time to growth was 25 months. The mean growth-free interval for the entire sample of 1,287 patients was 111 months.

From a univariate model (Table II), the most significant predictive factors for growth included: symptoms of blurred vision (P=.0001) and flashes/floaters (P=.0001) compared with no symptoms; visual acuity of 20/50 to 20/80 (P=.0001) and 20/100 or worse (P=.0001) compared with 20/20 to 20/40; posterior margin touching the the optic disc (P=.0001) and 0.1 to 3.0 mm from optic disc (P=.0001) compared with tumors > 3 mm from disc; subfoveal location (P=.0001) and 0.1 to 3.0 mm from foveola (P=.0005) compared with > 3 mm from foveola; increased largest basal dimension 5.1 to 10.0 mm (P=.0001) and 10.1 to 15.0 mm (P=.0001) compared with $\leq$ 5 mm; increased tumor thickness of 1.1 to 2.0 mm (P=.0001) and 2.1 to 3.0 mm (P=.0001)

compared with thickness ≤1 mm; subretinal fluid (P=.0001); and orange pigment (P=.0001). The relative risk for tumor growth was greatest for measures of tumor thickness (1.1 to 2.0 mm [rr 5.5] and 2.1 to 3.0 mm [rr 7.9] relative to thickness ≤1 mm), posterior 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 IV), 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 thickness 2.1 to 3.0 mm relative to thickness ≤1 mm was 5.2 and the relative risk for posterior margin touching the optic disc relative to > 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 interchangably in the multivariate model. Although patient sex was a significant factor (P=.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=.0001 [rr=0.20, 95% CI=.13, .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). For example, a tumor measuring over 1.1 mm in thickness with posterior margin touching the optic disc and with documented growth had a risk for metastasis 81 times greater 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 to develop metastases (Table V) with various combinations of risk features was also tabulated. For example, using the same features as mentioned previously, 17% of patients with a tumor measuring 2.0 mm in thickness, posterior margin touching the disc, and documented growth developed metastasis.

DISCUSSION

There is a continuing evolution in medicine toward early detection and management of a variety of cancers. Self-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 the prevention of colonic cancer.[31-33] The evidence is overwhelming that the detection and removal of small adenomatous and

TABLE V: 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)	(%)
One feature:				
Thickness>1 mm (T)	33 / 707	5%	2 / 622	<1%
Growth (G)	25 / 235	11%	10 / 1,084	<1%
Posterior margin touching disc (PM)	16 / 183	9%	19 / 1,146	2%
Symptoms (S)	16 / 301	5%	19 / 1,027	2%
Two features:				
T+G	24 / 198	12%	11 / 1,131	<1%
T+PM	16 / 119	13%	19 / 1,210	2%
T+S	16 / 213	8%	19 / 1,115	2%
G+PM	10 / 67	15%	25 / 1,262	2%
G+S	11 / 87	13%	24 / 1,241	2%
PM+S	9 / 68	13%	26 / 1,260	2%
Three features:				
T+G+PM	10 / 58	17%	25 / 1,270	2%
T+G+S	11 / 73	15%	24 / 1,255	2%
T+PM+S	9 / 57	16%	26 / 1,271	2%
G+PM+S	6 / 29	21%	29 / 1,299	2%
Four features:				
T+G+PM+S	6 / 24	25%	29 / 1,304	2%

*Thickness refers to ultrasound thickness measuring 1.1 to 3.0 mm. Growth refers to documented tumor enlargement. Posterior margin refers to posterior edge of tumor touching disc. Symptoms refers to blurred vision.

preinvasive adenocarcinomas prevent death caused by colorectal cancer.[33] Polyps measuring 1 cm are targeted for detection and removal. Furthermore, 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 very little over the past decades.[15,18] Zimmerman and McLean[15] reported on 2,627 cases of choroidal melanoma treated by enucleation and submitted to the Armed Forces Institute of Pathology over a 40-year period (1936 to 1975); they found that the survival rate was practically unchanged, despite an increasing proportion of smaller tumors. They stated that in contrast with the improvement in sur-

vival 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 coworkers[18] found that small choroidal melanoma carried a 16% mortality over 5 years. Risk for death within 5 years was 1.3 times greater in individuals with a small choroidal melanoma than in the general population of similar age and gender. The investigators recommended treatment as early as possible to provide the best chance for a normal life span. Increased survival with choroidal melanoma, similar to other cancers, depends on improvements in early detection of malignant or premalignant lesions and/or advancements in treatment methods.

