The Small Fatal Choroidal Melanoma Study. A Survey by the European Ophthalmic Oncology Group

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• PURPOSE: To determine the size at which choroidal melanomas can metastasize and to report the characteristics of small fatal choroidal melanomas (SFCM).
• DESIGN: Retrospective case series.
• METHODS: Ten ocular oncology services submitted 45 patients with a choroidal melanoma 3 mm or less in thickness and 9 mm or less in largest basal diameter (LBD), when treated, who developed metastases.
• RESULTS: Median tumor thickness was 2.4 mm (range, 1.0–3.0 mm) and LBD 7.3 mm (range, 3.0–9.0 mm). Of 14 (31%) tumors that were first observed, 12 grew a median of 0.5 mm (range, 0.1–1.2 mm) in thickness and 1.0 mm (range, 0–3.0 mm) in LBD within a median of 7 months; 3 were initially smaller than 3 mm in LBD. Number of risk factors for growth and metastasis was 0 for 4% of the tumors; 60% were over 2 mm in thickness, 63% had subretinal fluid, 84% caused symptoms, 57% had orange pigment, and 92% were within 3 mm of the disc. Local recurrence occurred in 8 of 31 eyes (26%) treated conservatively. Median metastasis-free survival was 4.5 years (range, 0.8–15.7 years). Kaplan-Meier estimate of metastasis developing was 15% (95% confidence interval [CI], 7–26), 51% (95% CI, 36–64) and 85% (95% CI, 71–92) by 2, 5, and 10 years, respectively. By the time of analysis, 37 patients had died of metastasis after a median of 7 months.
• CONCLUSIONS: Choroidal melanomas less than 3.0 mm in LBD are highly unlikely to metastasize. Risk factors of an SFCM are similar to those for all choroidal melanomas of similar size. (Am J Ophthalmol 2019;202:100–108.

SMALL CHOROIDAL MELANOCYTIC TUMORS ARE treated if their appearance or growth suggests malignancy. Several studies have identified risk factors for growth[1–6] and metastasis[3–5] of suspicious small melanocytic choroidal lesions so as to aid in making treatment decisions. These include in particular tumor thickness over 2 mm, subretinal fluid, symptoms, orange pigment, and tumor margin either touching or within 3 mm from the optic disc margin, giving rise to the TFSOM ("To Find Small Ocular Melanoma") mnemonic.[3,4] Small choroidal melanocytic tumors, especially those without risk factors, have frequently been observed for growth to confirm diagnosis before being treated.[7] Especially small perifoveolar tumors have often been watched, because treating them likely compromises vision. However, observation before treatment might increase the risk for metastases.[8] Consequently, the practice of observing suspicious small melanocytic tumors of the choroid remains controversial.[7,9–13]

In contrast to an abundance of case series that have explored risk factors for growth and metastasis to tell small melanomas from other lesions, reports of small fatal choroidal melanomas (SFCM) that metastasized and killed the patient are scarce and typically do not describe such tumors in detail.[3,14–25] Based on their size, one might infer that the smallest choroidal melanomas that metastasize range from 1.7 to 2.5 mm in thickness and from 5.0 to 8.0 mm in largest basal diameter (LBD),[14,19–26] and that several have shown evidence of growth before[20,21] or—in the form of local recurrence[18,19,22,24]—after they were treated. Theoretical calculations based on tumor doubling times have suggested that uveal melanomas as

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small as 3 mm in LBD already might metastasize, however.[27,28] What the actual size limit is for a choroidal melanoma to gain the ability to metastasize remains unknown.[5,13,17]

The European Ophthalmic Oncology Group initiated this retrospective, collaborative Small Fatal Choroidal Melanoma Study (Supplemental Text; Supplemental Material available at AJO.com) in order to determine whether or not a size limit for a choroidal melanoma to metastasize can be determined, and to characterize the appearance and course of an SFCM before and after it is treated. Such data should be valuable to inform clinicians when to treat a small, suspicious pigmented choroidal tumor.

METHODS

• **AIMS OF THE STUDY:** The primary aim was to determine the size of the smallest choroidal melanomas that can metastasize. Secondary aims were to describe the characteristics of an SFCM at the time of treatment, local tumor control, metastasis-free interval, and survival of patients with an SFCM.

• **STUDY DESIGN:** Eligible for this retrospective study were consecutive patients who were diagnosed with a choroidal melanocytic tumor 3 mm or less in thickness and 9 mm or less in LBD when treated and who subsequently developed metastases. All tumors were thus a subset of American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) classification (7th and 8th Edition) T1a, stage I melanomas.[29,30] Data on consecutive patients were requested from members of the European Ophthalmic Oncology Group. This retrospective study, which was conducted using patient charts, archival images, and pathology data acquired in the course of past treatment, primarily from patients who already had died, received from the Institutional Review Board of the Department of Surgery, Helsinki University Hospital (the coordinating center of the study), and subsequently from the participating centers a waiver for collecting these anonymous data. For the same reason, written informed consent was not applicable. The study adhered to the tenets of the Declaration of Helsinki and all federal or state laws in participating countries.

• **DATA COLLECTION:** Ten ocular oncology services submitted anonymous data through a secure survey website. Tumor dimensions had been recorded clinically in disc diameters (DD) and diopters of elevation, in millimeters with ultrasonography, or both, depending on the year of treatment. Disc diameters and diopters were converted to millimeters (1 DD = 1.5 mm, 1 D = 1/3 mm).[31] Median tumor dimensions were calculated using primarily ultrasound measurements, secondarily clinical measurements, and thirdly histologic measurements, as available. The data requested additionally included the date of birth, sex, ethnicity, date of diagnosis, involved eye, visual acuity, history of a previous nevus, high-risk factors for growth and metastasis (TFSOM),[3,4] observation before treatment, date and type of the primary treatment, histopathologic diagnosis, date of local tumor relapse, secondary treatments, date of diagnosis of metastases, systemic treatment, and last known survival status after metastases. If the tumor was first observed for growth, data were collected from 2 visits: the initial diagnostic visit and the last visit preceding primary treatment.

