

Combination of Clinical Factors Predictive of Growth of Small Choroidal Melanocytic Tumors

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Objective: To better define the effect of individual risk factors and combinations thereof on the growth of small choroidal melanocytic tumors.

Design: Retrospective analysis.

Setting: Clinical practice of ocular oncology.

Patients: The study included 1287 patients with small suspicious choroidal melanocytic tumors, measuring 3 mm or less in thickness, managed with observation.

Results: On multivariate analysis, the clinical risk factors predictive of growth of small choroidal melanocytic tumors include tumor thickness greater than 2.0 mm, posterior tumor margin touching the disc, visual symptoms, orange pigment, and subretinal fluid. Tumor growth was detected in 4% of those patients with no risk factors. Growth was detected in approximately 36% of patients with 1 risk factor, 45% of patients with 2 risk

factors, 50% of patients with 3 risk factors, 51% of patients with 4 risk factors, and 56% of patients with all 5 risk factors. The combination of risk factors offering the greatest risk for growth was tumor thickness greater than 2.0 mm, tumor margin touching disc, and subretinal fluid that was associated with tumor growth in 63% of the affected patients. The relative risk for growth was 1.9 for 1 factor, 3.8 for 2 factors, 7.4 for 3 factors, 14.1 for 4 factors, and 27.1 for all 5 risk factors combined.

Conclusions: Five risk factors for growth of small choroidal melanocytic tumors have been identified. The combinations of various factors increase the risk for tumor growth from 4% if no factors are present to more than 50% if 3 or more risk factors are present. These factors may be important when counseling patients with small suspicious choroidal melanocytic tumors.

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A COMPREHENSIVE dermatology textbook opens with a comment on cutaneous melanoma, the dreaded “black cancer.”¹ In the past, physicians feared that this cancer was associated with a dismal prognosis. They were instructed to recognize cutaneous melanoma as a pigmented mass with darkening, bleeding, ulceration, and documented growth. It was later realized that the obvious features of bleeding and ulceration were particularly suggestive of advanced disease and poor prognosis. In the past 40 years, extensive investigation into the clinical and histopathologic findings of cutaneous melanoma has improved the understanding of subtle features that predict eventual tumor growth and metastases and has stimulated interest in early detection of cutaneous melanoma.²⁻⁴ This has led to the establishment of diagnostic criteria for detection of early-stage melanoma by visual inspection. These simple

criteria are known as the “ABCDs” of skin melanoma—A for asymmetry, B for border change, C for color change, and D for diameter greater than a pencil eraser.⁵ Recognition of early cutaneous melanoma by clinicians using these diagnostic criteria has resulted in a dramatic improvement of the prognosis for patients with cutaneous melanoma.

With regard to choroidal melanoma, detection of tumors at a small size has been correlated with better prognosis than detection at a medium or large size.⁶ Similar to cutaneous melanoma, there is strong interest in identifying choroidal melanoma early and thus offering patients a better prognosis. However, even small tumors, measuring 3.0 mm or less in thickness, can lead to metastatic disease.^{7,8} In 1995, Shields et al⁷ reported that patients with small pigmented choroidal tumors are at risk for metastases if the tumor is greater than 2.0 mm in thickness, is located at the optic disc, is associated

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PATIENTS AND METHODS

We conducted further analysis on the database of a previously reported group of consecutive patients with small choroidal melanocytic tumors (3.0 mm or less in thickness) managed by observation at the Ocular Oncology Service at Wills Eye Hospital, Philadelphia, Pa, between April 1970 and December 1990. Entry criteria for management by observation were small tumor size (3.0 mm or less in thickness) and lack of previous documented growth. We identified patients who subsequently demonstrated growth of the choroidal tumor over time (**Figure 1**). Growth was defined by an increase in basal dimension of at least 0.3 mm or an increase in thickness of at least 0.5 mm. Clinical factors predictive of tumor growth were found using a series of univariate Cox proportional hazards regressions. Subsequent multivariate models included variables that were significant at a univariate level ($P < .05$) and identified the combination of factors best related to time to growth. The significant factors from the multivariate analysis included tumor thickness greater than 2.0 mm, tumor location at the optic disc, visual symptoms, orange pigment, and subretinal fluid, as determined in a prior report.⁷ We also