Since it appears well documented that earlier recognition and treatment of other cancers offers 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 long-standing teaching that one should wait until documented growth before suspecting a choroidal melanoma, and, importantly, the lack of evidence that early treatment is of benefit.[1,12,13,25]

This study has shown that documented growth of a small melanocytic choroidal tumor increases the risk for metastases almost 8 times over that of a tumor that does not grow. Furthermore, 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, risk of metastasis in a melanocytic choroidal tumor measuring more than 1 mm in thickness with documented growth is 28 times greater than risk in 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. On the basis of 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 better understand the impact of each clinical risk factor, we extracted the percentage of patients that developed metastases with various combinations of risk factors (Table V). For example, 14% of patients with a melanocytic choroidal tumor that measured more than 1.0 mm in thickness and touched the optic disc developed metastases, while a similar lesion with the same features but with documented growth resulted in metastases in 17% of the patients. Finally, a combination of all 4 risk factors showed that 25% of patients with symptoms of blurred vision who had a tumor measuring at least 1.0 mm in thickness, abutting the optic disc, and with documented growth developed metastases.

It seems reasonable that a preventative approach to this disease would be to treat high-risk lesions prior to documented growth in an effort 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 owing to the small number of metastatic events and nonrandomized retrospective approach.

A review of the literature reveals that attempts have been made using various analytical methods to investigate the risk of precursor lesions to evolve into choroidal melanoma .[23-26] Most recently, Butler and coworkers[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, 5% developed metastases. 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 a 7% to 15% mortality rate over 5- to 6-year follow-up period.[3,17,41,42] There have been no reports, prior to the present study, evaluating the malignant potential of all small melanocytic choroidal tumors, including those that were diagnosed initially as malignant melanoma and 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 previously described 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 logically associated with increased tumor activity and risk for 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 in-

creased 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 was not included as an outcome measure.[24]

Choroidal melanomas that show clinical evidence of growth have an increased mitotic activity histopathologically when compared with nongrowing tumors.[41] Mitotic activity has long been associated with malignant potential.[3] We found in our study that documented tumor growth carried a substantial relative risk of 7.6 for development of metastases as 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 previous, less comprehensive report from our department.[24] Identification of those patients at greatest risk for tumor growth raises the suspicion for potential malignancy, and thus a decision for preventative treatment should be considered.

Deductive reasoning from this analysis might suggest that early treatment of high-risk lesions prior to growth may eliminate "growth" as a risk factor 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 carry a 3% overall metastatic rate over the short term (approximately 5 years), they may carry a worse survival over the long term, as is seen with uveal melanoma in general. Furthermore, risk for metastases in patients with all of the high risk factors, is 154 times greater than in 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 carry a 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 would likely 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 initially treated. 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 should also 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.

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, of those precursor lesions with high-risk clinical features, as identified in this study. Hopefully, 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

DR D. JACKSON COLEMAN. THIS is a stimulating paper on a controversial subject in ophthalmic oncology. In this study, Dr Carol Shields and coworkers analyzed data from a cohort of 1,547 patients with melanocytic tumors seen over a 20-year period. The object of the study is twofold: first, the authors seek to identify clinical factors that correlate with tumor growth and regression; second, they argue that clinical prognostic factors, along with estimates of metastasis rates, suggest the need for more aggressive treatment of selected tumors. I believe they have succeeded admirably in identifying and classifying clinical risk factors (provided the inclusion of patients lost to follow-up and those subsequently enucleated would not have appreciably changed the model). As to the study's other objective, more aggressive treatment for smaller tumors remains an unsettled issue.

The current study's results concerning risk factors and metastasis rates are similar to those seen in a smaller patient population described by Butler and associates. The present study's larger patient population is certainly one of its strong points. However, it is unfortunate that the need for data collection over a long period of time, due to the low hazard rate per annum, effectively precludes the inclusion of newer examination technologies as study variables as they evolve. The inclusion of additional risk factors based on newer diagnostic techniques (such as fluorescein angiography or ultrasound parameters described as risk factors in the study of Butler and associates) may improve risk modeling as well as provide a clearer understanding of differences in tumor growth rate and its relation to metastasis.