We received data from 56 patients diagnosed between 1962 and 2010. Eleven patients were excluded after eligibility check, leaving 45 (80%) in our analysis. Excluded were 5 patients who had tumors larger than the eligibility criteria by the time of treatment after observation for growth, and 3 patients who had incomplete key data. Moreover, we found that a patient diagnosed in 1990 with pulmonary metastases from an epithelioid cell melanoma showed by immunohistochemistry a melanoma marker-negative, cytokeratin-positive tumor consistent with a primary pulmonary carcinoma with satellites. Finally, we excluded 2 patients who in 1973 and 2010 had only extrahepatic metastases detected because these were not biopsied and we were thus unable to verify them to have originated from their uveal melanoma without reasonable doubt.

• **STATISTICAL ANALYSIS:** All analyses were performed with Stata (release 13.0, Stata Corp, College Station, Texas, USA). Median and range are given as descriptive statistics. We used Fisher exact test to compare unordered contingency tables. All tests were 2-tailed unless otherwise specified, and $P < .05$ was considered statistically significant.

For comparison of the cumulative frequency of age at diagnosis of an SFCM with that of any small choroidal melanoma fulfilling the size criteria for inclusion, we constructed a reference group by drawing for each case 3 controls that had been treated at the Helsinki University Eye Hospital in the same year as the study patient.

Time to local recurrence was calculated from the date of primary treatment and analyzed using the cumulative incidence method, modeling death of systemic metastasis as a competing risk.[32,33] Analysis of time to systemic metastasis and survival was based on the Kaplan-Meier product-limit method and the log-rank test because all patients developed systemic metastases and none died of other causes, and thus competing risks were not an issue.

RESULTS

THE MEDIAN AGE OF THE 45 PATIENTS, ALL WHITE, WAS 57 years (range, 26–81 years). The cumulative frequency

plot of having an SFCM diagnosed began to rise more rapidly at the age of 45 years. Before the age of 50 years, we observed no difference in the plot between patients with an SFCM and the control group of small choroidal melanomas fulfilling the inclusion size criteria (Supplemental Figure 1; Supplemental Material available at AJO.com). Thereafter an SFCM was diagnosed a median of 4 years earlier than in controls. Of patients with an SFCM and controls, 25 (51%) and 73 (51%) were female, respectively.

• **OBSERVATION FOR GROWTH:** Of the 45 tumors, 31 were treated immediately (Figure 1 and Figure 2A–C) and 14 (31%) were observed before treatment. Twelve of the latter (86%) grew during a median observation time of 7 months (range, 2.5 months to 5.8 years; Figure 2D–L). Of the 14 tumors, 3 had been followed for more than a year (Figure 2D, E, G and H). The median observed growth was 0.5 mm (range, 0.1–1.2 mm) in thickness and 1.0 mm (range, 0–3.0 mm) in LBD. Three tumors that had the smallest initial tumor diameters grew only in LBD (Figure 2D–F), whereas 2 of the larger tumors grew only in thickness (Figure 1). The 2 tumors that did not grow had been observed for 1.6 and 6.7 months and then treated.

• **TUMOR CHARACTERISTICS AND SIZE AT THE TIME OF TREATMENT:** The visual acuity of the tumor eye ranged from counting fingers to 25/20 (median, 20/40) at the time of treatment. The tumor was dark brown in 16 (36%) eyes, light brown to amelanotic in 24 (53%) eyes, and of mixed color in 3 (7%) eyes. The distances from the posterior tumor margin to the foveola and the optic disc were a median of 0.8 mm (range, 0–5.0 mm) and 1.0 mm (range, 0–4.3 mm) for 26 tumors, respectively (Supplemental Figure 2; Supplemental Material available at AJO.com). The tumor margin involved the foveola in 11 (24%) eyes and extended to within 2 DD of it in 12 (27%) eyes. Twenty-four (57%) tumors were located temporal and 18 (43%) were nasal.

The median thickness of an SFCM when treated was 2.4 mm (range, 1.0–3.0 mm) and its median LBD was 7.3 mm (range, 3.0–9.0 mm; Figure 1). None of the 45 tumors were less than 3.0 mm in LBD at the time of treatment, whereas 12 (27%) were 3.0–6.0 mm (Figure 2B, E and L), and 33 (73%) were 6.1–9.0 mm (Figure 2H–J). The LBDs for the 4 smallest tumors were 3.0, 3.4, 4.8, and 5.0 mm (Figure 2B). For 31 tumors measured with ultrasound, the acoustic profile was lower than that of the surrounding choroid in 26 (84%) eyes, equal in 3 (10%) eyes, and higher in 2 (6%) eyes. No extraocular extensions were present clinically.

