

# Posterior uveal melanoma in adolescents and children: current perspectives

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**Abstract:** Recognizing that <1% of all uveal melanomas occur in young persons, and that very few clinicians encounter more than a few such cases over an extended career, we felt that a retrospective review of literature and sharing of our clinical experience would be appropriate to remind readers about this age subgroup of patients with posterior uveal melanoma. This interest stems from the increase in reported cases of uveal melanoma in younger individuals and recent advances in the field.

**Keywords:** uveal melanoma, choroid melanoma, ciliary body melanoma, posterior uveal melanoma, prognosis melanoma, incidence

## Introduction

Primary uveal melanoma is a form of cancer that affects mostly older adults, as the average age at detection of this tumor is between 60 and 62 years.<sup>1</sup> The average annual incidence of this malignant intraocular neoplasm among Caucasians across all age groups has been estimated to be approximately 5 and 8 new cases per million persons per year.<sup>2</sup> However, <1 new case per million persons per year is generally encountered in individuals <30 years, even in early series.<sup>3-6</sup> The percentage of primary posterior uveal melanomas (PUMs) diagnosed in persons <21 years of age has been estimated to be <1%.<sup>5,6</sup> Because PUMs in young patients are quite uncommon, relatively few studies of patients in this age range have ever been published.<sup>4,5,7</sup> The purpose of this study is to review the pertinent literature available on PUM presenting in children and adolescent patients and to share our clinical experience.

## Methods

We performed a PubMed review, focused on the available literature, on PUM in young patients (<21 years of age). For this online search we used the keywords melanoma, uveal, melanoma, choroid, melanoma, survival, melanoma, children, melanoma, adolescents. The senior author obtained the full text articles of all retrieved references. The papers were evaluated on their category (original research, small case series [<5 patients], and single case reports), content (clinical information and survival outcomes reported), and redundancy. Our exclusion criteria were articles from the same institution reporting redundant patients (only the most recent papers were selected) and review or opinion papers that did not offer any new information.

Subsequently, the papers were categorized into case reports, small case series, and original research. The information was extracted based on the number of patients reported, their age at diagnosis, tumor features and evaluation performed, treatment, and survival outcomes. The information obtained was then compared to our series of

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patients.<sup>11</sup> In total, 18 articles met our search criteria. Four papers were omitted because they documented the same patient population identified through authorship, so we used only the most recent publication. Seven articles reviewed were single case reports documenting particular aspects of disease presentation, and the remaining 8 were case small case series. The 8 case series and their respective significant findings are compiled in Table 1.

This retrospective review follows the Declaration of Helsinki. An IRB waiver was obtained for retrospective review of de-identified patient information at the University of Cincinnati College of Medicine.

## Results and discussion

### Prevalence/epidemiology

Uveal melanoma is an uncommon malignant intraocular neoplasm that typically affects older Caucasian individuals. Although uveal melanoma has an estimated average annual incidence across all age groups of about 5–8 new cases per million persons per year,<sup>2</sup> its curve of annual incidence by decade of life is especially low prior to the 4th decade then rises abruptly to approximately 50 new cases per million persons per year by the 8th decade.<sup>1,2</sup>

Patients <21 years of age can develop primary uveal melanoma albeit less frequently than adults. It appears that 1% of the uveal melanoma patient population consists of individuals diagnosed before the age of 21.<sup>4,5,8,9</sup> Between 1973 and 1997, the calculated age-specific incidence of uveal melanoma in the USA, per million population, for 0–4 years was 0, 10–14 years was 0.2%, and 15–20 years was 0.4%. After that, the incidence continues to increase with age: 14.9 per million between 60–69 years, and 24.5 per million between 70–79 years.<sup>10</sup> Another significant difference is that young patients have historically presented with a greater proportion of iris melanoma compared to older adults that more frequently have a posterior presentation of their uveal melanoma.<sup>5,8</sup> That being said, PUM in young patients is, therefore, even scarcer. Multiple authors including our group have shown that approximately 1% of patients with PUM have been found to be <21 years.<sup>5,7,9,11</sup>

