Clinical factors in the identification of small choroidal melanoma

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ABSTRACT

The detection and treatment of choroidal melanoma early in its natural course is critical to providing the patient with the best prognosis. Studies of tumour doubling time have indicated that metastasis from choroidal melanoma can occur quite early in the course of the disease, when the tumour is about 3.0 mm in basal dimension and 1.5 mm in thickness. Clinical studies have shown that, at 5 years, metastasis occurs in 16% of patients with small choroidal melanomas (less than 4 mm thick), compared with 32% of those with medium-sized (4–8 mm thick) choroidal melanomas and 53% of those with large (more than 8 mm thick) choroidal melanomas. The difficulty with early detection of choroidal melanoma relates to its clinical similarity to benign choroidal nevus. Factors that assist in differentiating small choroidal melanoma from choroidal nevus can be remembered using the mnemonic "TFSOM" (*to find small ocular melanoma*), where T = thickness greater than 2 mm, F = subretinal fluid, S = symptoms, O = orange pigment and M = margin touching optic disc. Choroidal melanocytic tumours that display none of these factors have a 3% risk of growth into melanoma at 5 years and most likely represent choroidal nevi. Tumours that display one factor have a 38% risk of growth, and those with two or more factors show growth in over 50% of cases. Most tumours with two or more risk factors probably represent small choroidal melanomas, and early treatment is generally indicated. Therefore, ophthalmologists should be aware of the clinical factors that identify small choroidal melanoma so that early treatment and better prognosis can be achieved for their patients.

There is increasing interest in early detection and intervention for human cancers. We have learned much about the behaviour of uveal melanoma from the literature on management of cutaneous melanoma. Detection and treatment of cutaneous melanoma at an early stage have been correlated with improved patient survival, and this observation has been especially notable during the past 40 years.[1–5] Cutaneous melanoma is now recognized when the tumour is thinner and less invasive than in the past.[3] In addition, cutaneous melanoma now tends to be treated when the tumour is in a radial growth phase (superficial spreading) and is less likely to be ulcerated than in the past.[3] Dermatologists have taught clinicians to identify early cutaneous melanoma by using the mnemonic "ABCD": *a*symmetry, *b*order irregularity, *c*olour variegation and *d*iameter larger than a pencil eraser.[5] Pigmented skin lesions with one or more of these features should be excised and inspected histopathologically for cutaneous melanoma. With this approach, cutaneous melanoma is most often detected at an early stage.

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Cutaneous melanoma is classified according to three stages based on systemic involvement, with stage I disease representing cutaneous melanoma without lymph node involvement, stage II accounting for disease with associated lymph node spread, and stage III representing disease with distant metastasis. Emphasis has been placed on detecting this malignant disorder in stage I.[6] In an analysis of 4000 patients with cutaneous melanoma, the 10-year survival rate was 71% for patients with stage I disease and 25% for those with stage II disease; stage III disease carried a grim prognosis, with a median survival of 6 months.[3]

There are several clinical and histopathological features of stage I cutaneous melanoma that predict ultimate metastasis, but the single most important predictor is tumour thickness.[7] Before 1960 the median thickness of stage I cutaneous melanomas was 3.0 mm, whereas in 1985 the median thickness had decreased to 1.0 mm owing to efforts aimed at early detection.[4] The 10-year survival rates by tumour thickness are shown in Table 1. The prognosis of stage I cutaneous melanoma worsens on a continuum of thickness, with no natural break points where prognosis changes abruptly, even with very thin tumours.[3,8] Hence, with cutaneous melanoma, early detection is emphasized, especially when the tumour is thin and before obvious nodularity develops.[1,3,4] This principle also applies to uveal melanoma.