• **RISK FACTORS FOR GROWTH AND METASTASIS:** When either first observed or observed later at the time of treatment, 27 of the 45 tumors (60%) were over 2 mm in thickness, 20 (63%) had subretinal fluid, 37 (84%) had caused

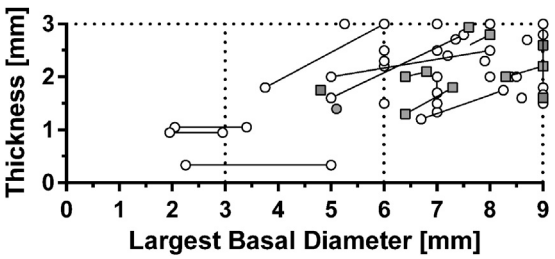

FIGURE 1. The size of 45 small fatal choroidal melanomas. Scatterplot of largest basal tumor diameter against tumor thickness. White circles indicate tumors without local recurrence and gray squares tumors that recurred; connected symbols indicate tumors that were observed to grow before diagnosis and treatment (measurements at initial visit and at last visit before treatment).

symptoms, 21 (57%) had orange pigment, and 24 (92%) had a margin within 2 disc diameters of the optic disc and 7 (27%) touched the disc margin (Table). Of 3 eyes, subretinal fluid over or around the tumor was diagnosed in 16 (50%) and an inferior retinal detachment in 4 (13%). Symptoms included blurry vision, a field defect, floaters, photopsia, and metamorphopsia. For tumors observed for growth, orange pigment developed or increased before treatment in 1 of 9 eyes, and subretinal fluid emerged or increased in 1 of 10 eyes.

• **PRIMARY TREATMENT:** Patients were typically treated if they had a presumed small choroidal melanoma diagnosed either because the tumor had been observed to grow (27%) or it showed at least 1 high-risk facture (69%; Supplemental Table 1; Supplemental Material available at AJO.com). Two tumors (4%) with no observed risk factors were immediately treated.

Fifteen (33%) eyes were enucleated, and an extraocular extension 0.5 mm in diameter was detected from 1 peripapillary tumor that was 9 mm in LBD (pT1c, stage IIA). Eighteen tumors (40%) were treated with brachytherapy: ruthenium in 13 and iodine in 5 patients. The median dose to tumor apex and sclera with ruthenium was 100 Gy (range, 80–150 Gy) and 341 Gy (range, 173–443 Gy), respectively. Five of these patients received adjunctive transpupillary thermotherapy within 7 months from brachytherapy. The median dose to tumor apex with iodine was 85 Gy (range, 81–95 Gy). Proton beam therapy (60 cobalt gray equivalents) was delivered to 11 (24%) eyes. One patient received primary transpupillary thermotherapy. No genetic analyses had been done.

• **LOCAL RECURRENCE:** None of the 15 enucleated eyes developed an orbital recurrence. Local recurrence occurred in 8 of 31 (26%) eyes treated conservatively (Figure 2B and C). Four (50%) of the recurrent tumors had been observed to grow also before treatment. The cumulative incidence of

