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The Pediatric Choroidal and Ciliary Body Melanoma Study

A Survey by the European Ophthalmic Oncology Group

Rana'a T. Al-Jamal, MD,[1] Nathalie Cassoux, MD,[2] Laurence Desjardins, MD,[2] Bertil Damato, MD,[3] Lazaros Konstantinidis, MD,[3] Sarah E. Coupland, MD,[3,4] Heinrich Heimann, MD,[3] Aleksandra Petrovic, MD,[5] Leonidas Zografos, MD,[5] Ann Schalenbourg, MD,[5] Juan P. Velazquez-Martin, MD,[6] Hatem Krema, MD,[6] Anna Bogdali, MD,[7] Anna Markiewicz, MD,[7] Bozena Romanowska-Dixon, MD,[7] Claudia H.D. Metz, MD,[8] Eva Biewald, MD,[8] Norbert Bornfeld, MD,[8] Hayyam Kiratli, MD,[9] Inge H.G. Bronkhorst, MD,[10] Martine J. Jager, MD,[10] Marina Marinkovic, MD,[10] Maria Fili, MD,[11] Stefan Seregard, MD,[11] Shahar Frenkel, MD,[12] Jacob Pe'er, MD,[12] Sachin M. Salvi, MD,[13] Ian G. Rennie, MD,[13] Iwona Rospond-Kubiak, MD,[14] Jaroslaw Kociecki, MD,[14] Jens Folke Kiilgaard, MD,[15] Steffen Heegaard, MD,[15] Victoria M.L. Cohen, MD,[16] Mandeep S. Sagoo, MD,[16] Anush Amiryan, MD,[17] Svetlana Saakyan, MD,[17] Nils Eide, MD,[18] Jørgen Krohn, MD,[19] Edoardo Midena, MD,[20] Raffaele Parrozzani, MD,[21] Jean-Daniel Grange, MD,[22] Emine Kilic, MD,[23] Maria Antonietta Blasi, MD,[24] Maria Antonia Saornil, MD,[25] Tero T. Kivelä, MD[1]

Purpose: To collect comprehensive data on choroidal and ciliary body melanoma (CCBM) in children and to validate hypotheses regarding pediatric CCBM: children younger than 18 years, males, and those without ciliary body involvement (CBI) have more favorable survival prognosis than young adults 18 to 24 years of age, females, and those with CBI.

Design: Retrospective, multicenter observational study.

Participants: Two hundred ninety-nine patients from 24 ocular oncology centers, of whom 114 were children (median age, 15.1 years; range, 2.7−17.9 years) and 185 were young adults.

Methods: Data were entered through a secure website and were reviewed centrally. Survival was analyzed using Kaplan-Meier analysis and Cox proportional hazards regression.

Main Outcome Measures: Proportion of females, tumor-node-metastasis (TNM) stage, cell type, and melanoma-related mortality.

Results: Cumulative frequency of having CCBM diagnosed increased steadily by 0.8% per year of age between 5 and 10 years of age and, after a 6-year transition period, by 8.8% per year from age 17 years onward. Of children and young adults, 57% and 63% were female, respectively, which exceeded the expected 51% among young adults. Cell type, known for 35% of tumors, and TNM stage (I in 22% and 21%, II in 49% and 52%, III in 30% and 28%, respectively) were comparable for children and young adults. Melanoma-related survival was 97% and 90% at 5 years and 92% and 80% at 10 years for children compared with young adults, respectively ($P = 0.013$). Males tended to have a more favorable survival than females among children (100% vs. 85% at 10 years; $P = 0.058$). Increasing TNM stage was associated with poorer survival (stages I, II, and III: 100% vs. 86% vs. 76%, respectively; $P = 0.0011$). By multivariate analysis, being a young adult (adjusted hazard rate [HR], 2.57), a higher TNM stage (HR, 2.88 and 8.38 for stages II and III, respectively), and female gender (HR, 2.38) independently predicted less favorable survival. Ciliary body involvement and cell type were not associated with survival.

Conclusions: This study confirms that children with CCBM have a more favorable survival than young adults 18 to 25 years of age, adjusting for TNM stage and gender. The association between gender and survival varies between age groups. *Ophthalmology 2016;123:898-907 © 2016 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Uveal melanoma (UM) has an annual incidence of 2 to 8 per million in North America and Europe, varying by age, ethnicity, and latitude.[1−3] It is generally a disease of middle-aged and older adults, with a low incidence before 45 years of age; the median age at diagnosis has increased to 62 years because of increasing life expectancy.[3,4] Nevertheless, UM can occur at any age, even as a congenital tumor.[5,6] Oculo(dermal) melanocytosis, neurofibromatosis type 1, familial

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atypical multiple mole and melanoma syndrome, and germline mutations in the BRCA1-associated protein 1 (*BAP1*) gene have been alleged to play a role in its development, especially in younger patients.[7–10]

The randomized Collaborative Ocular Melanoma Study did not provide data on UM in patients younger than 21 years, who were ineligible for the study.[11] However, in a single-center series of 8033 patients and in several smaller series, patients younger than 21 years have constituted 0.8% to 1.1% of the studied cohorts.[7,8,12–15] Given an estimated annual world incidence of 6700 to 7100 cases of UM, this translates to approximately 65 young patients per year.[3] The reported features of UM in the latter as compared with adults include a higher incidence of iris melanoma and better survival prognosis, attributed to smaller tumor size and, perhaps, a more active immune system in younger patients.[7,12–15] Histopathologic or molecular pathologic studies of UM in children have not demonstrated any differences from their adult counterparts.[16,17]

Two of the authors (T.T.K. and R.A.J.) recently undertook a meta-analysis of 88 patients younger than 25 years of age with choroidal and ciliary body melanoma (CCBM) that suggested that female gender and higher American Joint Committee on Cancer tumor-node-metastasis (TNM) stage both adversely influence survival.[18] The meta-analysis also suggested that patients younger than 18 years may have an excellent life prognosis, especially if they are male, compared with those 18 to 24 years of age, especially if they are female and if the ciliary body is involved.[18]

To test these hypotheses and to collect more comprehensive data on CCBM in patients younger than 25 years of age than what are available from the literature, we established the collaborative Pediatric Choroidal and Ciliary Body Melanoma Study of the European Ophthalmic Oncology Group (http://www.oog.eu.com). Herein, we present our data obtained from children younger than 18 years compared with young adults 18 to 24 years of age. To the best of our knowledge, ours is the largest series to characterize CCBM in these age groups.

