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Proton therapy for uveal melanoma in 43 juvenile patients: long term results

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Running head: Proton therapy for juvenile uveal melanoma

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ABSTRACT:

Objectives

To examine the metastatic and survival rates, eye retention probability and the visual outcome of juvenile patients after proton beam radiotherapy (PBRT) for uveal melanoma (UM).

Design

Retrospective case-factor matched control study.

Participants and controls

Forty-three patients aged less than 21 years treated with PBRT for UM were compared to 129 matched adult control patients.

Methods

Information on patient demographics and clinical characteristics were recorded before and after treatment from patients' files. The control group was composed of adult patients (>21years) matched on tumor size (largest tumor diameter +/- 2mm, height +/- 2 mm) and anterior margin location (iris, ciliary body, pre or post equatorial choroid). For each juvenile patient, three adults were selected.

Main outcome measures

Comparing outcomes of juvenile and adult patients in terms of metastatic and eye retention rates using the log rank statistic, relative survival using the Hakulinen method as well as their visual outcome.

Results

Forty-three juvenile and 129 control cases were reviewed. The metastatic rate at 10 years was significantly lower in juvenile UM patients than in adult controls (11% versus 34%; $p<0.01$) with an associated relative survival rate of 93 % versus 65% ($p=0.02$). Six juvenile patients (14%) developed metastases. One patient underwent enucleation because of a presumed local tumor recurrence and 4 additional patients because of complications (9.3%). In the adult control group,

27 % (n=35) of matched patients developed metastases, there were 2 cases of local recurrence and 16% (n=21) underwent enucleation due to complications. A visual acuity of >0.10 was maintained in most cases, without any significant differences before or after treatment observed between both groups.

Conclusions

Following PBRT, metastatic and survival rates are significantly better for juvenile than for adult patients with UM. Clinically, juvenile and adult eyes react similarly to PBRT, with a comparable eye retention probability and maintaining a useful level of vision in the majority of cases. This is the largest case-control study on proton therapy in juvenile eyes to date, and further validates PBRT as an appropriate conservative treatment for UM in patients less than 21 years of age.

INTRODUCTION:

Uveal melanoma (UM) is the most common primary ocular malignancy in adults, with an overall incidence of about 6 new cases per million per year.[1,2] In 1962, Apt was the first to report on a series of 46 UM patients less than 20 years old, which he labeled "juvenile melanoma".[3] The second cohort, published by Verdaguer in 1965, used 21 years as the upper age limit.[4] Ever since, series of juvenile UM patients have used this same age as the cut-off point; which has the additional benefit of agreeing with the American Pediatric Academy definition of a child.

Juvenile UM is rare, with only one UM patient in a hundred being less than 21 years old.[5-7] As a consequence, to the best of our knowledge, there are only ten retrospective series reporting on juvenile UM patients.[3-12] In most of these reports, young patients were treated with enucleation, brachytherapy or surgical resection. Following our publication in 1992,[8] only one other study has described the clinical profile and prognosis of juvenile UM eyes (n=17) treated with proton beam radiotherapy (PBRT).[9]

While all reports concluded that young patients tended to have a lower metastatic rate, very little information is available on eye retention probability or visual acuity.[8,9] The first aim of this study is to compare the long term metastatic and survival rates for a group of juvenile and matched control adult patients following PBRT for UM. The second aim is to examine whether ophthalmologic outcomes such as the eye retention probability, complications requiring surgery or visual function of these juvenile patients differ from their adult counterparts.

METHODS:

Patients

In this single center, retrospective, case-control study, files were reviewed from all patients 20 years old or less at the time of their UM diagnosis who were treated with PBRT since 1984. For each juvenile patient, three matched adult control patients were selected. Matching was based on tumor size (largest tumor diameter +/- 2 mm; height +/- 2 mm) and location of the anterior tumor margin (iris, ciliary body, pre or post equatorial choroid). Eyes with prior tumor resection or brachytherapy were excluded. Ethical approval for this study was obtained from the 'Commission Cantonale d'Éthique', Canton of Vaud, Switzerland.