Choroidal melanoma

With regard to choroidal melanoma, thinner tumours also carry a better prognosis than thicker tumours.[9,10] The 5-year death rate for patients with small tumours (less than 3 mm thick) is 16%, for those with medium-sized tumours (3–8 mm) 32% and for those with large tumours (more than 8 mm) 53%.[9] In addition, there is no natural break point at which prognosis changes abruptly. Even flat melanoma, also termed diffuse melanoma, leads to metastatic disease in 28% of patients at a mean of 5 years and, in fact, carries a relatively poor prognosis despite its thinness.[11] Diffuse melanoma has other features, such as increased invasiveness with extrascleral extension and aggressive epithelioid cell type, that contribute to its poor prognosis.[11]

Table 1—Stage I cutaneous melanoma: 10-year survival rate by tumour thickness[3]

Tumour thickness, mm	10-year survival rate, %
< 0.76	90
0.76–1.50	79
1.51–2.50	62
2.51–4.00	48
> 4.00	Very poor

The size at which choroidal melanoma may metastasize is unclear. Clinical studies have shown that small tumours, even those about 1 mm thick, have metastasized.[12,13] Based on mathematical studies of tumour doubling time and related metastasis, some authors have speculated as to the tumour size at the time of metastasis. Eskelin and colleagues[14,15] estimated that 30 doubling times of a metastatic tumour will occur before metastasis is clinically detectable at 1000 mm^3 in volume. They then theorized that the average volume of an intraocular melanoma at the time of tumour metastasis is about 7 mm^3. This tumour volume could represent a dome-shaped melanoma of 3 mm in basal dimension and 1.5 mm in thickness.[15] Therefore, based on mathematical calculations, metastasis of choroidal melanoma can potentially occur early in the course of the visible tumour, when it is small and easily confused with a benign choroidal nevus. These observations underscore the need for early detection of choroidal melanoma, even when the tumour is less than 1.5 mm thick, in an effort to prevent metastatic disease.

Differentiating small choroidal melanoma from choroidal nevus

There is increasing emphasis on early detection and management of choroidal melanoma. However, controversy remains regarding the overlapping clinical features of small choroidal malignant melanoma and benign choroidal nevus.[16] Choroidal nevi are far more common than choroidal melanomas. It is estimated that about 6% of the white population have a choroidal nevus.[17] In the Blue Mountains Eye Study of the general population west of Sydney, Australia, of 160 benign nevi in adults aged 49 to 83 years followed for 5 years, only 1 (0.6%) showed growth.[18] None of the other choroidal nevi showed growth or other indicators of progression, such as subretinal fluid or orange pigment.

In contrast, choroidal melanoma is rare, manifesting in about six in 1 million white people. Thus, it is important to be able to recognize the clinical features

that differentiate small choroidal melanoma from benign choroidal nevus. Both lesions can appear as a variably pigmented or nonpigmented choroidal mass with associated dormant features of overlying subretinal fluid and orange pigment. Choroidal nevi tend to have clearly defined margins and a flat or slightly elevated configuration, and to remain stable in size. Over time, these lesions can display more chronic features of retinal pigment epithelium atrophy, hyperplasia and fibrous metaplasia, and drusen. Small choroidal melanomas can show features identical to those of choroidal nevi. However, choroidal melanomas often show more signs of activity within and overlying the mass, with relatively nondiscrete margins, an irregular or oblong configuration, abruptly elevated edges, and overlying subretinal fluid and orange pigment (Fig. 1). Many clinicians rely on the observation of tumour growth to differentiate choroidal malignant melanoma from benign choroidal nevus, as tumour growth suggests that microscopically the cell is mitotically active. However, it is ideal to detect choroidal melanoma before growth is recognized, as documented growth of these small lesions carries a greater risk of metastasis. In one series of 1287 patients with a small choroidal melanocytic tumour (nevus versus melanoma) measuring 3 mm or less in thickness, tumours with documented growth were associated with an eight-fold greater risk of metastasis on univariate analysis and a three-fold greater risk on multivariate analysis compared with those without growth.[12]