PUM in pediatric patients appears to manifest preferentially during or after puberty (ages 13.1 to ≤20 years).<sup>4,7–9,11–13</sup> Such an observation has led our group (and others) to speculate a positive association between PUM and increased levels of growth hormone. Interestingly, a study examining the prevalence of PUM among young children (ages 2.7–17.9) vs young adults (ages 18–24) found that the cumulative frequency of having a ciliary body or choroidal melanoma

diagnosed substantially increases between the age of 11 and 17 from 0.8% per year of age to 8.8% per year of age.<sup>14</sup> In this study, 90% of PUM were diagnosed during adolescence.<sup>14</sup> This phenomenon further emphasizes the connection between pubescent changes and PUM occurrence. Interestingly, a similar transition was found to occur between the ages of 40 and 45 years.<sup>15</sup> The Pediatric Choroidal and Ciliary Body Melanoma Study has suggested the existence of discreet peak periods for the development of PUM that may correlate with age-dependent differences in tumor development and progression.<sup>15</sup>

We recently reported our clinical observations related to this specific patient population.<sup>11</sup> Only 18 young patients out of 2,265 patients with PUM were encountered during the study interval (33 years). Our series showed a slight gender difference with female predominance (55.6%), which was similar to findings in other reported studies, yet no statistical significance related to this variable has been reported.<sup>7,9,14,16</sup>

### Prognosis

A favorable prognosis related to iris melanoma has been reported by several authors.<sup>17</sup> Data and discussion on iris melanoma has been omitted from this review given our focus on PUM. The prognosis of PUM in pediatric patients is not completely known. However, comparison of available studies revealed some interesting insights.

In a retrospective cohort case series of 92 pediatric PUM patients, matched for gender, tumor location, location of anterior tumor margin, largest basal diameter (within 2 mm), ultrasonographic thickness (within 1 mm), and extraocular extension, younger patients (ages 0–20) reported a statistically significant lower risk of PUM metastasis vs mid- (ages 21–60) and older (ages 61+) adults.<sup>7</sup> Using univariate and multivariate analysis the authors claimed that increasing age was the sole predictive factor for tumor metastasis in young patients.<sup>7</sup> However, the authors failed to exclude other competing causes of death among older patients such as cardiovascular disease, among others. Interestingly, our recent series showed that due to the lack of these competing causes of death, our young patient population had similar, if not more, melanoma related deaths when compared to the general PUM population.<sup>11</sup> Our young patient series (ages 0–20) showed Kaplan–Meier estimates of tumor-related metastasis at 5, 10, and 15 years of 36.6%, 60.8% and 60.8%, respectively – numbers that far exceed the metastatic prognoses of PUM for both pediatric patients and adult patients given by Kaliki et al.<sup>7,11</sup> Moreover, AJCC T4 tumors have reported Kaplan–Meier mortality estimates of

**Table 1** Peer reviewed literature (in chronological order) of published series of young patients with primary uveal melanoma (PUM) with their respective significant findings

First author	Journal/year	No of pts	% female	Age range (years)	Average age at dx (years)	Average diameter (mm)	Average tumor thickness (mm)	Mean follow-up duration (months)	% of pts with metastasis	% of pts who died from metastasis	Mean overall survival time s/p treatment (months)	Significant findings/comments
Apt et al <sup>12</sup>	<i>Int Ophthalmol Clin</i> /1962	46	48	0–19	N/A	N/A	N/A	N/A	N/A	14.6	N/A	Of the 7 deceased patients, 2 were pre-puberal, 5 were post-puberal; 1 had diffuse iris melanoma, the rest had posterior uveal melanoma. Tumor incidence increased with puberal/post-puberal changes
Verdager J <sup>13</sup>	<i>Am J Ophthalmol</i> /1965	17	N/A	0–20	12.4	N/A	N/A	91.7	N/A	N/A	N/A	29.4% of patients had associated ocular melanosis; choroidal melanomas predominantly affected the puberal and post-puberal groups; 3 patients lost to follow-up; no documented metastasis or death from metastasis
Barr et al <sup>4</sup>	<i>Arch Ophthalmol</i> /1981	78	46	2–20	14 (choroidal)	N/A	N/A	180	N/A	21.8 (31.0 choroidal)	N/A	17 patients died of uveal melanoma metastasis – 13 had choroidal tumors and 4 had iris tumors; mortality was related to older age (≥ 16 years)
Singh et al <sup>16</sup>	<i>Arch Ophthalmol</i> /2000	63	60	3–20	16	N/A	N/A	51	N/A	6.3	N/A	11% patients had ocular melanocytosis (n=7); short term (5 years) survival

(Continued)

Table 1 (Continued)