Methods

Aims of the Study

The study aimed to test 3 hypotheses derived from a meta-analysis and a large single-center study of CCBM in young patients[18,19]: (1) children have a more favorable life prognosis than young adults and, when both groups are combined, (2) males have higher survival rates than females and (3) ciliary body involvement (CBI) is a parameter for poor prognosis.[18]

Study Design

For the purpose of our study, cases were defined as patients younger than 18 years at the time of diagnosis of a CCBM, corresponding to the joint definition of children by the European Medicines Agency and the European Union of Pediatrics,[20] and controls were defined as adults younger than 25 years at diagnosis. This age limit was chosen because it was predicted to yield a second group of comparable size on the basis of the meta-analysis[18] and because previous series of UM in adolescents adhered to this or a lower age limit.[7,13,15,19,21–24]

We formulated our hypotheses based on the meta-analysis of 88 patients younger than 25 years (none with an iris melanoma)[18] extracted from 6 series and a single-center, referral-based cohort study including 86 patients younger than 20 years[19] (25% had an iris melanoma), as follows. First, children have better 10-year survival versus young adults (meta-analysis, 100% vs. 85%; cohort study, 91% for younger than 20 years with CCBM). To calculate the sample needed, we presumed a 10-year survival of 97% for children (allowing for a small number of deaths, based on the cohort study) and 85% for young adults. We further presumed 44% to be children and 44% to be censored from the analysis (both percentages taken from the meta-analysis). Second, for children and young adults combined, males have better 10-year survival than females (meta-analysis, 100% vs. 85%). Third, for children and young adults combined, those without CBI have better 10-year survival than those with such involvement (meta-analysis, 96% vs. 70%). A total sample of 289 patients was needed (power, 0.80; 1-sided α, 0.05) for the first comparison, which was a sample in excess to that required for the other 2 comparisons.

Eligible for our retrospective cohort study were all patients in whom a CCBM was diagnosed at an age younger than 25 years and for whom at least the following data were available: birth date, date of diagnosis, gender, treatment type, presence or absence of local or systemic tumor recurrence, last survival status, date of last known status, and cause of death (UM, second cancer, or nonmalignant cause) determined by reviewing patient charts, registry data, histologic samples, and death certificates. Patients with iris melanomas were ineligible. All treatment methods were eligible. This investigation was approved by the institutional review boards of the participating centers as required and adhered to the tenets of the Declaration of Helsinki.

Data Collection

Data on consecutive eligible patients were collected from members of the European Ophthalmic Oncology Group. The data additionally acquired included presence of congenital oculo(dermal) melanocytosis or neurofibromatosis; visual acuity and intraocular pressure at diagnosis and at last visit; tumor thickness; largest basal diameter of tumor; CBI; extraocular extension; tumor distance from the center of the fovea and the margin of the optic disc; tumor cell type; tumor cytogenetic features; dates of any local tumor recurrence; secondary enucleation, and metastasis; and second primary malignancies. We staged the tumors according to the seventh edition of the TNM system of the American Joint Committee on Cancer.[25,26]

Twenty-four participating ocular oncology services submitted data anonymously through a secure survey website from 356 patients diagnosed between February 1968 and February 2014, of whom 57 patients were excluded upon central review, leaving 299 (84%) for analysis, comprising 114 children (38%) and 185 young adults (62%) (for details see Appendix, available at www.aaojournal.org).

Statistical Analysis

All analyses were performed with Stata software version 13.0 (Stata Corp., College Station, TX). We used the Fisher exact test and nonparametric test for trend to compare unordered and singly ordered contingency tables, respectively, and the Mann–Whitney *U* test to compare continuous variables between groups. All tests were 2-tailed, and $P < 0.05$ was taken as statistically significant unless otherwise specified. Statistics other than those related to our 3 predetermined hypotheses should be regarded as exploratory. The percentage of females was compared using the binomial test against the expected percentage, taken from the World Population Prospects of the United Nations for the participating countries,[27] and averaged for the observed years of diagnosis.

Survival was calculated from the date of diagnosis to death. We based univariate analysis on the Kaplan-Meier product-limit method and log-rank test or test for trend. The small number of deaths in many subcategories did not allow a separate analysis in children and young adults. Multivariate analysis was based on Cox proportional hazards regression. Independent variables are allowed in the model if $P < 0.10$, and models are compared with the likelihood ratio test.[28] We restricted the number of variables in models to 3, based on a rule to have at least 15 to 20 events per each additional variable (we observed 35 melanoma deaths).[29] We verified the assumption of proportional hazards according to Therneau and Grambsch.[30] Because only 4 patients died of causes other than UM, we did not perform a separate competing risk analysis.

Results

Characteristics of Primary Tumors

The median age of the 114 children was 15.1 years (range, 2.7−17.9 years) and that of the 185 young adults was 21.9 years. The cumulative frequency of having a CCBM diagnosed increased by a mean of 0.8% per year of age between ages 5 and 10 years and, after a 6-year transition from 11 to 16 years, by a mean of 8.8% per year between 17 and 24 years of age (Fig 1). Of children and young adults, 65 (57%) and 116 (63%) were female, respectively (Table 1). This percentage tended to be higher than expected (estimate, 51%) among children ($P = 0.053$, 1-tailed binomial test) and was significantly higher than expected among young adults ($P = 0.0001$). Of 268 participants (90%) with a known preexisting condition, 2 children (1.9%; 12 and 14 years of age) and 7 young adults (4.3%) had congenital oculo(dermal) melanocytosis, whereas 2 children (1.9%; 11 and 12 years of age) and 1 young adult (0.6%) had neurofibromatosis (Table 1).