Several investigators have attempted to identify small choroidal melanoma versus choroidal nevus.[12,13,19,20] These studies focused on risk factors predictive of growth of small choroidal tumours. Butler and associates[19] reviewed 293 indeterminate suspicious pigmented choroidal tumours and found that the actuarial 5-year rate of growth was 36%. Risk factors for tumour growth included greater tumour thickness, presence of symptoms, presence of orange pigment, acoustically hollow B-scan ultrasonograms and "hot spots" (pinpoint leaks) on fluorescein angiography. The Collaborative Ocular Melanoma Study Group[20] reviewed the cases of 204 patients with small choroidal "melanoma" 1.0 mm to 3.0 mm in thickness and found that, at 5 years, 31% had grown. The factors associated with tumour growth included greater initial tumour thickness and diameter, presence of orange pigment, absence of drusen and absence of retinal pigment epithelial changes adjacent to the tumour. Both of these studies provided important information on "indeterminate lesions" and "small melanoma," but the selection of patients in these relatively undefined groups makes the data somewhat difficult to apply to the general population.

In an effort to provide a more comprehensive perspective on the risk of growth of all choroidal melanocytic lesions, we reviewed the cases of all patients in our ocular oncology practice with a choroidal melanocytic tumour 3 mm or less in thickness.[12,13] This analysis of 1287 patients thus included patients with choroidal nevi as well as those with small choroidal melanomas. The study was biased in that it originated in an ocular oncology centre and not in the general population, but the results were quite important. The goal was to identify factors that could differentiate choroidal melanoma from choroidal nevus. We found that 18% of choroidal lesions grew and were thus classified as active small choroidal melanomas. Risk factors for growth included thickness greater than 2 mm, presence of subretinal fluid, presence of symptoms, presence of orange pigment overlying the surface of the tumour, and tumour margin touching or within 3 mm of the optic disc (Fig. 1). To assist in identifying early small choroidal melanomas at risk for growth, we devised the mnemonic "TFSOM" (*to find small ocular melanoma*), where T = thickness greater than 2 mm, F = subretinal fluid, S = symptoms, O = orange pigment and M = margin touching optic disc (Table 2). Choroidal melanocytic tumours that display none of these factors carry a 3% risk of growth at 5 years and most likely represent choroidal nevi.[13] Tumours that display one factor carry a 38% risk of growth, and those with two or more factors show growth in over 50% of cases (Table 3). Tumours that have two or more factors most likely represent small choroidal melanomas, and early intervention may be warranted. The exact risk imparted by each of the risk factors and each combination of risk factors is shown in Table 3. These

Table 2—Clinical features predictive of growth of small choroidal melanoma (3 mm thick or less)[12]

TFSOM: mnemonic for "to find small ocular melanoma"
T = thickness greater than 2 mm
F = subretinal fluid
S = symptoms
O = orange pigment
M = margin touching optic disc