First author	Journal/year	No of pts	% female	Age range (years)	Average age at dx (years)	% of tumors with posterior (choroidal) involvement	Average tumor diameter (mm)	Average tumor thickness (mm)	Mean follow-up duration (months)	% of pts with metastasis	% of pts who died from metastasis	Mean overall survival time s/p treatment (months)	Significant findings/comments
Shields et al <sup>8</sup>	Saudi J Ophthalmol/2013	122	57	3–20	15	67	9.8	5.0	N/A (64 months) <sup>7</sup>	N/A (5% <sup>7</sup> )	N/A	N/A	better than general population, long term survival (15 years) is similar to adults Same patient data was analyzed in Kaliki 2013; <sup>7</sup> 3% patients had ocular melanocytosis (n=4), most common in teenagers (>13 years) vs children; tumor location: iris 25%, ciliary body 8%, choroid 67%; incidence of metastasis at 10 years was 8.8%, at 20 years was 36%; tumors tended to be smaller and located in the iris in pre-puberal patients 15% had metastasis – 1 patient (8%) died from systemic metastasis 6 months post-diagnosis Patients were divided into children (age 2.7–17.9 years) and young adults (age 18.0–24.9 years). Iris tumors were excluded from this study. All tumors were choroidal and ciliary body melanomas (CCBMs),
Yousef et al <sup>20</sup>	Hematal Oncol Stem Cell Ther/2015	13	46	0 (0–19 months)	0 (7 months)	46	N/A	N/A	25	15	8	N/A	
Al-Jamal et al <sup>14</sup>	Ophthalmology/2016	114; 185	57; 63	2.7–17.9; 18.0–24.9	15.1; 21.9	N/A	12.3; 12.4	6.1; 6.0	79.2; 61.2	8; 17	7; 15	N/A	

but the distribution between each was not specified cumulative frequency of PUM; diagnosis increases by 0.8% per year of age between 5 and 10 years and by 8.8% per year between 17 and 24 years; melanoma-related survival in children compared with young adults was 97%, 90% at 5 years and 92% and 80% at 10 years, respectively; among children, males tended to have a more favorable survival than females

Fry et al <sup>11</sup>	JAMA <i>Ophthalmol</i> /2018	18	55.6	4.4–20.8	16.6	100	12.8	7.2	90	44.4	44.4	142.8
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**Note:** % of pts with metastasis refers to percentage of patients diagnosed with metastasis during available follow-up and % of pts who died from metastasis refers to percentage of patients who died from metastasis during available follow-up.

**Abbreviations:** dx, diagnosis (of uveal melanoma); pts, patients; s/p, status post.

30% at 5 years, 43% at 10 years, and 51% at 20 years among the general population,<sup>18</sup> while similar tumors in young adults have Kaplan–Meier mortality estimates of 35.1% at 5 years, 45.6% at 10 years, and 59.4% at 15 years with a median survival time of 11.9 years.<sup>11</sup> In our experience, not only do these numbers exceed those of the worst tumors in the general PUM population, they far outdo the actuarial estimates of pediatric PUM-related mortality put forth in earlier studies.<sup>5,7</sup> The median survival time of our patients after detection of metastasis was just 2.3 months, and only 1 of the patients survived for >1 year following detection of metastatic uveal melanoma.<sup>11</sup>

There are potential explanations for the discrepancy between the survival rates in our study and those in other studies. One is our longer follow-up data vs that available in the current literature.<sup>11</sup> It is important to realize that PUM metastasis has been documented to emerge in some patients >10 years and 20 years following treatment.<sup>7,19</sup> This could explain, in part, why previous studies that have an average patient follow-up time of  $\leq 5$  years show a better prognosis in young PUM patients.<sup>5,7,8,13,20</sup> This trend is also consistent with observations by Singh et al that, while the 5-year survival of young uveal melanoma patients appear better than the general patient population, their long term survival (15 years) is similar to adults.<sup>16</sup>

Another explanation is the limited documentation of tumor size among young patients as a predictive factor for the development of PUM metastasis and metastatic death.<sup>21,22</sup> Although some studies provide average maximal thickness and average largest basal diameter, the discrimination between large and small tumors, as well as anterior vs PUM involvement, when calculating survival seems relevant but has been overlooked. Another study involving patients diagnosed with PUM at the age  $\leq 24$  years or younger showed survival estimates similar to ours and the general PUM population, again questioning the role of competing age related factors for mortality.<sup>9</sup> We and Al-Jamal et al concluded that the prognosis of PUM in pediatric patients resembles that of the general PUM population<sup>9,11</sup> is consistent with older studies which found that uveal melanoma in children and adolescents does not differ significantly in clinical appearance or prognosis from its adult counterpart.<sup>3,4,12,16</sup>

Because our series (as others) had a limited number of cases that are insufficient for multivariate analysis and identification of tumor size as a prognostic factor in this subgroup, a reliable comparative analysis between studies cannot be performed.