analyzed each of the 5 risk factors individually and the combined effect of 2, 3, 4, and all 5 risk factors on ultimate tumor growth. Empirical data regarding number and percent of patients demonstrating tumor growth for individual and a combination of factors were tabulated. Using Kaplan-Meier methods, the raw percentages were then adjusted for differing lengths of follow-up among the patients and 5-year estimates of percentage tumor growth with various combinations of risk factors were calculated.

Relative risks for growth given a single factor or a constellation of factors were calculated. The statistical method used to derive the RRs was as follows: all of the covariates were fit simultaneously into a final multivariable model and the risk estimates were computed for each covariate. The formula for computing the RR for combinations of factors¹² was

$$RR = \text{Exponentiation} (\beta^1 + \beta^2 + \beta^n).$$

For a 2-factor model, β^1 was the parameter estimate for the first factor (eg, symptoms = 0.665284) and β^2 was the parameter estimate for the second factor (eg, posterior margin touch optic disc = 0.8426256). The combined risk was then

$$\begin{aligned} &\text{Exponentiation} (0.665284 + 0.8426256) = \\ &\text{Exponentiation} (1.5079096) = 4.5. \end{aligned}$$



Figure 1. Suspicious choroidal melanocytic lesion. Left, Clinical photograph (1985). This 37-year-old woman had photopsia and a 1.7-mm-thick choroidal pigmented mass touching the optic disc. Note the prominent orange pigment and subtle subretinal fluid. This patient had 4 of 5 risk factors for tumor growth, including symptoms, orange pigment, subretinal fluid, and margin touching the optic disc. In keeping with traditional management in 1985, serial observation was advised. Right, Clinical photograph (1986). Growth was documented in base and in thickness 1 year later. Enucleation was performed. Eight years later, she died from metastatic melanoma.

with symptoms, and has evidence of growth. The presence of documented growth in these small tumors adds 3 times the risk for metastatic disease compared with a tumor without growth.⁷ As physicians, the only risk factor for metastasis that we can modify or eliminate is documentation of tumor growth. We cannot change tumor thickness, location, or symptoms at the initial visit. In an effort to ascertain patients at risk for tumor growth, we and others have identified clinical factors predictive of eventual growth of small melanocytic choroidal tumors.^{7,9-11} In this article, we further expand on these risks for growth and specifically calculate the percent growth

and relative risk (RR) for each factor and every combination of risk factors. These calculations may be helpful in the counseling of patients with borderline lesions and may assist in identifying those tumors with greatest potential for growth.

RESULTS

There were 1287 patients with small, melanocytic choroidal tumors measuring 3.0 mm or less in thickness managed with observation during the 20-year period of this study. The median follow-up period was 51 months