Treatment and Follow-up

Clinical baseline visits, tantalum clip surgery and follow-up took place at the Ocular Oncology Unit of the Jules-Gonin Eye Hospital (University of Lausanne, Switzerland). PBRT was performed at the Paul Scherrer Institute (Villigen, Switzerland), with a 60 Gy (RBE) delivered in four fractions, on four consecutive days.[13,14]

Standard baseline and follow-up visits consisted of a complete clinical ophthalmologic examination, color tumor photography and ultrasonography. Examinations were performed before the tantalum clip surgery, six months after PBRT, and then annually for 15 years in our hospital. Juvenile patients lost to follow-up (or their family) were contacted by telephone with regard to information such as metastatic occurrence, vital status and eye retention. To obtain ophthalmic details, a letter was sent to their local ophthalmologist. Metastatic screening, consisting of liver function tests (aspartate transaminase, alanine transaminase, alkaline phosphatase, gamma glutamyltransferase and lactate dehydrogenase) and imaging (ultrasonography or computed tomography scan), was done before treatment, twice a year during the first five years and then once a year for another ten years after PBRT. Any clinical diagnosis of metastases was confirmed by biopsy.

Baseline and outcome measures included age, gender, best corrected visual acuity (BCVA) with the Snellen chart, intraocular pressure (IOP), tumor size, tumor location, tumor related complications prior to treatment (intraocular inflammation, glaucoma, cataract, intravitreal hemorrhage, retinal detachment, rupture of Bruch's membrane), radiation related complications, eye retention, metastatic occurrence and vital status.

Statistical analysis

Metastatic disease, relative survival and eye retention probability were examined. Additionally we looked at local tumor control as well as tumor and treatment related complications and visual acuity. Patients lost to follow-up were censored at their last visit. If a patient had died, these data were censored at the time of his last visit. Metastatic rates and eye retention rates were estimated using the Kaplan-Meier method and compared between juvenile and adult control groups using the log rank test statistic at a 5% level of significance using the "survival" R package (R Foundation for Statistical Computing, Vienna, Austria).[15] To correct for increased age-related mortality rates when comparing both groups, we looked at relative rather than observed survival rates (relative survival = observed survival/expected survival, with expected survival being the survival of a general population group with age and gender characteristics similar to the studied cohort). Relative survival statistics (Hakulinen method) were calculated using the "relsurv" R package,[16] where the rate table was calculated using Swiss demographics from the *Human Mortality Database.*[17] Univariate and multivariate analyses were performed using the glm base package; significance was assessed using the chi-squared test statistics.

Search of Literature

A computerized search was performed in MEDLINE using the keywords "Juvenile", "Adolescent", "Children", "Uveal melanoma", and "Proton beam radiotherapy". The bibliography of each article was also reviewed. Articles published prior to 1966 were identified using the Excerpta Medica Abstract Journal, Ophthalmology (Section 12 EMBASE), with the same first three keywords.

RESULTS:

Between 1984 and 2011, 44 of the 5340 UM patients treated with proton therapy were 20 years or younger at the time of diagnosis (0.8%). The first 11 of those patients have already been reported upon in a previous paper, one of whom, previously treated with brachytherapy, was excluded from this study.[8] There were no differences in gender or laterality between the juvenile and adult control UM groups ($p>0.37$; chi squared test, **Table 1,** available at http://aaojournal.org). In both groups the majority of tumors were exclusively located in the choroid whereas approximately 20% reached the iris (**Table 2,** available at http://aaojournal.org). Significantly more adult than juvenile eyes presented a rupture of Bruch's membrane. Mean follow-up time for the juvenile UM group was 155 months (range: 6- 336), and for the adult control group 79 months (range: 4- 281).

Six of 43 juvenile patients developed liver metastases (14%) between 2 and 14 years after radiotherapy, five of whom had died less than a year later (12%) (**Table 3**). The surviving patient was treated with immunotherapy, Fotemustine® chemotherapy and radiofrequency, and is in remission, eight years after the biopsy proven presence of ganglion and liver metastases. The primary uveal tumors of these patients were classified[19] as T3 (N=2) or T4 (N=4) and half of them involved the ciliary body. A baseline retinal detachment of at least 2 quadrants was present in four of these patients, which persisted until the last visit for three of them. No juvenile patients with a T1 or T2 tumor developed metastases. On the other hand, in the adult control group, 35 patients developed metastases (27%), all of whom died less than 3 years later. Ten of these 35 adults had a T2 tumor, the remainder presenting a T3 (N=6) or a T4 (N=19) tumor. Kaplan-Meier curves comparing the metastatic rates in both groups (**Figure 1**) show a statistically significant difference, with a metastatic rate in juvenile patients of 8% at 5 years (95% Confidence Interval (CI) [0-16], n=34), 11% at 10 years (95% CI [0-20], n=25) and 19% at 15 years (95% CI [3-32], n=18), whereas the adult controls had a metastatic rate of 24% at 5 years (95% CI [16-33], n=67), 34% at 10 years (95% CI [23-43], n=29), and 48% at 15 years (95% CI [28-63], n=5).