The median visual acuity of the tumor eye was 20/80 for children, worse than the median of 20/40 for young adults ($P = 0.005$; Table 1). Median tumor thickness (6.1 vs. 6.0 mm) and largest basal diameter (12.3 vs. 12.4 mm), respectively, were comparable (Fig 2A, available at www.aaojournal.org), as was CBI (28% vs. 33%; Table 1). Three children (3%; 12, 17, and 17 years of age; diameter 5 mm in the only known case) and 5 young adults (3%; diameter <5 mm in all 4 known cases) had extraocular extension. The median distance to the foveola was shorter in children than in young adults (1.4 vs. 3.0 mm; $P = 0.040$), whereas the median distance to the disc was comparable (2.5 vs. 3.5 mm, respectively; $P = 0.23$, Table 1; Fig 2B, available at www.aaojournal.org).

The tumor could be staged in 281 participants (94%), and the TNM size categories and stages showed comparable distributions among children and young adults (Table 1): T1 in 27% versus 25%, T2 in 23% versus 34%, T3 in 29% versus 29%, and T4 in 21% versus 12%, respectively ($P = 0.27$, nonparametric test for trend); and stage I in 22% versus 21%, stage II in 49% versus 52%, and stage III in 30% versus 28%, respectively ($P = 0.85$).

Primary Treatment

Three children (3%) were treated with laser (Table 2). Radiotherapy alone was delivered to 72 children (63%) versus 125 young adults (68%), and 42 children (37%) versus 57 young adults (31%) underwent surgical treatment with or without adjuvant radiotherapy.

Histopathologic Characteristics

Cell type was known for 39 children (34%) and 67 young adults (36%), corresponding to 82 of 99 patients (83%) treated surgically and to 24 of 200 patients (12%) managed conservatively who underwent a biopsy. The thickness ($P = 0.99$, Mann−Whitney U test), largest basal diameter ($P = 0.37$), TNM category ($P = 0.86$, nonparametric test for trend), and TNM stage ($P = 0.25$) of these tumors were comparable for children and young adults. The percentages of spindle-cell, mixed cell, and epithelioid cell melanomas were similar for both groups ($P = 0.93$; Table 2).

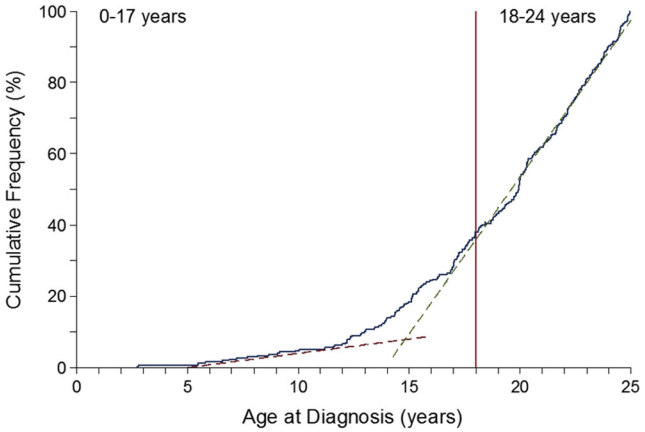

Figure 1. Cumulative frequency distribution plot of age at diagnosis for 114 children younger than 18 years and 185 young adults 18 to 24 years of age with choroidal and ciliary body melanoma. Note an initial period of a slower (dashed red line) and later faster (dashed green line) steady increase with a gradual transition occurring between 11 and 17 years of age.

Cytogenetic Characteristics

Cytogenetic results were available for 15 children (13%) and 25 young adults (14%; for details, see the Appendix, available at www.aaojournal.org). Monosomy 3 was found in 8 children (53%; 11−17 years of age) and 6 young adults (24%; $P = 0.089$, Fisher exact test), of whom one half in both groups had an additional 8q gain (Table 2). Five children and 5 young adults had been screened for somatic *BAP1* mutations. One patient in both groups showed positive results.

Local Tumor Control

The median follow-up time was 5.9 years (range, 1.4−31.1 years; interquartile range, 3.1−10.6 years) for 35 patients who died of melanoma, 5.5 years (range, 1 day−41.3 years; interquartile range, 2.2−11.9 years) for survivors, and 6.6 years (range, 1 day−41.3 years) for children versus 5.1 years (range, 3 days−37 years) for young adults ($P = 0.12$; Table 2).

Local tumor recurrence was diagnosed in 7 children (6%; 10−17 years of age) and 9 young adults (5%; Table 2). Kaplan-Meier estimates of the cumulative proportion with local tumor recurrence were comparable ($P = 0.79$, log-rank test; Fig 3, available at www.aaojournal.org). The median visual acuity at the last visit was counting fingers (Table 2; Appendix, available at www.aaojournal.org).

Univariate Survival Outcome

By the end of the follow-up, 8 children (7%) versus 27 young adults (15%) had died of metastatic UM, and 1 patient (1%) versus 4 patients (2%), respectively, were alive with metastases a median of 4.8 months (range, 1 week−10.7 years) after diagnosis of dissemination. In children, these primary tumors that metastasized were diagnosed at a median age of 14 years (range, 11−17 years). One young adult died of a second cancer (adenocarcinoma of the

Table 1. Patient and Tumor Characteristics for 114 Children Younger than 18 Years and 185 Young Adults 18 to 24 Years of Age with Choroidal and Ciliary Body Melanoma

