THE PEDIATRIC CHOROIDAL AND CILIARY BODY MELANOMA STUDY

A Survey by the European Ophthalmic Oncology Group

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Running head: Choroidal and ciliary body pediatric melanoma study

Financial Support: Grants from the Finnish Eye Foundation, Eye and Tissue Bank Foundation, Evald and Hilda Nissi Foundation, Mary and Georg C. Ehrnrooth Foundation, and Emil Aaltonen Foundation, Finland (RTA), Helsinki University Central Hospital Research Fund TYH2013316 and the Sigrid Jusélius Foundation, Helsinki, Finland (TK) and Fight for Sight, Copenhagen, Denmark (JK). The funding organizations had no role in the design or conduct of this research.

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Conflict of Interest: None of the authors has any conflicts of interest to disclose

**ABSTRACT**

***Purpose***: To collect comprehensive data on choroidal and ciliary body melanoma (CCBM) in children and validate hypotheses regarding pediatric CCBM: children <18 years, males, and those without ciliary body involvement (CBI) have more favorable survival prognosis than young adults 18–24 years old, 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) and 185 were young adults.

***Methods:*** Data were entered through a secure website and 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 ages 5 and 10 years and, after a 6-year long transition period, by 8.8% per year from age 17years. Of children and young adults, 57% and 63% were female, respectively, that exceeded the expected 51% in young adults (*P*<0.001). Cell type, known for 35% of patients, and the 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% at 5 and 92% at 10 years for children as compared to 90% and 80% for young adults (*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 (stage I-III; 100% vs. 86% vs 76%; *P*=0.011). In multivariate analysis, being a young adult (adjusted hazard rate [HR] 2.57), a higher TNM stage (HR 2.88 and 8.38 for stage II and III, respectively), and female gender (HR 2.38) independently predicted less favorable survival. CBI 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 varied by the age group.

Uveal melanoma (UM) has an annual incidence of 2-8 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, and 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 atypical multiple mole 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 (COMS) did not provide data on UM in patients under 21 years of age, who were ineligible.11 However, in a single center series of 8,033 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 6,700 to 7,100 cases of UM, this translates to about 65 young patients per year.3 The reported features of UM in the latter as compared to 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 Histo- or molecular pathological studies on UM in children have not demonstrated any differences from their adult counterparts.16,17

Two of us recently undertook a meta-analysis of 88 patients younger than 25 years of age with choroidal and ciliary body melanoma (CCBM), which suggested that female gender and higher American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) stage both adversely influence survival.18 The meta-analysis also suggested that patients younger than 18 years of age may have an excellent life prognosis, especially if the latter are male, as compared to those aged 18-24 years, 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 is available from the literature, we established the present collaborative Pediatric Choroidal and Ciliary Body Melanoma Study of the European Ophthalmic Oncology Group (OOG). Herein, we present our data obtained on children younger than 18 years of age as compared to young adults 18 to 24 years old. To the best of our knowledge, ours is the largest series to characterize CCBM in these age groups.

# Patients and Methods

## Aims of the Study

To test three 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 poor prognostic parameter.18

## Study design

For the purpose of our study, cases are defined as patients younger than 18 years of age 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 Pediatrics20 and controls are defined as adults younger than 25 years of age 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-analysis18 and because previous series on 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 of age (none with an iris melanoma),18 extracted from 6 series, and a single-center, referral-based cohort study including 86 patients younger than 20 years19 (25% had an iris melanoma):

1. Children have a better 10-year survival vs. 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 analysis (both percentages taken from the meta-analysis).
2. For children and young adults combined, males have a better 10-year survival than females (meta-analysis: 100% vs. 85%).
3. For children and young adults combined, those without CBI have a 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 and one-sided alpha 0.05) for the first comparison, which was a sample in excess to that required for the other two comparisons.

Eligible to our retrospective cohort study were all patients who had a CCBM diagnosed when younger than 25 years of age and at least the following data: birthdate, 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 non-malignant cause) determined by reviewing patient charts, registry data, histologic samples, and death certificates. Iris melanomas were ineligible. All treatment modalities 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 OOG. The data additionally acquired included presence of congenital oculo(dermal) melanocytosis or neurofibromatosis, visual acuity (VA) and intraocular pressure (IOP) at diagnosis and at last visit, thickness, largest basal diameter (LBD), CBI, extraocular extension, tumor distance from the center of the fovea and the margin of the optic disk, cell type, cytogenetics, dates of any local tumor recurrence, secondary enucleation and metastasis, and second primary malignancies. We staged the tumors according to the 7th edition of the TNM system of the AJCC.25,26

Twenty-four participating ocular oncology services submitted data anonymously through a secure survey website on 356 patients diagnosed between February 1968 and February 2014 as summarized in Supplementary Text (available at www.aaojournal.org). Upon central review, data of 57 patients were excluded, leaving 299 (84%) for analysis, divided in 114 (38%) children and 185 (62%) young adults.