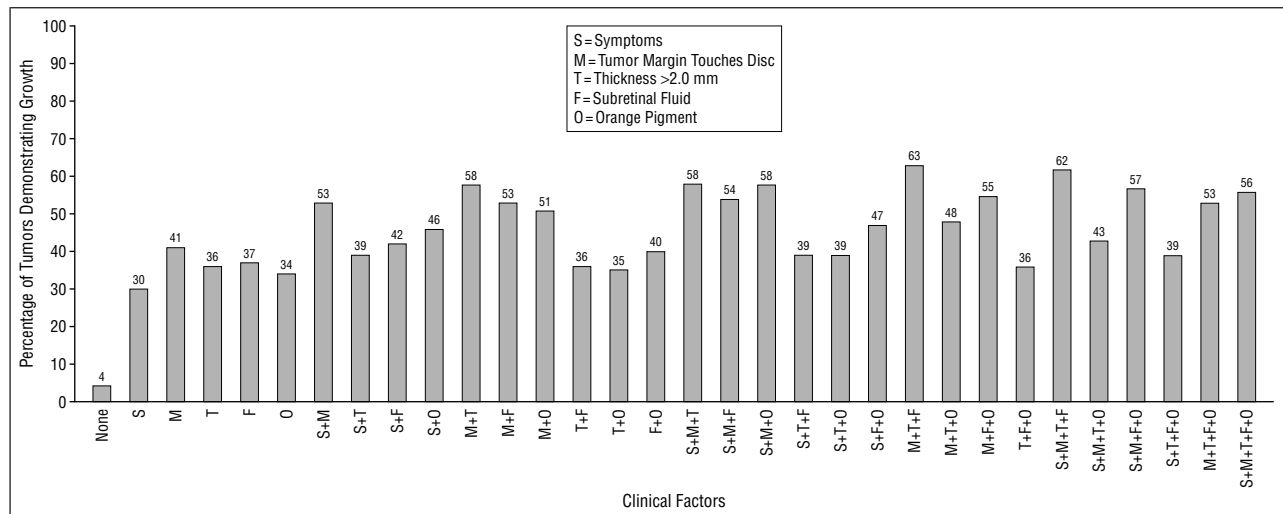


Figure 2. Percent growth of 1287 small melanocytic choroidal tumors (3.0 mm or less in thickness) based on combination of clinical risk factors.

Tumor Growth in 1287 Small Melanocytic Choroidal Tumors Measuring 3.0 mm or Less in Thickness Based on a Combination of Clinical Factors*

Clinical Features	No. With Growth/No. With Feature(s) (%)	Kaplan-Meier 5-Year Growth, %	No. With Growth/No. Without Feature(s) (%)
No features	18/519 (4)	3	
1 Feature			
S	130/429 (30)	33	105/857 (12)
M	67/163 (41)	44	168/1124 (15)
T	108/301 (36)	38	127/986 (13)
F	114/308 (37)	39	121/979 (12)
O	115/337 (34)	37	120/950 (13)
2 Features			
S + M	41/77 (53)	60	194/1209 (16)
S + T	51/131 (39)	39	184/1155 (16)
S + F	83/198 (42)	45	152/1088 (14)
S + O	77/168 (46)	51	158/1118 (14)
M + T	27/47 (58)	68	208/1240 (17)
M + F	36/68 (53)	60	199/1219 (16)
M + O	39/76 (51)	56	196/1211 (16)
T + F	57/156 (36)	38	178/1131 (16)
T + O	47/135 (35)	38	188/1152 (16)
F + O	69/171 (40)	47	166/1116 (15)
3 Features			
S + M + T	15/26 (58)	69	220/1260 (18)
S + M + F	26/48 (54)	59	209/1238 (17)
S + M + O	27/47 (58)	62	208/1239 (17)
S + T + F	35/89 (39)	41	200/1197 (17)
S + T + O	26/67 (39)	40	209/1219 (17)
S + F + O	55/118 (47)	53	180/1168 (15)
M + T + F	17/27 (63)	66	218/1260 (17)
M + T + O	12/25 (48)	46	223/1262 (18)
M + F + O	26/47 (55)	56	209/1240 (17)
T + F + O	31/86 (36)	40	204/1201 (17)
4 Features			
S + M + T + F	10/16 (62)	64	225/1270 (18)
S + M + T + O	6/14 (43)	43	229/1272 (18)
S + M + F + O	20/35 (57)	60	215/1251 (17)
S + T + F + O	20/51 (39)	42	215/1235 (17)
M + T + F + O	9/17 (53)	49	226/1270 (18)
5 Features			
S + M + T + F + O	5/9 (56)	56	230/1277 (18)

*S indicates symptoms, M, posterior margin touches optic disc; T, thickness greater than 2 mm; F, subretinal fluid; and O, orange pigment.