Characteristic	Young Adults (18–25 yrs, n = 185)	Children (1–17 yrs, n = 114)	P Value	Children		
				1–10 yrs (n = 15)	*11-17 yrs (n = 99)*	*P Value*
Median age, y (range)	21.9 (18–24.9)	15.1 (2.7–17.9)	N/A	7.2 (2.7-10)	15.4 (11.1–17.9)	N/A
Gender, no. (%)			0.33*			0.58*
Male	69 (37)	49 (43)		5 (33)	44 (44)	
Female	116 (63)	65 (57)		1 (67)	55 (56)	
Predisposing factors, no. (%)						
Melanocytosis	7 (4.3)	2 (1.9)	0.21*	0 (0)	2 (2)	0.70*
Neurofibromatosis	1 (0.6)	2 (1.9)	0.13*	0 (0)	2 (2)	0.69*
Initial visual acuity, no. (%)			0.005†			0.56†
20/20	46 (26)	16 (14)		3 (20)	13 (13)	
20/25–20/40	50 (28)	29 (26)		4 (27)	25 (26)	
20/50–20/200	45 (25)	32 (28)		4 (27)	28 (29)	
CF–LP	31 (17)	25 (22)		2 (13)	23 (23)	
NLP	7 (4)	11 (10)		2 (13)	9 (9)	
Median IOP, mmHg (range)	14 (8–59)	14 (7–59)	0.27‡	7 (3–10)	15 (11–18)	0.20‡
IOP, no. (%)						
Normal	125 (90)	83 (93)	0.48*	9 (82)	74 (95)	0.16*
High	14 (10)	6 (7)		2 (18)	4 (5)	
Median thickness, mm (range)	6.0 (0.8–16.9)	6.1 (0.9–20)	0.69‡	7.2 (2.0–14.5)	6 (0.9–20.0)	0.54‡
Median LBD, mm (range)	12.4 (3.0–24.4)	12.3 (2.0–24.3)	0.76‡	12.4 (3.1–24)	12.2 (2.0–24.3)	0.63‡
Median distance to fovea, mm (range)	3.0 (0–25)	1.4 (0–22)	0.040‡	2.0 (0–10.5)	1.4 (0–22)	0.92‡
Median distance to disc, mm (range)	3.5 (0–22)	2.5 (0–24)	0.23‡	1.25 (0–10.5)	3.0 (0–24)	0.20‡
Ciliary body involvement, no. (%)			0.44*			0.76*
Yes	60 (33)	31 (28)		5 (33)	26 (27)	
No	124 (67)	81 (72)		10 (67)	71 (73)	
Extraocular extension, no. (%)			0.99*			0.99*
Yes	5 (3)	3 (3)		0 (0)	3 (3)	
No	179 (97)	110 (97)		15 (100)	110 (97)	
TNM category, no. (%)			N/A			N/A
T1a	37 (20)	25 (22)		5 (33)	20 (20)	
T1b	7 (4)	7 (6)		2 (13)	5 (5)	
T2a	50 (27)	21 (18)		0 (0)	21 (22)	
T2b	9 (5)	3 (3)		0 (0)	3 (3)	
T2d	1 (0.5)	1 (1)		0 (0)	1 (1)	
T3a	24 (13)	22 (19)		4 (27)	18 (18)	
T3b	24 (13)	8 (7)		1 (7)	7 (7)	
T3c	1 (0.5)	1 (1)		0 (0)	1 (1)	
T3d	1 (0.5)	0 (0)		0 (0)	0 (0)	
T4a	6 (3)	11 (10)		1 (7)	10 (10)	
T4b	14 (8)	10 (9)		2 (13)	8 (8)	
T4d	1 (0.5)	1 (1)		0 (0)	1 (1)	
Unknown	10 (5)	4 (3)		0 (0)	4 (4)	
TNM stage, no. (%)			0.98†			0.46†
I	37 (20)	25 (22)		5 (33)	20 (20)	
IIA	57 (31)	28 (25)		2 (13)	26 (26)	
IIB	33 (18)	25 (22)		4 (28)	21 (21)	
IIIA	32 (17)	21 (18)		2 (13)	19 (19)	
IIIB	15 (8)	10 (9)		2 (13)	8 (8)	
IIIC	1 (0.5)	1 (1)		0 (0)	1 (1)	
Unknown	10 (5.5)	4 (3)		0 (0)	4 (4)	

CF = counting fingers; IOP = intraocular pressure; LBD = largest basal diameter; LP = light perception; N/A = not applicable or meaningful; NLP = no light perception; TNM = tumor-node-metastasis.
*Two-tailed Fisher exact test.
†Two-tailed nonparametric test for trend.
‡Two-tailed Mann–Whitney *U* test.

colon, Dukes B, pT3), 2 young adults died of nonneoplastic disease, and 1 young adult died of unknown causes.

Based on all-cause mortality, survival was 97% versus 89% at 5 years and 91% versus 78% at 10 years for children versus young adults ($P = 0.0034$; Fig 4A, available at www.aaojournal.org). By Kaplan-Meier analysis, survival based on melanoma-related mortality was 97% (95% confidence interval [CI], 90%–99%) at 5 years and 92% (95% CI, 81%–97%) at 10 years for children versus 90% (95% CI, 84%–94%) and 80% (95% CI, 71%–87%) for young adults (Fig 5A; $P = 0.013$, log-rank test). For children 1 to 10 years of age versus 11 to 17 years of age at diagnosis, the proportions were 100% at 5 and 10 years versus 97% (95% CI,

Table 2. Posttreatment Patient and Tumor Characteristics for 114 Children Younger than 18 Years and 185 Young Adults 18 to 24 Years of Age with Choroidal and Ciliary Body Melanoma