## Statistical analysis

All analyses were performed with Stata (release 13.0, Stata Corp., College Station, TX). We used Fisher’s exact and nonparametric test for trend to compare unordered and singly ordered contingency tables, respectively, and Mann Whitney *U*-test to compare continuous variables between groups. All tests were two-tailed and *P*<0.05 was taken as statistically significant unless otherwise specified. Statistics other than those related to our three 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 countries27 and averaged for the observed years of diagnosis.

Survival was calculated from the date of diagnosis to death. Univariate analysis was based 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 The number of variables in models was restricted to three, based on a rule to have at least 15 to 20 events per each additional variable (35 melanoma deaths were observed).29 We verified the proportional hazards assumption according to Thernau and Grambsch.30 Because only four patients died of causes other than UM, a separate competing risks analysis was not performed.

**Results**

***Characteristics of primary tumors***

The median age of the 114 children was 15.1 years (range, 2.7-17.9) and that of the 185 young adults 21.9 years (Table 1). 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 long transition from 11 to 16 years, by a mean of 8.8% per year between ages 17 and 24 years (Fig 1).

Of children and young adults, 65 (57%) and 116 (63%) were female, respectively (Table 1). This percentage tended to be higher than the expected one (estimate, 51%) for children (*P*=0.053, binomial test, one-tailed), and was significantly higher than expected for young adults (*P*=0.0001).

Of 268 (90%) participants with known pre-existing condition, 2 (1.9%) children (age, 12 and 14 years) and 7 (4.3%) young adults had congenital oculo(dermal) melanocytosis, whereas 2 (1.9%) children (age, 11 and 12 years) and 1 (0.6%) young adult had neurofibromatosis (Table 1).

The median VA 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 LBD (12.3 vs. 12.4 mm), respectively, were comparable (Fig 2A, available at http://www.aaojournal.org) as was CBI (28% vs. 33%; Table 1). Three (3%) children (ages 12, 17 and 18 years; diameter known in one patient: 5 mm) and five (3%) young adults (diameter less than 5 mm in all 4 known cases) had extraocular extension. Tumor distance to the center of the fovea and the optic disk margin were available for 65% and 71% of the participants (Fig 2B, available at http://www.aaojournal.org). The median distance to foveola was shorter in children than young adults, 1.4 mm vs. 3.0 mm (*P*=0.040; Table 1) whereas the median distance to the disk was comparable, 2.5 mm vs. 3.5 mm, respectively (*P*=0.23).

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

## Primary treatment

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

## Histopathologic characteristics

Cell type was known for 39 (34%) children and 67 (36%) young adults, corresponding to 82 (83%) of 99 patients treated surgically and for 24 (12%) of 200 patients managed conservatively who underwent a biopsy. The thickness (*P*=0.99, Mann-Whitney *U*-test), LBD (*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, mixed and epithelioid cell melanomas were similar for both groups (*P*=0.93; Table 2).

## Cytogenetic characteristics

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

## Local tumor control

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

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

## Univariate survival outcome

By the end of the follow-up, 8 (7%) children vs. 27 (15%) young adults had died of metastatic UM and 1 (1%) vs. 4 (2%) patients, respectively, were alive with metastases a median of 4.8 months after diagnosis of dissemination (range, 1 week to 10.7 years). In children, these primary tumors that metastasized were diagnosed at the median age of 14 years (range, 11 to 17). One young adult died of a second cancer (adenocarcinoma of the colon, Dukes B, pT3), two of non-neoplastic disease, and one of unknown causes.

Based on all-cause mortality, survival was 97% vs. 89% at 5 years and 91% vs. 78% at 10 years for children vs. young adults (*P=*0.0034; Supplementary Fig 4A). By Kaplan-Meier analysis, survival based on melanoma-related mortality was 97% (95% CI, 90-99) at 5 and 92% (95% CI, 81-97) at 10 years for children vs. 90% (95% CI, 84-94) and 80% (95% CI, 71-87) for young adults (Fig 5A; *P*=0.013, log-rank test). For children 1-10 years vs. 11-17 years at diagnosis, the proportions were 100% at 5 and 10 years vs. 97% (95% CI, 88-99) at 5 years and 91% (95% CI, 79-96%) at 10 years, respectively (*P*=0.002; Supplementary Fig 4B, available at www.aaojournal.org).