(range, 1-277 months). In an earlier report, we identified 5 factors predictive of growth of these tumors, including thickness greater than 2.0 mm ($P < .001$), margin touching the optic disc ($P = .001$), visual symptoms ($P = .002$), orange pigment ($P = .004$), and subretinal fluid ($P = .05$).⁷ Of all 1287 patients, if none of the risk factors mentioned were present, growth was detected in only 4%. Growth was detected in 30% to 41% of patients with 1 risk factor, 35% to 58% of patients with 2 risk factors, 36% to 63% of patients with 3 risk factors, 39% to 62% of patients with 4 risk factors, and 56% of patients with all 5 risk factors (Figure 2). The various combinations of individual risk factors as they affect ultimate tumor growth are given in the Table. The combination of factors imparting the greatest risk for growth included margin touching optic disc, thickness greater than 2.0 mm, and subretinal fluid (with or without symptoms), which was associated with eventual tumor growth in more than 60% of patients (Table). Thirteen of the 31 combinations of risk factors were associated with at least a 50% risk for tumor growth. Using Kaplan-Meier 5-year estimates, the percentage of tumors demonstrating growth over time was found and is listed in the Table.

The RR for growth was 1.6 to 2.3 for 1 factor, 2.8 to 5.0 for 2 factors, 5.5 to 9.6 for 3 factors, 11.6 to 17.3 for 4 factors, and 27.1 for all 5 risk factors combined (Figure 3). The various combinations of individual risk factors as related to RR for growth are shown in Figure 3. The greatest RR for growth occurred when all 5 risks were present, giving 27.1 times greater risk for growth than a tumor with no risk factor. The computation of RR assumes independence among the factors (eg, the presence of subretinal fluid conveys no information about thickness). This may not be the case, given that there is not a concomitant increase in the proportion of growth with combinations of factors.

COMMENT

There is continued interest in methods of early detection and intervention for human cancers. Detection and treatment of cutaneous melanoma at an early stage has

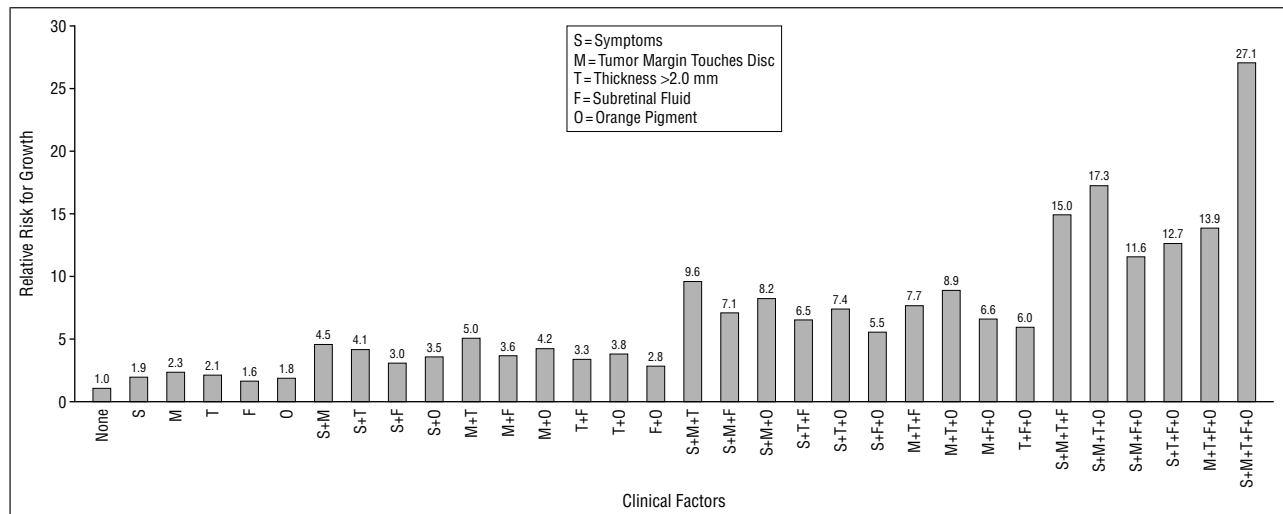


Figure 3. Relative risk for growth of 1287 small melanocytic choroidal tumors (3.0 mm or less in thickness) based on combination of clinical risk factors.