Characteristic	Young Adults 18–25 yrs (n = 185)	Children 1–17 yrs (n = 114)	P Value	Children		
				1–10 yrs (n = 15)	*11–17 yrs (n = 99)*	*P Value*
Primary treatment type, no. (%)			N/A			N/A
Laser						
Transpupillary thermotherapy	2 (1)	0 (0)		0 (0)	0 (0)	
Photodynamic therapy	1 (0.5)	0 (0)		0 (0)	0 (0)	
Radiotherapy						
Proton beam	67 (36)	39 (34)		4 (27)	35 (36)	
Iodine plaque	21 (11)	10 (9)		0 (0)	10 (10)	
Ruthenium plaque	35 (19)	21 (18)		1 (7)	20 (20)	
Stereotactic	1 (0.5)	0 (0)		0 (0)	0 (0)	
Gamma knife	1 (0.5)	2 (2)		1 (7)	1 (1)	
Surgery						
Enucleation	38 (20.5)	26 (23)		7 (46)	19 (19)	
Local resection	17 (9)	13 (11)		2 (13)	11 (11)	
Combined: enucleation + EBT	1 (0.5)	3 (3)		0 (0)	3 (3)	
Combined: resection + gamma knife	1 (0.5)	0 (0)		0 (0)	0 (0)	
Cell type, no. (%)			0.93*			0.78*
Epithelioid	11 (17)	7 (18)		1 (14)	6 (19)	
Spindle	33 (49)	20 (51)		3 (43)	17 (53)	
Mixed	23 (34)	12 (31)		3 (43)	9 (28)	
Chromosomal abnormality, no. (%)			0.069*			0.025*
No abnormality	19 (76)	7 (46)		4 (100)	3 (28)	
Monosomy 3	3 (12)	4 (27)		0 (0)	4 (36)	
Monosomy 3 with 8q gain	3 (12)	4 (27)		0 (0)	4 (36)	
Somatic *BAP1* mutation, no. (%)			0.65†			0.51†
Yes	1 (25)	1 (25)		0 (0)	1 (25)	
No	4 (75)	4 (75)		1 (100)	3 (75)	
Median follow-up, yrs (range)	5.1 (0–37)	6.6 (0–41.3)	0.12‡	7.2 (2.7–10)	15.4 (11.2–18)	0.53‡
Local tumor recurrence, no. (%)			0.79†			0.99†
Yes	9 (5)	7 (6)		1 (7)	6 (6)	
No	177 (95)	107 (94)		14 (93)	93 (94)	
Median local recurrence time, yrs (range)	2.3 (1.2–20)	6.6 (1.4–12)	0.35‡	1.3	6.8 (2.8–12)	0.13‡
Final visual acuity, no. (%)			0.087*			0.45*
20/20	23 (15)	8 (8)		0 (0)	8 (9)	
20/25–20/40	26 (17)	11 (12)		1 (11)	10 (12)	
20/50–20/200	28 (19)	17 (18)		3 (33)	14 (17)	
CF–LP	35 (23)	29 (31)		1 (11)	28 (33)	
NLP or enucleated	39 (26)	29 (31)		4 (45)	25 (29)	
Median final IOP (mmHg)	14 (2–50)	13 (1–28)	0.13‡	7.2 (2.7–10)	15.4 (11.2–18)	0.89‡
Final IOP, no. (%)			0.99†			0.99†
Normal	97 (95)	60 (95)		5 (100)	55 (95)	
High	5 (5)	3 (5)		0 (0)	3 (5)	
Survival status, no. (%)			N/A			N/A
Alive	150 (81)	105 (92)		15 (100)	90 (91)	
Alive with metastasis	4 (2)	1 (0.9)		0 (0)	1 (1)	
Dead from metastasis	27 (15)	8 (7)		0 (0)	8 (8)	
Dead from other cancer	1 (0.5)	0 (0)		0 (0)	0 (0)	
Dead from other causes	2 (1)	0 (0)		0 (0)	0 (0)	
Dead from unknown cause	1 (0.5)	0 (0)		0 (0)	0 (0)	

CF = counting fingers; EBT = external beam radiotherapy; IOP = intraocular pressure; LP = light perception; N/A = not applicable or meaningful; NLP = no light perception.
*Two-tailed nonparametric test for trend.
†Two-tailed Fisher exact test.
‡Two-tailed Mann–Whitney *U* test.

88%–99%) at 5 years and 91% (95% CI, 79%–96%) at 10 years, respectively ($P = 0.002$; Fig 4B, available at www.aaojournal.org).

Nine of 65 female children and 1 of 49 male children died of metastases, and males tended to have a more favorable 10-year survival compared with females (100% vs. 85%; $P = 0.058$; Fig 4C, available at www.aaojournal.org). No such difference was observed in young adults (81% vs. 80%; $P = 0.75$; Fig 4D, available at www.aaojournal.org) and when combining both groups (90% vs. 82%; $P = 0.16$; Fig 5B). Survival was associated with oculo(dermal) melanocytosis; 3 of 9 affected patients died ($P = 0.0016$; Fig 5C). Too few patients had neurofibromatosis to allow analysis. Combining both age groups, the 10-year survival