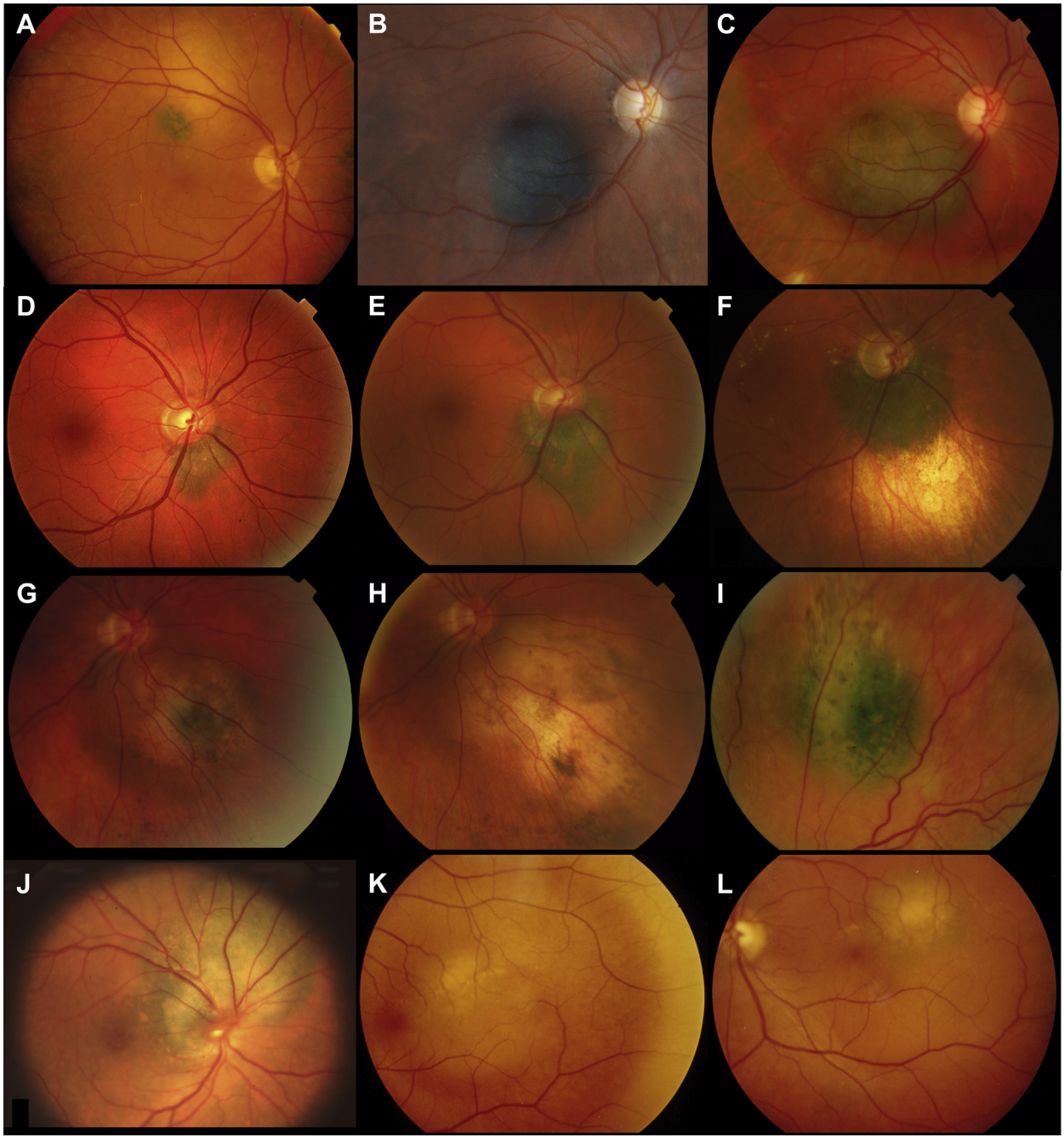

FIGURE 2. Representative small fatal choroidal melanomas. (A) A mostly amelanotic tumor 3 mm thick and 5.3 mm in largest basal diameter (LBD) with 4 risk factors (thickness over 2 mm, subretinal fluid, symptoms, minor orange pigment) was treated with proton beam. (B) A parafoveal tumor 1.7 mm thick and 4.8 mm in LBD with 2 risk factors (subretinal fluid, symptoms) was irradiated with a ruthenium plaque; (C) the tumor developed a local recurrence 3 years later and received a secondary iodine plaque followed by further recurrences a year later. (D) A minimally elevated peripapillary tumor 2.4 mm in LBD with 2 risk factors (orange pigment, margin touching disc) that had doubled in area (E) after 6 years and was irradiated with an iodine plaque. (F) Flat scar and radiation retinopathy 8 years later when metastases were detected. (G) A variably pigmented tumor 1.6 mm thick and 6.7 mm in LBD had 1 risk factor (margin touching disc), turned amelanotic (H), and grew to 2.1 mm in thickness and 8.2 mm in LBD in 15 months before iodine plaque treatment. (I) A partially amelanotic tumor 1.6 mm thick and 5.0 mm in LBD with 2 risk factors (symptoms, orange pigment) was treated with proton beam after it grew to 2.8 mm in thickness and 7.5 mm in LBD in 11 months. (J) A circumpapillary tumor 2.8 mm thick and 8 mm in LBD with all 5 risk factors after growing an unspecified amount in 7 months before treatment with a ruthenium plaque. (K) An amelanotic tumor 2 mm in thickness, 4 mm in LBD with 1 risk factor (symptoms), and 3 mm from disc was when first diagnosed. (L) It grew to 3.0 in height and 6.2 in LBD over observation time of 3 months before proton beam treatment.

TABLE. TFSOM High-Risk Characteristics for Growth and Metastasis for 45 Small Fatal Choroidal Melanomas as Compared to Literature Data for 35 Small Melanocytic Choroidal Tumors That Metastasized[3]

		Small Fatal Choroidal Melanoma Study			
			Local Tumor Recurrence		
Risk characteristic	TFSOM[3,4] Description[a] (N = 35), N (%)	All Cases (N = 45), N (%)[b]	Yes (N = 8), N (%)[b]	No (N = 31), N (%)[b]	*P* Value[c]
Thickness over 2 mm	19 (54)	27 (60)	5 (63)	17 (55)	1.00
Subretinal fluid	19 (54)	20 (63)	6 (75)	12 (67)	.11
Symptoms	22 (62)	37 (84)	7 (88)	25 (80)	1.00
Orange pigment	16 (46)	21 (57)	6 (75)	12 (52)	.11
Margin					
Touching disc[d]	16 (46)	7 (27)	3 (50)	4 (27)	.14
Within 2 DD from disc[e]	20 (57)	24 (92)	6 (100)	14 (93)	.24
Observed growth	25 (71)	12 (27)	4 (50)	6 (19)	.17

DD = disc diameters.
[a]Seven tumors were up to 5.0 mm, 21 were 5.1–10.0 mm, and 7 were 10.1–15.0 mm in largest basal diameter.[1]
[b]Percentages calculated from the number of patients with known data.
[c]Fisher exact test.
[d]Original criteria.[3]
[e]Later criteria.[4]

developing a local recurrence was 17% (95% confidence interval [CI], 7–29) by 5 years and 19% (95% CI, 9–32) by 10 years (Figure 3A). Twenty-seven patients died of metastatic melanoma without developing a recurrence, and 4 (9%) were lost to ocular follow-up. We did not have enough evidence to either confirm or exclude that tumors with a local recurrence were more often located closer to the optic disc (Table; $P = .14$, Fisher exact test), more often had orange pigment ($P = .11$) and subretinal fluid ($P = .11$), and had more often been observed to grow ($P = .17$). Two of the 8 recurrences were enucleated, 4 were treated with brachytherapy, and 2 received transpupillary thermotherapy (1 was enucleated later).

• **HISTOPATHOLOGIC CHARACTERISTICS:** Of 20 SFCM with known histopathology, epithelioid cells were present in 15 (75%), including those in all 3 eyes enucleated after local recurrence, and 5 (25%) were of spindle cell type. One of the 3 enucleated recurrent tumors was found to have a 5-mm extrascleral extension following primary brachytherapy and secondary transpupillary thermotherapy.

• **METASTATIC DISEASE:** By study design, all patients developed metastatic uveal melanoma. Of 34 patients with available data, 22 (65%) had participated in regular surveillance and 19 (86%) of them remained asymptomatic at the time of diagnosis of metastases. Of the 12 patients who were not under regular surveillance, 1 was asymptomatic and the metastases were detected during evaluation for an unrelated disease.