been correlated with improved survival, especially notable in the past 40 years.^{3,4,13} Currently, cutaneous melanoma is recognized when the tumor is thinner, less invasive, less likely to be ulcerated, and more likely to exhibit radial growth (superficial spreading) than in the past.³ Before 1960, the median thickness of stage I cutaneous melanoma (without lymph node involvement) was 3.0 mm, whereas in 1985, the median thickness had decreased to 1.0 mm for the same group owing to efforts of early detection.⁴ Tumor thickness is the single most important predictor of survival in stage I cutaneous melanoma.^{13,14} An analysis of 4000 patients with cutaneous melanoma revealed that the mean 10-year survival rate for patients with stage I disease (without lymph node involvement) was 71%.³ The mean survival rate for stage II disease (with associated lymph node involvement) was approximately 25%; for stage III disease (with distant metastases), the survival rate was very poor, with a median survival of only 6 months. When considering only stage I cutaneous melanoma, the prognosis was strongly correlated with thickness. The 10-year survival rate for tumors smaller than 0.76 mm in thickness was 90%; for those 0.76 to 1.50 mm in thickness, 79%; 1.51 to 2.50 mm in thickness, 62%; and 2.51 to 4.00 mm in thickness, 48%.³ The prognosis worsened on a continuum of thickness with no natural breakpoints where prognosis abruptly changed, even with very thin tumors.^{3,15} Hence, with cutaneous melanoma, early detection is emphasized, especially when the tumor is thin and before obvious nodularity develops.^{1,3,4}

Similarly, with choroidal melanoma, thinner tumors have a better prognosis than thicker tumors.⁶ In addition, there is no natural breakpoint at which the prognosis abruptly changes. There is an evolving emphasis toward early detection and management of these tumors. However, controversy remains regarding the overlapping clinical features of small choroidal malignant melanoma with benign choroidal nevus. Most clinicians rely on the observation of documented growth to differentiate malignant from benign tumors, as growth is more often found with malignant choroidal melanoma. In this article, we have specifically concentrated on individual and combined clinical features predictive

of tumor growth. This information provides scientific data that may be applicable to the clinician faced with a patient who has a small suspicious choroidal lesion. For example, a patient with none of the identified risk factors has only a 4% risk that the choroidal lesion will grow, and cautious observation is reasonable. If a patient demonstrates 1 risk factor, such as orange pigment, there is a 34% chance for tumor growth, and observation still remains a reasonable option, especially if the tumor is in a visually important location. Only a few of the 1287 patients had 3 or more factors for growth as indicated in the Table; however, the presence of growth in this small group was impressive. For example, for the patient with 3 risk factors, such as tumor thickness greater than 2.0 mm, margin touching the optic disc, and overlying subretinal fluid, a 63% chance for growth was found, strongly predicting eventual growth and indicating the need for early intervention. Therefore, the data from this report can be quite helpful in making a decision regarding either continued observation or therapy for patients with small suspicious choroidal lesions.

We did not assess the effect of treatment on outcome. Therefore, we cannot provide an opinion regarding the efficacy of therapy.¹⁶ This would be best addressed in a randomized study with a long follow-up period. In addition, we do not recommend that all small pigmented choroidal tumors be treated, as most will not grow and do not manifest risk factors for growth (Table); however, those patients who have a tumor with substantial risks for growth, as identified in this article, may be considered for early treatment before documented growth, as growth has been associated with an increased risk for metastasis.⁷ Prospective validation of these risk factors will be studied in the future.

We have constructed the mnemonic “TFSOM” (To Find Small Ocular Melanoma), which is similar to the ABCDs for early detection of cutaneous melanoma, to assist in identifying early small choroidal melanoma at risk for growth. TFSOM denotes tumor Thickness greater than 2 mm, subretinal Fluid, Symptoms, Orange pigment, and a Margin at the disc. Hopefully, this simple mnemonic will assist clinicians in detecting early choroidal mel-

noma and in recommending timely treatment in selected patients, with the hope of long-term improvement in systemic prognosis.

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