159 Splitting the juvenile group into children (<16years) and young adults (16-20 years), a subgroup
160 analysis was performed (**Table 4**). No metastases occurred in the children's group, whereas from
161 16 years onwards the juvenile patients joined the adult controls with regard to the risk of
162 developing metastases.

163 Looking for metastatic risk factors using univariate analysis, age was confirmed to be a significant
164 risk factor for metastases in the juvenile group (p=0.04) and not in the adult control group
165 (p=0.41). Also the persistence of a large (≥2 quadrants) retinal detachment 6 months after PBRT,
166 was a metastatic risk factor for the former (p=0.01) and not for the latter (p=0.66), and remained
167 significant on multivariate analysis, when age had been taken into account for the juvenile group
168 (p=0.03). However, while tumor size was not a significant risk factor in patients less than 21
169 years old (p=0.99), it did prove to be a significant risk factor in the adult control group
170 (p<0.001).

171 Juvenile UM patients also had a significantly better survival than their adult controls (**Figure 2**).
172 The relative survival rate in the juvenile UM group was 93 % at 5 years (95% CI [84-100], n=35),
173 93% at 10 years (95% CI [85-100], n=27) and 85% at 15 years (95% CI [72-99], n=20). In the
174 adult control group, relative survival rate was 77% at 5 years (95% CI [69-86], n=74), 65% at 10
175 years (95% CI [57-79], n=27) and 50% at 15 years (95% CI [35-71], n=6).

176 Local tumor control was achieved in all but one juvenile patient, who had his eye removed 16
177 months after PBRT by his own ophthalmologist because of a presumed local recurrence. During
178 15 years of follow-up, this patient has not developed metastases. In the adult group, two patients
179 presented with a local recurrence, in addition to concurrent liver metastases of which they died
180 less than one year later.
181 Five juvenile patients (12%) were enucleated between 1 to 19 years following PBRT. One of
182 them due to a presumed local recurrence, and four others because of complications such as

neovascular glaucoma (n=2), phthisis bulbi (n=1) and a painful pseudophakic bullous keratopathy in an otherwise non-functional eye (n=1). In the adult control group, 21 eyes (16%) were enucleated, due to neovascular glaucoma (n=15), phthisis bulbi (n=5) and painful end stage glaucoma (n=1).

While the eye retention rate was higher in the juvenile UM group, a comparison of the Kaplan-Meier eye retention curves did not demonstrate a statistically significant difference (p=0.08) (**Figure 3**). An eye retention rate of 90% at 5, 10 and 15 years (95% CI [80-100]; n=31, 24, 18 respectively) was observed in the juvenile group, where all but one enucleation took place within the first 5 years following proton therapy. In the adult group the eye retention rate was 86% (95% CI [80-93]), 77% (95% CI [68-88]) and 67% (95% CI [50-90]) at 5, 10 and 15 years respectively.

Table 5 gives an overview of most of the tumor and radiation related complications in both groups, as well as the surgical interventions required due to these complications. Minor aesthetic side effects such as radiation related madarosis or eyelid atrophy are not listed. **Tables 6 and 7** (table 7 is available at http://aaojournal.org) summarize some basic ocular parameters, such as BCVA, IOP, lens status, presence of retinal detachment and/or vitreous/subretinal hemorrhage within both the juvenile and adult control UM group at three time points throughout follow-up, i.e. at baseline and at the first and last control visit after PBRT. With the exception of the prevalence of more lens opacities in the adult control, no significant differences were identified between either group.