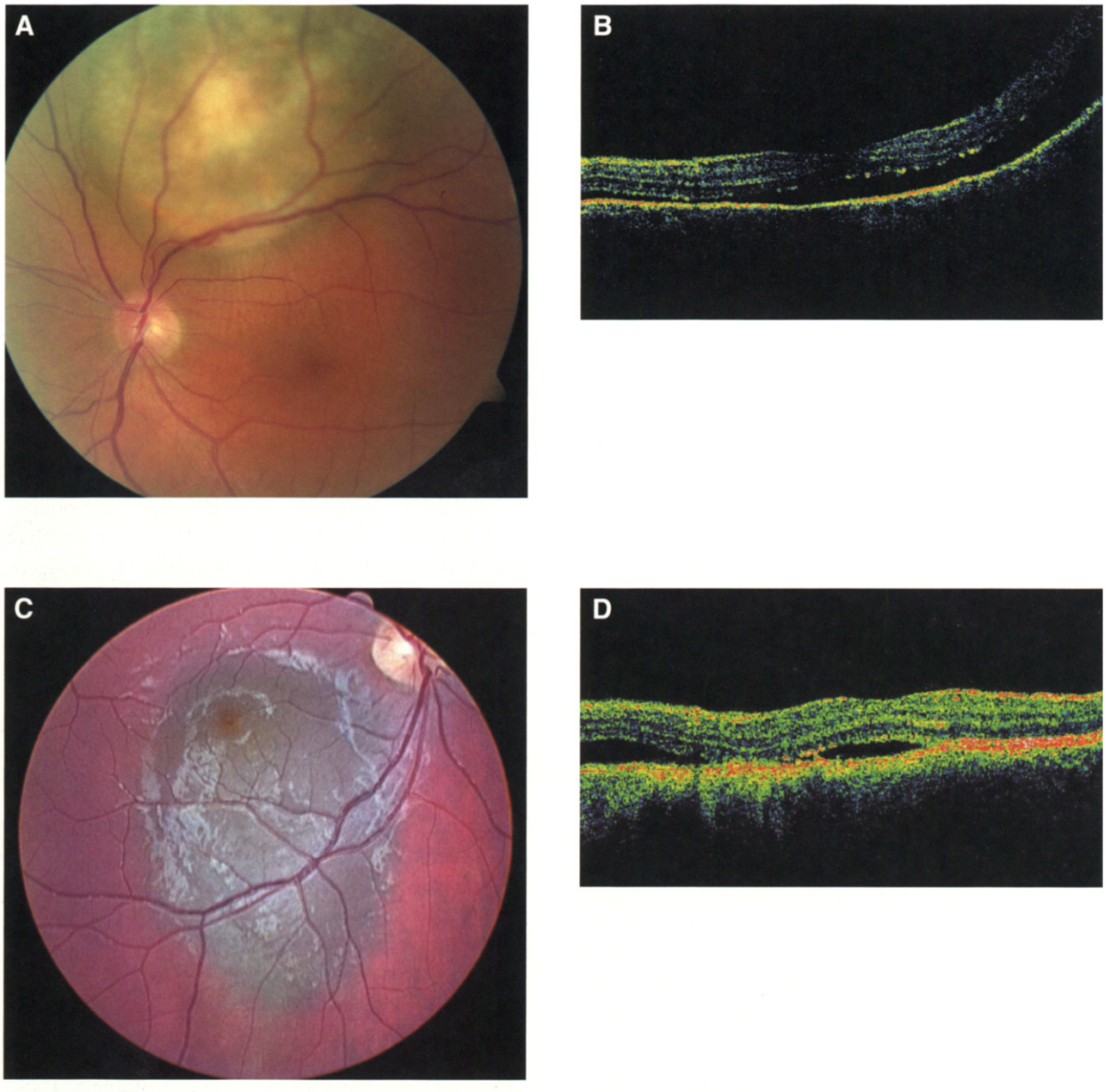

Fig. 1—Clinical risk factors for growth of small choroidal melanomas. **A:** Thickness over 2 mm: Paramacular small choroidal melanoma measuring 2.9 mm thick and with overlying orange pigment and subretinal fluid manifesting as retinal striae. **B:** Thickness over 2 mm: Optical coherence tomogram, showing subfoveal fluid in patient in Fig. 1, A. **C:** Subretinal fluid: Shallow subretinal fluid in 16-year-old patient with documented enlargement of small choroidal melanoma. **D:** Subretinal fluid: Optical coherence tomogram, showing subfoveal fluid in patient in Fig. 1, C. **E:** Symptoms: Small choroidal melanoma producing blurred vision from subfoveal fluid. Note overlying orange pigment. **F:** Symptoms: Small choroidal melanoma located superiorly with trough of subretinal fluid in foveola producing metamorphopsia. **G:** Orange pigment: Macular choroidal melanoma with prominent overlying orange pigment and rim of subretinal fluid. **H:** Margin at optic disc: Minimally elevated small choroidal melanoma touching optic disc. **I:** Other features: Juxtapapillary small choroidal melanoma with overlying orange pigment, shallow subretinal fluid and irregular margins, suggestive of tumour activity.