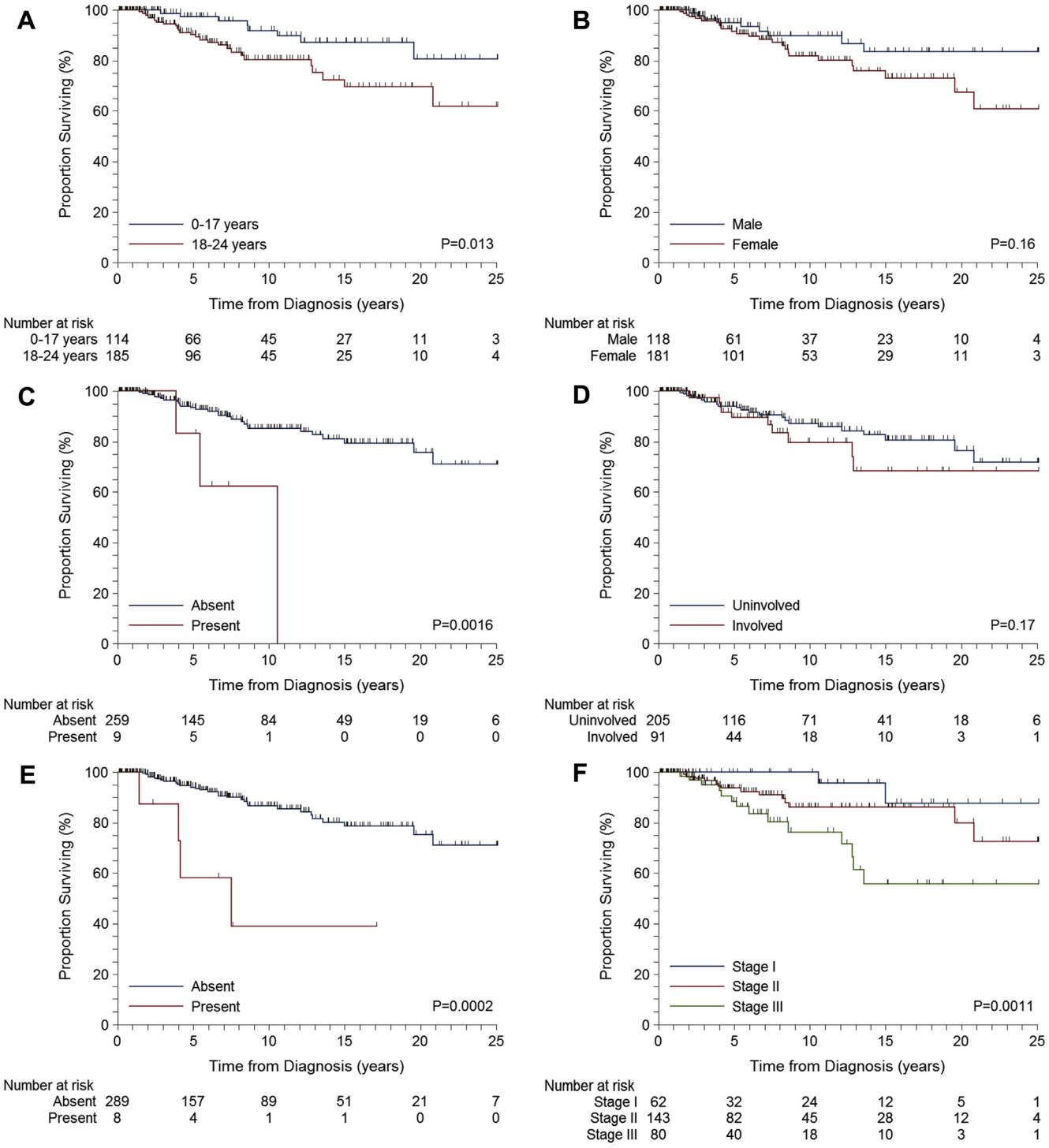

Figure 5. Kaplan-Meier estimates of melanoma-related mortality among 114 children younger than 18 years and 185 young adults 18 to 24 years of age with choroidal and ciliary body melanoma according to (**A**) age group, (**B**) gender, (**C**) presence of congenital oculo(dermal) melanocytosis, (**D**) ciliary body involvement, (**E**) extraocular extension, and (**F**) tumor-node-metastasis stage. Ticks show censored observations, and numbers below graphs represent patients at risk; (**A**–**E**) log-rank test and (**F**) test for trend. Three young adults died of other causes and 1 died of an unknown cause; all were censored. One further melanoma death occurred at 31 years of follow-up (age, 18–24 years; male; no ocular melanocytosis; ciliary body involved; no extraocular extension; stage III).

of young patients did not differ by CBI (87% for not involved vs. 80% for involved; $P = 0.17$; Fig 5D), whereas extraocular extension predicted a significantly worse survival; 4 of 8 patients died (87% for no extension vs. 39% for extension; $P = 0.0002$; Fig 5E).

TNM stage showed a trend with survival among children (stage I vs. stage II vs. stage III; 100% vs. 96% vs. 82%, respectively, at 10 years; $P = 0.091$, log-rank test for trend; Fig 4E, available at www.aaojournal.org) and was associated strongly with survival

both in young adults (100% vs. 80% vs. 73%, respectively; $P = 0.0043$; Fig 4F, available at www.aaojournal.org) and when both groups were combined (100% vs. 86% vs. 76%, respectively; $P = 0.0011$; Fig 5F).

Cell type was not associated with survival (78% vs. 80% vs. 72% for spindle-cell, mixed cell, and epithelioid cell melanomas, respectively; $P = 0.93$, log-rank test for trend; Fig 4G, available at www.aaojournal.org). Of the 8 children with monosomy 3, 1 died of metastasis 4.2 years after diagnosis, 1 is alive with metastasis at 2.2 years (both had an additional 8q gain), and 6 survive without metastases after a median follow-up of 2.2 years (range, 1 day–4.3 years; 2 with 8q gain), whereas of the 6 young adults, 1 (with 8q gain) died of an unknown cause and 5 survive after a median follow-up of 1.2 years (range, 3 days–21 years; 2 with 8q gain). None of the 26 patients with disomy 3 so far have demonstrated metastases (median follow-up, 3.8 years; range, 0.5–13 years; Fig 4H, available at www.aaojournal.org).

Multivariate Survival Outcome

Univariate Cox regression confirmed the associations between survival and age group (hazard rate [HR], 2.64), congenital melanocytosis, extraocular extension, and TNM stage (Table 3, available at www.aaojournal.org). Of bivariate models that combined TNM stage with age group (HR, 2.66), melanocytosis (HR, 16.6), or gender (HR, 2.46; an independent predictor when combined with TNM stage), the one including melanocytosis fit best to our data (likelihood ratio test, 268.23 vs. 232.60, chi-square test with 1 degree of freedom; $P < 0.0001$). However, because melanocytosis was associated with only 3 deaths, this model is easy to fit, but may not be reproducible.

We propose a trivariate model that combines TNM stage with age group (HR, 2.57) and gender (HR, 2.38; Table 4). The latter 2 variables are independent predictors of survival, and the model is preferred to the bivariate ones that include either of them (likelihood ratio test, 268.23 vs. 263.58, chi-square test with 1 degree of freedom; $P = 0.031$). Alternative trivariate models with congenital melanocytosis and age or gender are shown in Table 3 (available at www.aaojournal.org).

Table 4. Final Preferred Cox Proportional Hazards Multivariate Regression Model of Survival for 114 Children Younger than 18 Years and 185 Young Adults 18 to 24 Years of Age with Choroidal and Ciliary Body Melanoma

Characteristic	Chi-Square	P Value	Hazard Rate (95% Confidence Interval)
TNM stage*			
Stage I (reference)			1.00
Stage II	1.96	0.16	2.88 (0.65–12.7)
Stage III	7.84	0.005	8.38 (1.89–37.1)
Age group†	4.71	0.030	2.57 (1.09–6.01)
Gender‡	4.26	0.041	2.38 (1.04–5.48)

TNM = tumor-node-metastasis.
Trivariate analysis. Final preferred model: −2 log likelihood = 263.58.
*Categories: stage I = 0, stage II = 1, stage III = 2.
†Categories: age 0–17 years = 0, age 18–24 years = 1.
‡Categories: male = 0, female = 1.