Nine of 65 female and one of 49 male children died of metastases, and males tended to have a more favorable 10-year survival as compared to females (100% vs. 85%; *P=*0.058; Supplementary Fig 4C). No such difference was observed in young adults (81% vs. 80%; *P*=0.75; Supplementary Fig 4D) 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 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 (I vs. II vs. III) showed a trend with survival among children (100% vs. 96% vs 82% at 10 years; *P*=0.091, log-rank test for trend; Supplementary Fig 4E) and was strongly associated with survival both in young adults (100% vs. 80% vs. 73%; *P*=0.0043; Supplementary Fig 4F) and when both groups were combined (100% vs. 86% vs. 76%; *P*=0.0011; Fig 5F).

Cell type was not associated with survival (78% vs. 80% vs. 72% for spindle, mixed and epithelioid cell melanomas, respectively; *P*=0.93, log-rank test for trend; Supplementary Fig.4G).

Of the 8 children with monosomy 3, one died of metastasis 4.2 years after diagnosis, one 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 to 4.3 years; 2 with 8q gain) whereas of the 6 young adults, one (with 8q gain) died of an unknown cause, and 5 survive after a median follow-up of 1.2 years (range, 3 days to 21 years, 2 with 8q gain). None of the 26 patients with disomy 3 have so far developed metastases (median follow-up, 3.8 years; range, 0.5-13; Supplementary Fig.4H).

***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 (Supplemental 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 fitted best to our data (likelihood ratio test, 268.23 vs. 232.60, chi-square, 1 *df*, *P*<0.0001). However, because melanocytosis was associated with only three deaths, this model is easy to fit but might not be reproducible.

We prefer a trivariate model that combines TNM stage with age group (HR 2.57) and gender (HR 2.38; Table 4). The latter two 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, 1 *df*; *P*=0.031). Alternative trivariate models with congenital melanocytosis and age or gender are shown in Supplemental Table 3 (available at www.aaojournal.org).**Discussion**

In our collaborative study, 52% of children younger than 18 years with CCBM came from the oldest (abortive) 5-year cohort of 15-17 years; 41% were 10-14 years old, 11% were 5-9 years old, and only 2% less than 5 years old. A recent referral-based, single-center series of 122 young patients (with 25% 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 age 11 years at which point a transition to 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 again known to occur between the ages of 40 and 45 years.31 Taken together, observations suggest the existence of three periods of development of CCBM that might reflect age-dependent differences in initiation and progression of CCBM.

We had strong evidence of a higher percentage of females as compared to males among young adults less than 25 years old. We believe this to be true also among children, in line with the prior meta-analysis18 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 disparity in young patients are unclear.

Pre-existing conditions predisposing to development of CM were infrequent. Nevertheless, congenital oculo(dermal) melanocytosis that is estimated to affect 0.04% of white Caucasians,32 was present in 1.9% of children and 4.3% of young adults, percentages that were 47 and 107 times higher than the general population frequency. These percentages were of the same order of magnitude, however, than 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 rare among young adults. Recently, a germline *BAP1* mutation was found in 1 of 3 young adults less than 25 years old with a CCBM, but in neither of two children younger than 18 years.36 A case of a 16-year old patient in known, however.

The primary CCBM was equally advanced in children and young adults. A smaller tumor thickness in children as compared to young adults in the previous meta-analysis was thus likely due to chance.18 As was the case with anatomic extent, the groups were comparable as regards 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 of age, consistent with the possibility of distinct periods of tumor development, the first corresponding to the time before the transition period in cumulative incidence begins.

Our primary hypothesis was that children have a more favorable survival prognosis as compared to young adults. The 10-year survival percentages were 92% for children and 80% for young adults, with a 12 percent point difference, and Kaplan-Meier analysis led us to reject the null hypothesis of similar survival. The frequency of local recurrence was very similar and thus unlikely to lead to a survival difference between these two groups, which also was maintained in multivariate analyses. The single-center series of 122 patients 20 years of age or younger also found a survival proportion of 91% at 10 years.18 However, as mentioned, iris melanomas that generally have a favorable life prognosis constituted 25% patients in the latter series. None of our 15 patients who were diagnosed before the transition period in cumulative frequency have so far developed metastases, again supporting the possibility of distinct periods of tumor development.

Regarding our second hypothesis that males have a better survival prognosis than females, we could not discard the null hypothesis of similar survival by Univariate analysis. This was because no difference existed among young adults. However, eight female but only one male child developed metastases, and in this group boys tended to have a more favorable survival than females (100% vs. 85% at 10 years, the percentages we had postulated for both groups combined). Because metastatic deaths were infrequent in children, we did not have the statistical power to either confirm or discard this subgroup difference as a real one (*P*=0.058). Interestingly, the worse survival of girls was confined to those older than 10 years, the transition period in the cumulative frequency plot. Moreover, gender became an independent predictor of survival once adjusting for TNM stage by multivariate analysis. Our third hypothesis that CBI would translate to worse life prognosis of young patients with CCBM was clearly not substantiated.

