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# The Pediatric Choroidal and Ciliary Body Melanoma Study

## A Survey by the European Ophthalmic Oncology Group

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***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 $\alpha$, 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.