Metastases were typically detected first by liver imaging (either ultrasonography, computed tomography, or magnetic resonance imaging) and when active treatment was considered for them, they were staged with imaging of other organs and typically confirmed through biopsy or by documenting progression. Metastases were diagnosed histopathologically, by imaging, and clinically in 17 (38%), 20 (44%), and 2 (4%) patients, respectively (Supplemental Table 2; Supplemental Material available at AJO.com). Metastases were hepatic in 28 (62%) patients and hepatic and extrahepatic in 15 (33%) patients, and the distribution was incompletely specified in 2 (4%) patients. The median metastasis-free survival was 4.5 years (range, 10 months to 15.7 years). The cumulative incidence of metastasis developing was 15% (95% CI, 7–26) by 2 years, 51% (95% CI, 36–64) by 5 years, and 85% (95% CI, 71–92) by 10 years after treatment. Of 33 patients with known data, 23 (70%) received active treatment for metastatic disease while 10 (30%) received best supportive care (Supplemental Table 2). None of them had a known history of a second cancer, especially of cutaneous or mucous membrane melanoma.

• **SURVIVAL OUTCOME:** Thirty-seven (82%) patients died during follow-up, all of metastatic disease; 2 were lost to follow-up with progressive disease and are presumed dead; and 6 are alive with metastases (Figure 3B). Median survival was 6.0 years (range, 1.6–16.7 years) from primary treatment and did not differ between patients who were treated with enucleation and conservatively with or without developing local tumor recurrence after treatment

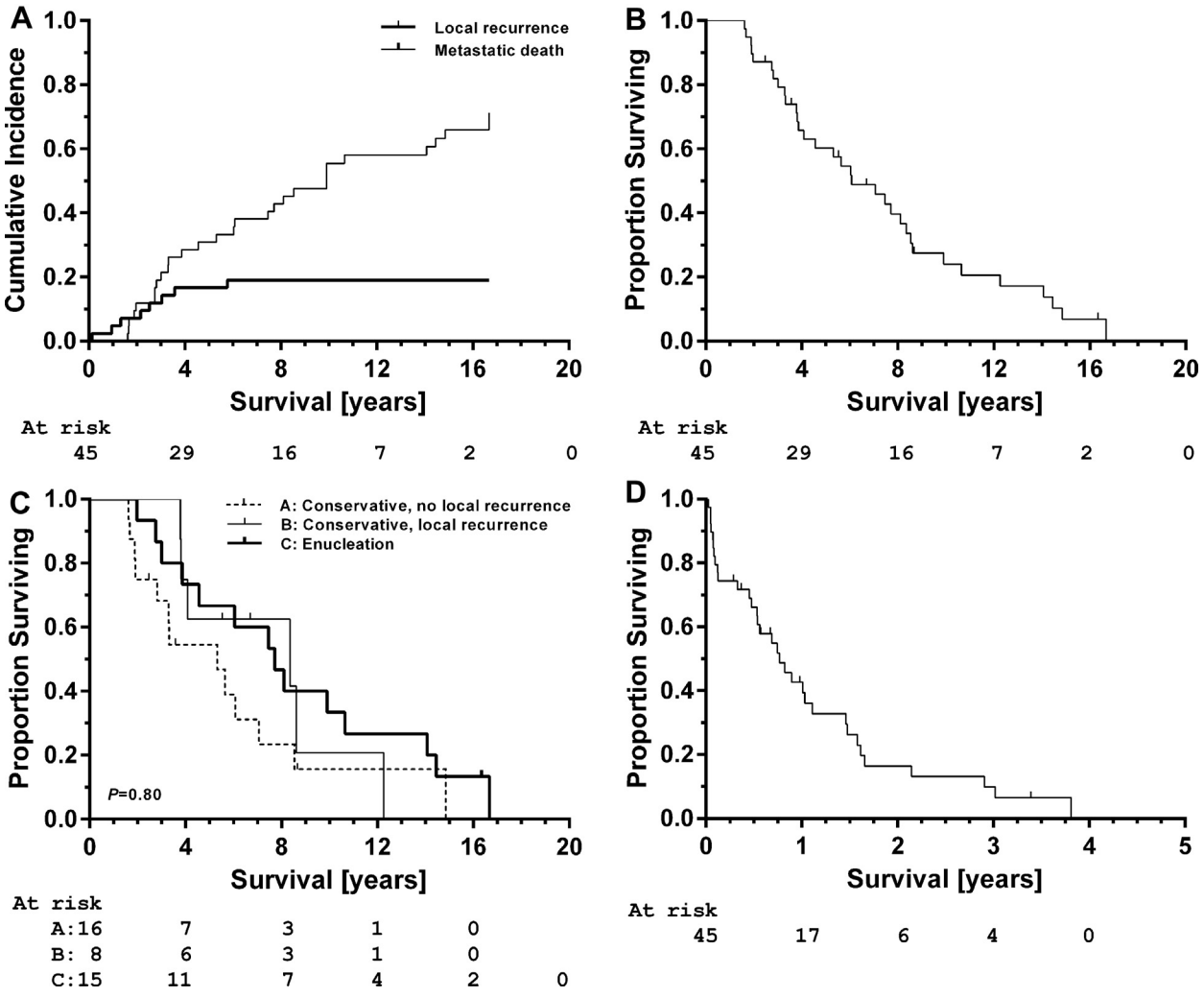

FIGURE 3. Outcome after treatment of 45 small fatal choroidal melanomas. (A) Cumulative incidence plot of time to first local recurrence (thick line) or to systemic metastases (thin line) modeled as a competing risk. (B) Kaplan-Meier plot of survival after primary treatment of the intraocular tumor for all patients. (C) No difference in survival is evident between patients whose tumor was enucleated (thick line) and those whose tumor was conservatively treated with (thin line) or without (dashed line) later local recurrence. (D) Kaplan-Meier plot of survival after development of metastases. Ticks indicate censored patients and numbers below graph are patients at risk.