Additionally, we confirmed the previous meta-analysis in that the TNM stage is a highly significant predictor of survival among young patients with CCBM.18 This finding was recently supported by a single-center study of 43 patients who were 20 years or younger (in whom 21% of tumors involved the iris) 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 six T2 (medium-sized, five were young adults) and one T1 (small, in a child) CCBM, but the latter and another one in an older young adult metastasized more than 10 years after diagnosis. Stage-specific 10-year survival proportions of 100%, 96% and 82% for children and 100%, 80% and 72% for young adults also suggest a better than average survival experience in young patients as compared to 5,403 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 7,872 patients, the risk of metastasis was 1.9-2.8 times higher for those 230 who had melanocytosis, depending on its extent.37 In our study, the risk was 5.6 times higher in young patients and also maintained in multivariate analysis. Previous series of CCBM in children have not reported this association, probably because they were too small.

Our preliminary data on monosomy 3 support the observation that monosomy 3 with 8q gain predicts the highest and disomy 3 the lowest risk for metastasis38-42 also in young patients with CCBM. In contrast, cell type was unassociated with survival, despite the fact that twice as many nonspindle (mixed or epithelioid) than spindle cell melanomas showed monosomy 3.

In summary, we found that children younger than 18 years with CCBM have a more favorable life prognosis than young adults aged 18 to 24 years (adjusted HR 2.6), and that TNM stage together with gender (adjusted HR 2.4) are additional independent predictors of survival in young patients whereas CBI is not associated with survival. We confirm an excess of females among young patients with CCBM as well as an association with congenital ocular melanocytosis (HR 5.7) and, as a preliminary finding, monosomy 3 with metastasis in young patients. Finally, we provide evidence to 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 lower incidence rate of CCBM, lack of monosomy 3, and a very low risk of metastasis in the former group.

# Acknowledgments

The authors are grateful to all personnel in the participating centers who collected patient data without participating in data analysis and writing the manuscript.

**Legends**

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

**Supplemental Figure 2**. Scatterplot of (**A**) tumor thickness against largest basal diameter (LBD) for 110 children younger than 18 years of age and 176 young adults 18 to 24 years old and of (**B**) proximity of the posterior tumor margin to the optic disk margin against proximity to the center of the fovea for 78 children and 118 young adults with choroidal and ciliary body melanoma. Note similar size distribution (**A**) and closer proximity of tumors to the foveola among children (**B**).

**Supplemental Figure 3**. Kaplan-Meier estimates of local tumor recurrence for 114 children younger than 18 years of age and 185 young adults 18 to 24 years old with choroidal and ciliary body melanoma. Ticks show censored observations, and numbers below graph represent patients at risk; log-rank test, two-tailed.

**Supplementary Figure 4**. Kaplan-Meier estimates of all-cause mortality for 114 children younger than 18 years of age and 185 young adults 18 to 24 years old with choroidal and ciliary body melanoma (**A**), and melanoma-related mortality when children are divided to those 10 years old or younger and 11 to 17 years of age (**B**; note absence of metastatic deaths among children younger than 11 years), for children (**C**) and young adults (**D**) according to gender, children (**E**) and young adults (**F**) according to Tumor, Node, Metastasis (TNM) stage, and for both groups combined according to cell type (**G**; note three late metastases more than 15 years after diagnosis from spindle cell melanomas but no overall difference in mortality by cell type) and presence or absence of monosomy 3 (**H**). Ticks show censored observations, and numbers below the graphs represent patients at risk; (**A,C-E,H**) log-rank test and (**B**,**F,G**) test for trend, two-tailed. Three young adults died of other causes and one of unknown cause and were censored.

**Figure 5**. Kaplan-Meier estimates of melanoma-related mortality among 114 children younger than 18 years and 185 young adults 18 to 24 years old with choroidal and ciliary body melanoma according to age group (**A**), gender (**B**), presence of oculo(dermal) melanocytosis (**C**), ciliary body involvement (**D**), extraocular extension (**E**), and Tumor, Node, Metastasis (TNM) stage (**F**). Note that some patients did not have a record of every characteristic. Ticks show censored observations, and numbers below graphs represent patients at risk; (**A-F**) log-rank test and (**F**) test for trend, two-tailed. Three young adults died of other causes and one of unknown cause and were censored.

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