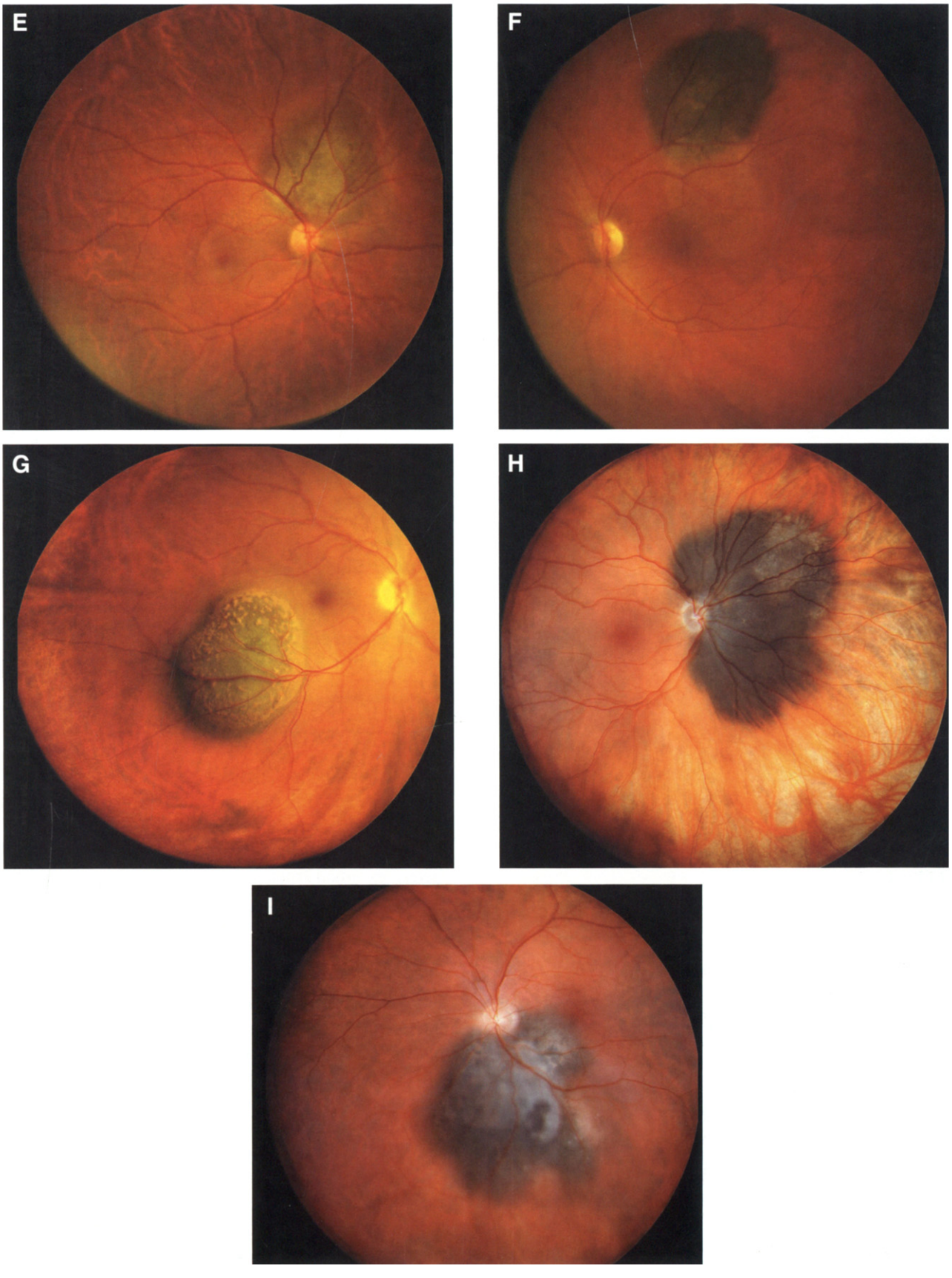
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Table 3—Specific combinations of clinical features predictive of growth of small choroidal melanoma at 5 years[13]