(Figure 3C; $P = .80$, log-rank test). Survival after developing systemic metastases was 8 months (range, 1 week to 3 years 9 months). The Kaplan-Meier estimate of metastatic death was 52% (95% CI, 37–66) at 1 year, 77% (95% CI, 60–88) at 2 years, and 84% (95% CI, 66–93) at 3 years (Figure 3D) after metastasis detection.

DISCUSSION

WE FOUND FROM 10 EUROPEAN OCULAR ONCOLOGY CENters 3 patients with an SFCM that were less than 5 mm (about 3 DD) in LBD when treated, but none that was less than 3 mm (2 DD). In the literature the smallest choroidal melanomas that metastasized were at least 1.7 mm thick[19] and 5.0 mm in LBD.[21] To the best of our knowledge, our 3 smallest tumors, which were 3.0, 3.4 (Figure 2D–F), and 4.8 mm (Figure 2B) in LBD, are the smallest fatal choroidal melanomas reported.[14,19–26] Their thickness was 1.0 mm (in 1 case, 1.7 mm), 1 had subretinal fluid, 2 caused blurred vision, and 1 touched disc margin. The observational arm of the Collaborative Ocular Melanoma Study defined a small choroidal melanoma as being 1–3 mm in thickness and 5–16 mm in LBD; tumors smaller than this were regarded as probable nevi.[17] A large single-center study estimated that when LBD is 5–6 mm, about 70 choroidal nevi are diagnosed for every melanoma, and stated that few melanomas would be less than 5 mm in diameter.[34] Our data confirm not only

that some choroidal melanomas indeed are smaller than 5 mm in LBD but also that tumors as small as this even can disseminate.

Based on estimated tumor doubling times of primary and metastatic lesions, choroidal melanomas were hypothesized to spread micrometastases when they reach 3 mm in LBD.[27,28] The same calculation suggested that by that time tumor cells already had divided 22 times over approximately 9 years, and that clinical metastases would be diagnosed on average 5 years afterward. The vast majority of choroidal melanomas are diagnosed and treated when they are much larger than 3 mm in diameter, and our study cannot tell which proportion of them actually first metastasize later.

In a collaborative cohort study of 7369 uveal melanomas used to build the current AJCC TNM staging of ciliary body and choroidal melanomas based on their anatomic extent,[30] altogether 12, 160, and 613 tumors that were 3.0 mm or less in thickness measured up to 3.0 mm, from 3.1 to 6.0 mm and from 6.1 to 9.0 mm in LBD, respectively, and 0 (0%), 8 (5%), and 33 (5%) of these patients died of metastases, respectively. This translated to a 10-year survival rate of 100% for tumors 3.0 mm or less in thickness, supporting the present results, as compared to 92% for the latter 2 groups.[30] Our results and the previous literature taken together[18–22,24,30] indicate that 3.0 mm most likely represents a size limit before which a choroidal melanoma does not yet have the capacity to metastasize.

One third of the 45 eyes with an SFCM were first observed for tumor growth, an approach that potentially increased the risk for metastases. Review of small case series likewise shows that an SFCM sometimes was observed for growth before treatment.[19,22] On the other hand, data on gene expression profile class 1B and 2 (recently found in 3 and 2 of 14 tumors, respectively, that were 2 mm or less in thickness but more than 5 mm in LBD, and either had been observed to grow or had caused symptoms) and on monosomy 3 (found in 4 of 11 tumors) at the time of treatment—tumor characteristics strongly associated with risk of metastasis—suggest that such intrinsic genetic factors rather than observation for growth might determine survival outcome.[8,35] Also, analysis of whole exome sequencing data from multiple sources suggested that somatic *BAP1* mutations—which like the gene expression profile class 2 and monosomy 3 are strongly associated with metastases developing from uveal melanoma—as well as other types of typical genetic driver aberrations apparently arise early in tumor evolution, whereafter occurrence of new canonical aberrations seemed to be rare.[36]

Be that as it may, our results provide evidence that if the diagnosis cannot be otherwise obtained it would be safe to briefly observe choroidal melanocytic tumors less than 3 mm in LBD to detect growth. It is challenging to biopsy for genetic analysis, or otherwise diagnose with certainty, a choroidal tumor less than 3 mm in LBD as a melanoma as an alternative. Upon observing growth not consistent with a choroidal nevus[37] it is prudent to consider immediate treatment, irrespective of tumor size. Indeed, 3 of our SFCM grew over the 3 mm limit while observed, and metastasis in these patients might have been prevented by earlier treatment. The risk of metastasis still seems to be relatively low until the melanoma exceeds 9 mm in LBD, provided that its thickness remains 3 mm or less: the collaborative cohort study mentioned reported an 8% risk of metastasis at 10 years for a choroidal melanoma of this size range, as opposed to 15% for one between 9.1 and 12 mm in LBD or more than 3 mm in thickness.[30] This relatively low risk may explain why small observational case series have not found a difference in mortality from small melanomas observed for growth as compared to immediately treated ones.[13,38]

More than a third of our eyes with an SFCM were managed with primary enucleation and did not develop local recurrence, so that micrometastases necessarily had arisen before treatment. It remains unknown, however, whether metastases spread before or after local recurrence, or both, in the 8 patients who were managed conservatively and experienced such a relapse, especially the one with an extraocular recurrence. Indeed, several patients with an SFCM reportedly have died after developing a local recurrence.[18,19,22,24] In our series, the recurrence rate was higher than usual, likely reflecting the fact that tumors in this location are anatomically more difficult to treat conservatively.[39] In these cases, a geographic miss in plaque placement might have provided a chance for dissemination. In our study, tumors that recurred did not show evidence of worse prognosis. However, half of the tumors that developed a local recurrence had also been observed to grow before treatment. This could indicate that at least some of the recurrent tumors may have been more malignant to begin with.[40,41] Indeed, three quarters of our SFCM with known histopathology had epithelioid cells.