Discussion

In our collaborative study, 52% of children younger than 18 years with CCBM came from the oldest (abortive) 5-year cohort of 15 to 17 years of age; 41% were 10 to 14 years of age, 11% were 5 to 9 years of age, and only 2% were younger than 5 years. A recent referral-based single-center series of 122 young patients (25% with iris melanomas) reported essentially identical percentages of 50%, 43%, 11%, and 3%.[19] Our novel observation is that the cumulative frequency of having CCBM diagnosed increased steadily but slowly until 11 years of age, at which point a transition to a more than 10-times faster increase after 17 years of age took place, and 90% of CCBM in children were diagnosed during this transition period. A similar transition is known to occur again between 40 and 45 years of age.[31] Taken together, observations suggest the existence of 3 periods of development of CCBM that may reflect age-dependent differences in initiation and progression of CCBM.

We had strong evidence of a higher percentage of females compared with males among young adults younger than 25 years. We believe this to be true also among children, in line with the prior meta-analysis[18] and most series,[13,15,18,21,23] but even our study was not large enough to confirm this ($P = 0.053$). The reasons for the gender difference in young patients are unclear.

Preexisting conditions predisposing to the development of CCBM were infrequent. Nevertheless, congenital oculo(dermal) melanocytosis that is estimated to affect 0.04% of white persons[32] was present in 1.9% of children and 4.3% of young adults, percentages that were 47 and 107 times higher, respectively, than the general population frequency. These percentages were of the same order of magnitude as the 3% reported in the single-center series of 122 patients younger than 20 years of age.[19] Neurofibromatosis type 1, also reported to be associated with UM,[33–35] was present in 1.9% of children in our series, but was rare among young adults. Recently, a germline *BAP1* mutation was found in 1 of 3 young adults younger than 25 years with a CCBM, but in neither of 2 children younger than 18 years.[36] An affected 16-year old patient is on record, however.[37]

The primary CCBM was equally advanced in children and young adults. A smaller tumor thickness in children compared with young adults in the previous meta-analysis thus was likely the result of chance.[18] As was the case with anatomic extent, the groups were comparable with regard to cell type. Cytogenetic analysis was available for a small but equal percentage of children and young adults. Monosomy 3 tended to be more frequent among children, but none of them were younger than 10 years, consistent with a hypothesis of 2 distinct periods of development of pediatric CCBM, the first one ending when the transition period in cumulative incidence begins.

Our main hypothesis was that children have a favorable survival prognosis compared with young adults. The 10-year survival percentages were 92% and 80%, respectively, with a 12 percentage points difference, and Kaplan-Meier analysis led us to reject the null hypothesis of similar survival. Local recurrence was equally frequent and unlikely to lead to the survival difference between the

groups, which also was maintained in multivariate analyses. The single-center series of 122 patients 20 years of age or younger also found a proportion of 91% surviving at 10 years.[18] None of our 15 patients diagnosed before the age of 10 years so far have demonstrated metastases, again supporting our hypothesis of distinct periods of development of pediatric CCBM.

Regarding our second hypothesis that males have a better survival prognosis than females, we could not discard the null hypothesis of similar survival after univariate analysis. However, gender became an independent predictor of survival when we adjusted for TNM stage, age group, or both. Notably among children, 8 females but only 1 male demonstrated metastases, and females tended to have a worse survival than males (85% vs. 100% at 10 years, the percentages we had postulated for both groups combined). However, the worse survival of girls began after 10 years of age, coinciding with the transition period in the cumulative frequency plot. Age and gender thus interact with regard to survival. Our third hypothesis that CBI would translate to worse life prognosis of young patients with CCBM clearly was not substantiated.

Additionally, we confirmed that TNM stage is a predictor of survival among young patients with CCBM.[18] This finding recently was supported by a single-center study of 43 patients 20 years of age or younger that reported metastasis only in TNM size categories T4 (very large) and T3 (large).[14] We observed metastatic death in this age group also from 6 T2 (medium-sized) CCBMs (in 1 child and 5 young adults) and 1 T1 (small) CCBM (in 1 child), but the latter, along with another T1 melanoma in a young adult, metastasized more than 10 years after diagnosis. The stage-specific 10-year survival proportions of 100%, 96%, and 82% for children and 100%, 80%, and 72% for young adults suggest a better-than-average survival in both groups compared with that of 5403 patients with a CCBM across all ages, reported to be 88%, 75%, and 30%, respectively.[26]

We also were able to confirm that congenital melanocytosis is associated with increased mortality from CCBM. In a recent study of 7872 patients, the risk of metastasis was 1.9 to 2.8 times higher for those 230 patients who had melanocytosis, depending on its extent.[38] In our study, the risk was 5.6 times higher in young patients and even higher by multivariate analysis.

Our preliminary data on monosomy 3 support the observation that monosomy 3 with 8q gain predicts the highest risk for metastasis and disomy 3 predicts the lowest risk for metastasis[39–42] also in young patients with CCBM. In contrast, cell type was unassociated with survival, although twice as many non–spindle-cell (mixed or epithelioid) than spindle-cell melanomas showed monosomy 3.

In summary, children younger than 18 years with CCBM have a more favorable life prognosis than young adults 18 to 24 years of age, and TNM stage and gender are additional independent predictors of survival in young patients. We propose a hypothesis that the biology of CCBM may differ between children 10 years of age or younger and those older than 10 years at the time of diagnosis, based on our evidence of a lower incidence of CCBM and the apparent rarity of both monosomy 3 and metastasis in the younger of these age groups.

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[1] Ocular Oncology Service, Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.

[2] Department of Ophthalmology, Institute Curie, Paris, France.

[3] Ocular Oncology Service, Royal Liverpool University Hospital, Liverpool, United Kingdom.

[4] Department of Cellular Pathology, Royal Liverpool University Hospital, Liverpool, United Kingdom.

[5] Department of Ophthalmology, University of Lausanne, Jules-Gonin Eye Hospital, Fondation Asile des Aveugles (FAA), Lausanne, Switzerland.

[6] Department of Ocular Oncology, Princess Margaret Hospital, University of Toronto, Toronto, Canada.

[7] Department of Ophthalmology and Ocular Oncology, Jagiellonian University, Collegium Medicum, Krakow, Poland.

[8] Department of Ophthalmology, Faculty of Medicine, University Duisburg-Essen, Essen, Germany.

[9] Ocular Oncology Service, Department of Ophthalmology, Hacettepe University School of Medicine, Ankara, Turkey.