Clinical feature(s)	Specific Kaplan–Meier probability of growth per individual features, %	Average Kaplan–Meier probability of growth per number of features, %
No features	3	3
One feature		38
S	33	
M	44	
T	38	
F	39	
O	37	
Two features		50
S + M	60	
S + T	39	
S + F	45	
S + O	51	
M + T	68	
M + F	60	
M + O	56	
T + F	38	
T + O	38	
F + O	47	
Three features		53
S + M + T	69	
S + M + F	59	
S + M + O	62	
S + T + F	41	
S + T + O	40	
S + F + O	53	
M + T + F	66	
M + T + O	46	
M + F + O	56	
T + F + O	40	
Four features		52
S + M + T + F	64	
S + M + T + O	43	
S + M + F + O	60	
S + T + F + O	42	
M + T + F + O	49	
Five features		56
S + M + T + F + O	56	

Table 4—Specific combinations of clinical features predictive of metastasis of small choroidal melanoma at a mean of 5 years[12]

Clinical feature(s)	Specific probability of metastasis per individual features, %	Average probability of metastasis per individual features, %
One feature		8
S	5	
M	9	
T*	5	
G†	11	
Two features		12
T + G	12	
T + M	13	
T + S	8	
G + M	15	
G + S	13	
M + S	13	
Three features		17
T + G + M	17	
T + G + S	15	
T + M + S	16	
G + M + S	21	
Four features		25
T + G + M + S	25	

*Thickness greater than 1 mm.
†Growth.

data can be quite helpful in making a clinical decision regarding continued observation or therapy for patients with suspicious small choroidal tumours.

Small choroidal melanomas can occasionally metastasize. Choroidal melanomas as small as 3 mm in basal dimension and 1.5 mm in thickness can be dangerous.[15] In our series there were four clinical factors associated with small choroidal melanoma that predicted eventual metastasis: thickness greater than 1 mm, presence of symptoms, tumour margin located at the optic disc and documented growth of the tumour[12] (Table 4). Tumours with documented growth were eight times more likely to metastasize than tumours without documented growth. Patients with documented growth of a small choroidal melanoma had an 11% risk of ultimate metastasis, and those with a tumour touching the optic disc and with documented growth had a 15% risk of metastasis (Table 4). Thus, it is clearly important to identify small melanomas before obvious tumour growth is documented.

Conclusion

In summary, it is critical for clinicians to understand

the seriousness of choroidal melanoma and the importance of early detection of this tumour. Detecting choroidal melanoma at a small size, before metastatic disease occurs, is a reasonable goal. It is helpful to carefully assess every pigmented choroidal mass, recording tumour thickness and other clinical features that may suggest potential for future growth or metastasis. We hope that our mnemonic "TFSOM" will assist clinicians in detecting early choroidal melanoma and in recommending timely treatment in selected patients, with the goal of long-term improvement in systemic prognosis.