Four percent of our patients with an SFCM had no TFSOM risk factors for growth and metastasis. Their frequencies at the time of diagnosis of an SFCM were similar to those reported for 35 small melanocytic choroidal tumors that metastasized in the study that introduced this mnemonic.[3] However, although tumor thickness, documented growth, margin touching the disc, and symptoms were associated with metastasis by multivariate modeling in that original study, comparison of our findings with those reported for unselected choroidal melanomas in this size range[39] suggested that neither the number nor the type of risk factors can tell an SFCM from other small melanomas. Moreover, although in the original study 71% of the 35 tumors that metastasized had been observed to grow, the percentage in our series was only 31%. In a recent series, high-risk factors for growth and metastasis were not associated with gene expression profiles predictive of patient survival either.[42]

Finally, our patients with an SFCM were a median of 4 years younger than historical controls with a small choroidal melanoma fulfilling the size criteria for inclusion; the median tumor thickness (2.4 mm vs 2.0 mm) and LBD (7.3 mm vs 7.4 mm) in the 2 groups also were comparable. In general, older patients are thought to be at higher risk of metastatic uveal melanoma.[43] Survival after metastases typically is short, a median of 8.4 months for unselected patients.[44] The survival after metastases from an SFCM did not differ from that of other uveal melanoma patients.[45] However, the metastasis-free interval of 4.5 years was longer than average, reported to be 2.7 years,[44] consistent with lead time bias from an earlier diagnosis of the primary tumor and, interestingly, close to the estimated 5-year interval from micrometastasis to clinical metastasis based on theoretical tumor doubling time calculations.[28]

To the best of our knowledge, our study is the first that provides an empirical answer to 2 pertinent questions already posed 4 decades ago: at what stage in the natural history a small choroidal melanoma develops the capacity to metastasize, and whether there is a recognizable clinical correlate to this event.[13] We suggest that 3.0 mm is the size limit for the ability of a choroidal melanoma to metastasize, and that no known clinical characteristic can predict this event. This information should help clinicians to reach a decision when to biopsy or treat a small choroidal melanocytic lesion.

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REFERENCES

1. Butler P, Char DH, Zarbin M, Kroll S. Natural history of indeterminate pigmented choroidal tumors. *Ophthalmology* 1994;101(4):710–717.
2. Singh AD, Mokashi AA, Bena JF, Jacques R, Rundle PA, Rennie IG. Small choroidal melanocytic lesions: features predictive of growth. *Ophthalmology* 2006;113(6):1032–1039.
3. 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(9):1351–1361.
4. Shields CL, Shields JA. Clinical features of small choroidal melanoma. *Curr Opin Ophthalmol* 2002;13(3):135–141.
5. Factors predictive of growth and treatment of small choroidal melanoma: COMS Report No. 5. The Collaborative Ocular Melanoma Study Group. *Arch Ophthalmol* 1997;115(12):1537–1544.
6. Augsburger JJ, Schroeder RP, Territo C, Gamel JW, Shields JA. Clinical parameters predictive of enlargement of melanocytic choroidal lesions. *Br J Ophthalmol* 1989;73(11):911–917.
7. Finger P, Kurli M, Shulman J. Treatment of small choroidal melanoma: an internet survey. *Internet J Ophthalmol Vis Sci* 2006;5(1):1–5.
8. Augsburger JJ, Correa ZM, Trichopoulos N. An alternative hypothesis for observed mortality rates due to metastasis after treatment of choroidal melanomas of different sizes. *Trans Am Ophthalmol Soc* 2007;105:54–60.
9. Augsburger JJ. Is observation really appropriate for small choroidal melanomas. *Trans Am Ophthalmol Soc* 1993;91:147–175.
10. Robertson DM. Changing concepts in the management of choroidal melanoma. *Am J Ophthalmol* 2003;136(1):161–170.
11. Murray TG, Sobrin L. The case for observational management of suspected small choroidal melanoma. *Arch Ophthalmol* 2006;124(9):1342–1344.
12. Shields JA. Treating some small melanocytic choroidal lesions without waiting for growth. *Arch Ophthalmol* 2006;124(9):1344–1346.
13. Char DH. The management of small choroidal melanomas. *Surv Ophthalmol* 1978;22(6):377–386.
14. Thomas JV, Green WR, Maumenee AE. Small choroidal melanomas. A long-term follow-up study. *Arch Ophthalmol* 1979;97(5):861–864.
15. Gass JD. Observation of suspected choroidal and ciliary body melanomas for evidence of growth prior to enucleation. *Ophthalmology* 1980;87(6):523–528.
16. McKnight SJ, Christensen GR. Metastasis of a very small choroidal melanoma without apparent clinical change. *Ann Ophthalmol* 1984;16(11):1016–1021.
17. Mortality in patients with small choroidal melanoma. COMS report no. 4. The Collaborative Ocular Melanoma Study Group. *Arch Ophthalmol* 1997;115(7):886–893.
18. Parrozzani R, Boccassini B, De Belvis V, Radin PP, Midena E. Long-term outcome of transpupillary thermotherapy as primary treatment of selected choroidal melanoma. *Acta Ophthalmol* 2009;87(7):789–792.
19. Robertson DM. Small choroidal melanomas treated with transpupillary thermotherapy and cryotherapy. *Arch Ophthalmol* 2008;126(8):1156–1157.
20. Sobrin L, Schiffman JC, Markoe AM, Murray TG. Outcomes of iodine 125 plaque radiotherapy after Initial observation of suspected small choroidal melanomas: a pilot study. *Ophthalmology* 2005;112(10):1777–1783.
21. Malclès A, Kivelä T, Svetlosakova Z, et al. Small metastasizing choroidal melanomas. *Acta Ophthalmol* 2015;93(2):e160–e166.