Ocular melanocytosis is a known risk factor to uveal melanoma,<sup>23</sup> and patients with uveal melanoma with

pre-existing ocular melanocytosis have a significantly increased risk of developing uveal melanoma metastasis. Studies looking at the overall proportion of uveal melanoma in eyes with ocular melanocytosis in the general population and among younger patients have shown similar results (approximately 3%).<sup>14,24</sup> However, congenital ocular melanocytosis has been associated with 5.6 times higher PUM-related mortality.<sup>14</sup>

## Prognosis and genetics

The data related to genomic and cytogenetic aberrations of PUM in young patients is almost non-existent. Preliminary data, recently published, has shown that monosomy 3 with 8q gain corresponds to the highest risk of tumor metastasis, and disomy 3 corresponds to the lowest risk of metastasis,<sup>14</sup> as in the general uveal melanoma patient population.<sup>25–28</sup> However, while tumor cell type has been shown to have a weaker correlation with prognosis for development of metastasis in the general uveal melanoma patient population,<sup>29</sup> more aggressive cell type (non-spindle B) has shown no correlation among the young patients reported. That is because studies have found that twice as many non-spindle tumors (mixed and epithelioid) also showed monosomy 3.<sup>14</sup>

Another recent study that examined the chromosomal mutations in young patients with PUM (defined as <32 years of age) found the majority of these tumors (64%) showed a disomy 3 (n=16) that was correlated with a good survival outcome.<sup>30</sup> These results concur with others finding that monosomy 3 with 8q gain correspond with an older age at treatment<sup>30,31</sup> as well as a poorer prognosis, which could explain why younger patients tend to have a better prognosis than the general PUM population. Due to the limited information available, further studies will be necessary to examine and determine metastatic risk in young patients diagnosed with uveal melanoma, and should include genomic testing (GEP) and Next-Gen sequencing for mutation analysis of these tumors.<sup>22,32,33</sup>

## Limitations of available literature

While the 8 key papers selected for this review included young patients, there are inherent differences in the patients, and tumors, reported that limit our ability to directly compare them, namely; patient age, tumor location, average tumor sizes, and follow-up that includes development of metastasis and survival. Moreover, because specific data such as exact length of follow-up for each patient was not readily available from these studies, a combined Kaplan–Meier estimate of metastatic tendency and patient survival cannot be generated.

Another limitation was the small number of published papers, some of them reporting redundant series, and availability of prognostic testing since some series were published before 1990. Even recent publications lacked this information for some patients. Given that a more thorough understanding of uveal melanoma in young patients is needed, we recognized the importance of utilizing all available data, so all these studies were included in this review.

To overcome these limitations associated with a retrospective literature review of a rare presentation such as uveal melanoma in young patients, a multicenter (national or international) database could be created for this patient population. Such an effort would provide a recognized definition of young patient age, tumor features (including tumor location and genomic or chromosomal abnormalities), and follow-up necessary for any future studies. The availability of a larger patient data set would address the limitations of this present review and allow a comprehensive statistical analysis related to prognosis and survival among this age group.

## Conclusion

Although there seems to be a common understanding among ocular oncologists that younger patients diagnosed with uveal melanoma have better survival prognosis, there are 2 important potential biases to be considered: 1) a large majority of these tumors are limited to the iris (and many without angle involvement) and; 2) young patients (assumedly healthy) have fewer competing mortality risk factors compared to older individuals and are also likely able to tolerate more aggressive treatment. One interesting finding is that the onset of metastasis in pediatric PUM patients seems to occur later than in the general (older) population, suggesting that these younger patients should be monitored by routine surveillance tests for >10 years. Multicenter prognostic studies with genomic testing of tumors would provide additional insight into the discrepancies found between pediatric PUM patient outcomes in current literature. The creation of a multicenter comprehensive database to collect data on uveal melanoma in young patients would provide a more thorough understanding on the impact of age in the outcome of uveal melanoma.

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## Author contributions

All authors made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval of the version to be published; and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Disclosure

JJA is a chair holder of the James J Augsburger Ocular Oncology Fund of the University of Cincinnati College of Medicine. CMZ is a chair holder of the Ophthalmic Pathology and Ocular Oncology Fund of the University of Cincinnati College of Medicine and a paid consultant for Castle Biosciences, Inc. The authors report no other conflicts of interest in this work.

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