[10] Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands.

[11] Department of Ophthalmic Oncology, St. Erik's Eye Hospital, Stockholm, Sweden.

[12] Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.

[13] Department of Ophthalmology, Royal Hallamshire Hospital, Sheffield, United Kingdom.

[14] Department of Ophthalmology, Poznán University of Medical Sciences, Poznán, Poland.

[15] Department of Ophthalmology, Copenhagen University Hospital Glostrup, Copenhagen, Denmark.

[16] Ocular Oncology Service, St Bartholomew's and Moorfields Eye Hospital, London, United Kingdom.

[17] Department of Ophthalmic Oncology and Radiology, Helmholtz Institute, Moscow, Russia.

[18] Department of Ophthalmology, Oslo University Hospital-HF and University of Oslo, Oslo, Norway.

[19] Department of Clinical Medicine, Section of Ophthalmology, University of Bergen, Bergen, Norway.

[20] Department of Ophthalmology, University of Padova, Padova, Italy.

[21] G. B. Bietti Foundation, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Ocular Oncology and Toxicology Research Unit, Rome, Italy.

[22] Department of Ophthalmology, Croix-Rousse Hospital, Lyon, France.

[23] Department of Ophthalmology, Erasmus University Medical Center, Rotterdam, The Netherlands.

[24] Department of Ophthalmology, Catholic University of Rome, Rome, Italy.

[25] Department of Ophthalmology, Ocular Oncology Unit, Valladolid University Hospital, Valladolid, Spain.

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Author Contributions:

Conception and design: Al-Jamal, Cassoux, Desjardins, Kivelä

Analysis and interpretation: Al-Jamal, Cassoux, Desjardins, Damato, Konstantinidis, Coupland, Heimann, Petrovic, Pe'er, Salvi, Rennie, Rospond-Kubiak, Kociecki, Folke Kiilgaard, Heegaard, Cohen, Kilic, Blasi, Saornil, Kivelä, Sagoo, Amiryan, Saakyan, Eide, Krohn, Midena, Parrozzani, Grange, Schalenbourg

Data collection: Al-Jamal, Cassoux, Desjardins, Damato, Konstantinidis, Coupland, Heimann, Petrovic, Zografos, Velazquez-Martin, Krema, Bogdali, Markiewicz, Romanowska-Dixon, Metz, Biewald, Bornfeld, Kiratli, Bronkhorst, Jager, Marinkovic, Fili, Seregard, Frenkel, Pe'er, Salvi, Rennie, Rospond-Kubiak, Kociecki, Folke Kiilgaard, Heegaard, Cohen, Kilic, Blasi, Saornil, Kivelä, Sagoo, Amiryan, Saakyan, Eide, Krohn, Midena, Parrozzani, Grange, Schalenbourg

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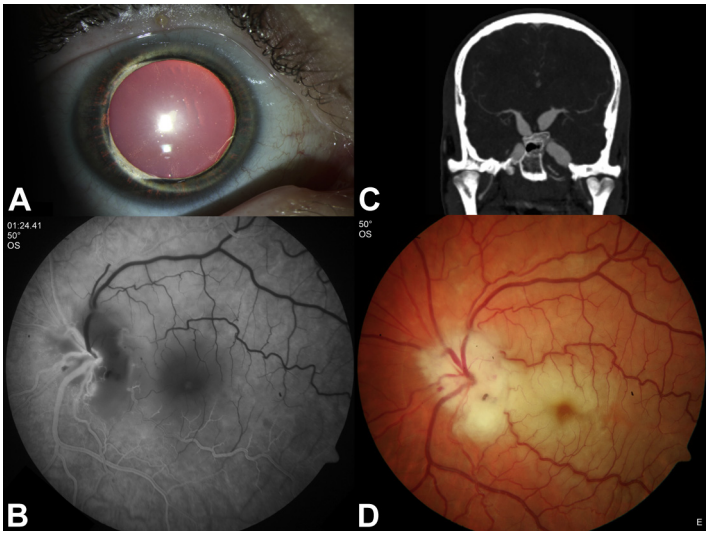
Overall responsibility: Al-Jamal, Cassoux, Desjardins, Damato, Konstantinidis, Coupland, Heimann, Petrovic, Zografos, Velazquez-Martin, Krema, Bogdali, Markiewicz, Romanowska-Dixon, Metz, Biewald, Bornfeld, Kiratli, Bronkhorst, Jager, Marinkovic, Fili, Seregard, Frenkel, Pe'er, Salvi, Rennie, Rospond-Kubiak, Kociecki, Folke Kiilgaard, Heegaard, Cohen, Kilic, Blasi, Saornil, Kivelä, Sagoo, Amiryan, Saakyan, Eide, Krohn, Midena, Parrozzani, Grange, Schalenbourg

Abbreviations and Acronyms:
CBI = ciliary body involvement; **CCBM** = choroidal and ciliary body melanoma; **CI** = confidence interval; **HR** = hazard rate; **TNM** = tumor-node-metastasis; **UM** = uveal melanoma.

Correspondence:
Rana'a T. Al-Jamal, MD, PhD, Department of Ophthalmology, Helsinki University Hospital, PL 220, Haartmaninkatu 4 C, FI-00029 HUS, Helsinki, Finland. E-mail: ranaa.aljamal@hus.fi.

Pictures & Perspectives



Central Retinal Artery Occlusion in a Teenager

A 17-year-old boy presented with recurrent headache for several weeks and sudden vision loss on the left eye to light perception. On slit lamp examination partial aniridia with transillumination was identified (Fig 1**A**). Ophthalmoscopy and angiography of the left eye revealed a central retinal artery occlusion (Fig 1**B**, **D**). Computed tomography of the cardiovascular and cerebrovascular system discovered ectasia of all major arterial vessels, including carotid and cerebral arteries (Fig 1**C**). Genetic analysis revealed a missense mutation of the ACTA2 gene, encoding for a smooth muscle isoform of α-actin. Despite anticoagulant treatment, the vision of the patient remained at light perception.

Matthias Fuest, MD
Yassin Djalali-Talab, MD
Peter Walter, MD

Department of Ophthalmology, RWTH Aachen University, Aachen, Germany