22. Shields CL, Shields JA, Perez N, Singh AD, Cater J. Primary transpupillary thermotherapy for small choroidal melanoma in 256 consecutive cases: outcomes and limitations. *Ophthalmology* 2002;109(2):225–234.
23. Barr CC, Sipperley JO, Nicholson DH. Small melanomas of the choroid. *Arch Ophthalmol* 1978;96(9):1580–1582.
24. Gündüz K, Karslioğlu MZ, Köse K. Primary transpupillary thermotherapy of choroidal melanocytic lesions. *Middle East Afr J Ophthalmol* 2011;18(2):183–188.
25. Lane AM, Egan KM, Kim IK, Gragoudas ES. Mortality after diagnosis of small melanocytic lesions of the choroid. *Arch Ophthalmol* 2010;128(8):996–1000.
26. Davidorf FH, Lang JR. The natural history of malignant melanoma of the choroid: small vs large tumors. *Trans Sect Ophthalmol Am Acad Ophthalmol Otolaryngol* 1975;79(2):Op310–Op320.
27. Eskelin S, Pyrhönen 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(8):1443–1449.
28. Eskelin S, Kivelä T. Author's reply. *Ophthalmology* 2001; 108(5):830–831.
29. Malignant melanoma of the uvea. In: Edge S, Byrd D, Compton C, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010:547–559.
30. Kujala E, Damato B, Coupland SE, et al. Staging of ciliary body and choroidal melanomas based on anatomic extent. *J Clin Oncol* 2013;31(22):2825–2831.
31. Mianowicz J, Laatikainen L. Estimation of tumor height and follow-up of radiation response in uveal malignant melanoma by ultrasonography. *Acta Ophthalmol* 1987;65:151–153.
32. Puusaari I, Heikkonen J, Kivelä T. Ocular complications after iodine brachytherapy for large uveal melanomas. *Ophthalmology* 2004;111(9):1768–1777.
33. Gooley TA, Leisenring W, Crowley J, Storer BE. Handbook of Statistics in Clinical Oncology. New York, NY: Marcel Dekker; 2001.
34. Augsburger JJ, Correa ZM, Trichopoulos N, Shaikh A. Size overlap between benign melanocytic choroidal nevi and choroidal malignant melanomas. *Invest Ophthalmol Vis Sci* 2008;49(7):2823–2828.
35. Nagiel A, McCannel CA, Moreno C, McCannel TA. Vitrectomy-assisted biopsy for molecular prognostication of choroidal melanoma 2 mm or less in thickness with a 27-gauge cutter. *Retina* 2017;37(7):1377–1382.
36. Field MG, Durante MA, Anbunathan H, et al. Punctuated evolution of canonical genomic aberrations in uveal melanoma. *Nat Commun* 2018;9(1):116.
37. Mashayekhi A, Siu S, Shields CL, Shields JA. Slow enlargement of choroidal nevi: a long-term follow-up study. *Ophthalmology* 2011;118(2):382–388.
38. Augsburger JJ, Vrabec TR. Impact of delayed treatment in growing posterior uveal melanomas. *Arch Ophthalmol* 1993; 111(10):1382–1386.
39. Salkola S, Heikkonen J, Eskelin S, Kivelä T. Management of choroidal melanomas less than 10 mm in largest basal diameter with a 10-mm ruthenium plaque. *Retina* 2014;34(10): 2110–2120.
40. Caujolle JP, Paoli V, Chamorey E, et al. Local recurrence after uveal melanoma proton beam therapy: recurrence types and prognostic consequences. *Int J Radiat Oncol Biol Phys* 2013;85(5):1218–1224.
41. Ophthalmic Oncology Task Force. Local recurrence significantly increases the risk of metastatic uveal melanoma. *Ophthalmology* 2016;123(1):86–91.
42. Nguyen BT, Kim RS, Bretana ME, Kegley E, Schefler AC. Association between traditional clinical high-risk features and gene expression profile classification in uveal melanoma. *Graefes Arch Clin Exp Ophthalmol* 2018;256(2): 421–427.
43. Shields CL, Kaliki S, Furuta M, Mashayekhi A, Shields JA. Clinical spectrum and prognosis of uveal melanoma based on age at presentation in 8,033 cases. *Retina* 2012;32(7): 1363–1372.
44. Eskelin S, Pyrhönen S, Hahka-Kemppinen M, Tuomaala S, Kivelä T. A prognostic model and staging for metastatic uveal melanoma. *Cancer* 2003;97(2):465–475.
45. Kivelä TT, Piperno-Neumann S, Desjardins L, et al. Validation of a prognostic staging for metastatic uveal melanoma: A Collaborative Study of the European Ophthalmic Oncology Group. *Am J Ophthalmol* 2016;168:217–226.