The Cox model used in this study performs well, when appropriately applied, in identifying the proportional hazard related to individual risk factors. However, for examining cumulative hazard over time, a life-table analysis may be more accurate, particularly when attempting to identify an acceptable decision boundary for observation of melanocytic lesions versus treatment.

For the authors to extend their argument that the existence of a sub-

class of melanocytic lesions with significantly higher risk factors entails the need for earlier therapeutic intervention, an additional level of analysis would be needed. This analysis would require a more complete understanding of tumor treatment response and efficacy of treatment modalities than is currently available. In light of our imperfect knowledge, perhaps the best course for clinicians is increased surveillance in cases with known risk factors. A demonstrable change in rate of tumor growth in these cases as measured by a volumetric imaging technique such as 3-D ultrasound, could provide the clinicians with an additional indicator for intervention. However, for the time being, a conservative approach to management probably remains the best course of treatment for the majority of patients with smaller tumors.

DR JAMES J. AUGSBURGER. In my opinion, the conclusion presented today by Dr. Shields appears to be based on two assumptions of questionable validity: (1) in an individual case, experienced clinicians can reliably differentiate a small choroidal malignant melanoma from a large benign choroidal nevus; and (2) most deaths that occur in patients with small melanocytic choroidal tumors that enlarge during observation could have been prevented by prompt locally effective treatment.

Regarding the first assumption, there is certainly clear evidence that experienced clinicians can effectively separate small melanocytic choroidal tumors into lower risk versus higher risk categories on the basis of clinical criteria;[1,2] however, this ability to classify melanocytic choroidal tumors into risk categories is not equivalent to the ability to classify an individual's survival prognosis reliably. It can be shown mathematically that even the best currently determinable predictive survival models based on clinical and histopathological variables in patients with primary posterior uveal malignant melanoma only explain a small proportion of the variability in patient survival times.[3]

Regarding the second assumption, only those deaths occurring after documented tumor enlargement that would not have occurred if the tumor had been treated promptly can be attributed to delay in treatment. To date, there has been only one peer-reviewed publication which deals with the relative survival of promptly treated versus initially observed patients with a small choroidal melanoma. That study showed no appreciable difference in melanoma-specific mortality rates between the groups.[4] Because the survival data presented by Dr. Shields are derived from an uncontrolled descriptive series and not from a comparative series, they do not provide valid scientific evidence that early treatment is better than delayed treatment.

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DR SLOAN WILSON. I would like to, very briefly, relate a case of a gentleman, approximate age 60 to 70, who I have followed for many years with a small choroidal melanoma which was not contiguous with the optic nerve, but which did fit your other characteristics of approximately 2 mm height. One day I received a call from his dermatologist stating that he had a very small lesion on his neck which had been biopsied and was a "metastatic" melanoma. In the process of going through the oncology clinic they did a very wide excision of his neck where the biopsy had been taken and concluded that it was a primary skin melanoma. In the process of reviewing his angiograms and slides, I did not feel that there had been any growth or enlargement of the choroidal melanoma. Here is the question that this raises in my mind, since your study was retrospective, is there any way that you could positively conclude that your metastases were indeed from the choroidal melanoma and not from some other small primary melanoma?

DR GEORGE SPAETH. Your whole paper, as the Shields' papers always are, is beautifully presented. The question I have is, since there seems to be so much interest in volume change, why have the tumor people been so slow to use quantitative imaging techniques to measure changes in volume?

DR CARL KUPFER. I enjoyed your paper primarily because this is probably one of the largest series that has been collected. And I would like to make a plea that when a large series is collected, one should really try to utilize the data to the maximum. I think risk analysis is very interesting, but as Dr. Coleman pointed out, life table analysis would even be better since it would account for all patients no matter what length of follow-up each patient represents. What would really be a marked improvement is for a clinical trial to be organized early on with patients randomly assigned to immediate versus delayed treatment. Without a clinical trial there is always going to be uncertainty as to the interpretation of uncontrolled data.