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References

1. Fitzpatrick TB, Mihm MC, Sober AJ, Rhodes AR. Clinical recognition of primary malignant melanoma and of its precursors. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, editors. *Dermatology in general medicine*. 3rd ed. New York: McGraw Hill Co; 1987. p. A38–9.
2. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg* 1970;172:902–8.
3. Balch CM, Soong SJ, Shaw HM, Milton GW. An analysis of prognostic factors in 4000 patients with cutaneous melanoma. In: Balch CM, Milton GW, editors. *Cutaneous melanoma: clinical management and treatment results worldwide*. Philadelphia: JB Lippincott; 1985. p. 321.
4. Balch CM, Soong SJ, Shaw HM, Maddox WA, Urist MM. Changing trends in the clinical and pathologic features of melanoma. In: Balch CM, Houghton AN, Milton GW, Sober A, Soong SJ, editors. *Cutaneous melanoma*. 2nd ed. Philadelphia: JB Lippincott; 1992. p. 40.
5. American Academy of Dermatology. *Melanoma/skin cancer. You can recognize the signs*. Washington: The Academy. 1989.
6. Balch CM, Murad TM, Soong SJ, Ingalls AL, Richards PC, Maddox WA. Tumor thickness as a guide to surgical management of clinical stage I melanoma patients. *Cancer* 1979;43:883–8.
7. Balch CM, Murad TM, Soong SJ, Ingalls AL, Halpern NB, Maddox WA. A multifactorial analysis of melanoma: prognostic histopathological features comparing Clark's and Breslow's staging methods. *Ann Surg* 1978;188: 732–42.
8. Day CL Jr, Lew RA, Mihm MC Jr, Harris MN, Kopf AW, Sober AJ, et al. The natural break points for primary-tumor thickness in clinical Stage I melanoma. *N Engl J Med* 1981;305:1155.
9. Diener-West M, Hawkins BS, Markowitz JA, Schachat AP. A review of mortality from choroidal melanoma. II. A meta-analysis of 5-year mortality rates following enucleation, 1966 through 1988. *Arch Ophthalmol* 1992;110:245–50.
10. Shields JA, Shields CL. *Intraocular tumors: a text and atlas*. Philadelphia: WB Saunders; 1992. p. 117–36.
11. Shields CL, Shields JA, De Potter P, Cater J, Tardio D, Barrett J. Diffuse choroidal melanoma: clinical features predictive of metastasis. *Arch Ophthalmol* 1996;114:956–63.
12. Shields CL, Shields JA, Kiratli H, De Potter P, Cater JR. Risk factors for growth and metastasis of small choroidal melanocytic lesions. *Ophthalmology* 1995;102:1351–61.
13. Shields CL, Cater J, Shields JA, Singh AD, Santos MC, Carvalho C. Combination of clinical factors predictive of growth of small choroidal melanocytic tumors. *Arch Ophthalmol* 2000;118:360–4.
14. Eskelin S, Pyrhonen S, Summanen P, Hahka-Kemppinen M, Kivelä T. Tumor doubling times in metastatic malignant melanoma of the uvea: tumor progression before and after treatment. *Ophthalmology* 2000;107:1443–9.
15. Eskelin S, Kivelä T. Uveal melanoma: implications of tumor doubling time. *Ophthalmology* 2001;108:830–1.
16. Shields JA, Shields CL. *Atlas of intraocular tumors*. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 53–94.
17. Sumich P, Mitchell P, Wang JJ. Choroidal nevi in a white population: the Blue Mountains Eye Study. *Arch Ophthalmol* 1998;116:645–50.
18. Thiagalingam S, Wang JJ, Mitchell P. Absence of change in choroidal nevi across 5 years in an older population. *Arch Ophthalmol* 2004;122:89–93.
19. Butler P, Char DH, Zarbin M, Kroll S. Natural history of indeterminate pigmented choroidal tumors. *Ophthalmology* 1994;101:710–6; discussion 717.
20. Collaborative Ocular Melanoma Study Group. Factors predictive of growth and treatment of small choroidal melanoma: COMS Report No. 5. *Arch Ophthalmol* 1997; 115:1537–44.

Key words: eye; cancer; uvea; choroid; melanoma, small; clinical features; thickness; subretinal fluid; orange pigment; location; symptoms; growth; metastasis; management; transpupillary thermotherapy; plaque; radiotherapy; enucleation