I have just two questions. There is no mention about the width of the tumor. I recall that in the Collaborative Ocular Melanoma Study (COMS) a small tumor was defined as being at least 5 mm in basal diameter.[1] The second question is, do you have any information as to the five-year all cause mortality rate and its confidence interval? In the COMS study, the Kaplan-Meier estimate of five-year all cause mortality was 6% (95% confidence interval 2% to 9%).[1]

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DR CAROL SHIELDS. I would like to thank all of the members who have provided comments. Dr. Coleman correctly pointed out that the topic of my presentation was controversial. We chose to investigate the subject of small choroidal melanocytic lesions due to the prevailing controversy. The exact point in time that a benign tumor develops into a malignant tumor is unknown. For this reason there is strong emphasis in other medical fields on early detection and treatment of cancer. In other specialities, preventive medicine has been found to improve patient survival. Therefore we investigated very small pigmented choroidal lesions to assess their risk for metastatic disease. Dr. Coleman mentioned that our study had only a small number of patients who developed metastasis. In fact, only 35 of the 1,329 patients developed metastatic disease. I agree that this is a small number of metastases, but indeed this is the largest series to detail the risks of small choroidal melanocytic tumors and in fact statistical significance was achieved despite the small number of metastatic cases. We expect an increase in the number of patients with metastasis with longer follow-up and hopefully we can provide even more definitive answers in five or ten years.

Dr. Coleman correctly stated that our study initally had 1,547 patients with small choroidal melanocytic tumors and 218 of these patients were eliminated because they had inadequate follow-up. Follow-up was attempted in every case but was not available for those 218 patients. Furthermore, 42 eyes were promptly enucleated following the initial visit. These 42 patients and their clinical parameters were included in our evaluation for metastasis. They were not, of course, included in our evaluation for tumor growth. Dr. Coleman stated that our paper is very similar to one by Drs. Butler, Char, and coworkers. I agree with the general similarities, but the one major difference was the criteria used for inclusion in the study. We included all pigmented choroidal tumors 3 mm or less in thickness. Butler and associates chose to be more selective and evaluated "indeterminate" lesions measuring between 1.5 mm and 4.0 mm in thickness and/or more than 6 mm in diameter. We felt it would be best to be more inclusive, objective, and simple with our analysis so we assessed all small tumors 3 mm or less in thickness. This avoided the issue of subjective interpretation as to whether a lesion was a suspicious nevus or small malignant melanoma. Base measurements were not a part of the inclusion criteria but were certainly assessed for their impact on growth and metastasis, and, in fact, tumor base could be substituted for tumor thickness yielding similar results in the multivariate analysis. Growth was judged as an increase in thickness or base.

Dr. Augsburger provided comments regarding a prior publication that found delayed treatment for choroidal melanoma to carry no impact on metastasis. The goal of our paper was not to assess the impact of treatment

of small choroidal melanoma. Our goal was to identify the risks for metastasis of small choroidal melanocytic tumors. Furthermore, our series was much broader with 1,329 patients as compared to the 60 patients in the publication he mentioned. Not only were there differences in the numbers of patients between the two reports but there were differences in the tumor dimensions. Our analysis concentrated on very little tumors, 3 mms or less in thickness at the initial visit whereas his report assessed tumors of varying sizes and in fact over two-thirds were larger than 3 mm in thickness at the time of treatment. Maybe a delay in treatment with larger tumors has no impact on survival, but there are no reports on the impact of delayed treatment for very small tumors. We will hopefully be able to answer that question when more patients are treated and longer follow-up is attained.

Dr. Wilson questioned whether the metastases were from choroidal melanoma or possibly from an unrecognized cutaneous melanoma. All of our patients routinely have dermatologic and systemic examinations. We feel quite certain that the metastases were from the choroidal tumor.

Dr. Spaeth mentioned that we should be looking at the volume change rather than thickness or base change. I agree that volume measurements may be interesting and even more scientific, but it is likely impractical and expensive to the patient. We used ultrasound measurement of tumor thickness and ophthalmoscopic measurement of tumor base because these instruments are readily available to us and to clinicians and this makes our report more applicable to the clinician.

Dr. Kupfer mentioned that a clinical trial might be necessary. I agree that a clinical trial evaluating early versus delayed treatment with small choroidal lesions is worthwhile but depending on the mode of treatment it may be difficult to perform. It would be difficult to randomize small tumors to enucleation versus observation, but randomization to an eye conserving treatment may be more successful for a study of this type. The Kaplan-Meier estimate of tumor metastasis at 3 years was less than 1%, at 4 years was 2%, and at 5 years was 3%. The Kaplan-Meier estimate of tumor growth at 1 year was 6%, at 2 years was 10%, at 3 years was 14%, and at 5 years was 19%.