DISCUSSION:

The comparison of the metastatic and relative survival rates between juvenile and adult control UM patients demonstrated a significantly better prognosis for patients less than 21 years old. In particular, a 10-year relative survival rate of 93% was observed in the juvenile patients, opposed to 65% in the matched adult controls. Similarly the 10-year metastatic rate was much lower in the juvenile group. This supports the 5-year metastatic rates already reported by Kaliki,[11] as well

those by Vavvas reported at a median of 16 years.[9] Shields et al. have previously highlighted the difficulties of comparing survival rates reported in the non-matched series,[3-8, 12] as it can be susceptible to bias,[11] and lead to specious results.[10] For example, juvenile UM series do contain a greater proportion of iris melanoma which would contribute to a better vital prognosis,[5,7] By matching for tumor characteristics, as done in this article, this source of bias has been reduced. **Table 8** (available at http://aaojournal.org) provides a summary of the mortality rates reported in the ten available juvenile UM series. Important to note is that metastases continue to occur after 10 years' follow-up (**Figure 1**) in both groups. This finding stresses the importance of checking the mean follow-up before interpreting the metastatic rates of studies on patients treated for uveal melanoma.

Examining risk factors for metastases within the juvenile UM group, showed that increasing age proved to be a significant risk factor, which has previously been reported by Kaliki et al.[11] In contrast to the traditional 21st birthday of political majority, Swiss pediatricians stop following their patients after their 16th birthday, considering that most of them by then have reached biological maturity. Respecting this distinction, the juvenile group was split into children (<16years) and young adults (16-21years), and the difference in vital prognosis of -mostly prepubescent- children compared to the adults became even more evident; here no UM children developed metastases. On reviewing the literature, including all case reports, it was found that approximately 470 cases of juvenile UM have been reported worldwide.[19-57] Of these, only 14 children (<16 years; 3%) were reported to have died from metastatic disease, [3,5,19-23,55] **(Table 9,** available at http://aaojournal.org**)** though it should be noted that not all juvenile series specify the age at UM diagnosis of their patients having died from metastases.

These results have led some authors to speculate that children are somehow 'protected' from metastatic disease and may have a more 'robust' immune system keeping micro-metastases under better control.[9,11] Dimaras et al recently published the cytogenetic results after enucleation of an epithelioid juvenile melanoma, reporting an absence of monosomy 3 or trisomy 8, indicating a

lack of the somatic mutations usually found in adults. This may be related to the favorable prognosis of children.[25]

Retinal detachments which persisted six months after PBRT, were shown to be a significant risk factor for developing metastases in the juvenile group. Though retinal detachment has been shown to be a function of tumor size,[58] the correlation between its persistence after radiotherapy and shrinking tumor size or metastatic risk has not been previously studied. In this report, tumor size was not correlated with a higher metastatic risk in juvenile eyes, in contrast to the adult matched control group. This lack of correspondence between tumor size and metastases in juvenile UM eyes was previously reported by Kaliki et al.[11] Despite this outcome it should be noted that no patient less than 21 years old with a small T1 or T2 tumor has ever been reported to develop metastases.

This case-matched control study is the first to compare eye retention rates after conservative radiotherapy between juvenile and adult control patients with UM. Though in the former group 88% of patients kept their eye against only 76% in the latter, this difference was not statistically significant. No significant differences in visual outcome or other ocular parameters were found between juvenile and adult eyes, indicating that following PBRT, juvenile UM eyes do not require a different follow-up and/or management than adult eyes.

Since this study is not a randomized clinical trial, there are likely sources of bias and variability, originating from the use of historical data or possible differences in adherence or attendance which could affect the study outcomes. Considering the rarity of juvenile uveal melanoma a randomized clinical trial is not achievable and the size of this cohort is substantial. In the statistical analysis, every effort has been made to control for the known risk factors of metastases, and decreased survival.

To the best of our knowledge, this is the largest cohort of juvenile UM patients treated with PBRT.[8, 9] Here it was shown that juvenile patients treated with PBRT have a significantly better prognosis in terms of survival and metastatic rates than a corresponding adult group, especially

prepubescent children. PBRT also maintains useful vision in the majority of cases, with an excellent local tumor control and similar eye retention rates as reported in the adult population. This long term case-control study confirms that PBRT is an appropriate conservative treatment for UM patients less than 21 years old.

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Table 1: Patient characteristics and baseline symptoms

Patient characteristics	Juvenile UM group (N=43)	Adult control UM group (N=129)
Mean age at diagnosis (±SD) [range]	17.3 years (±3.5) [9-21]	50.4 years (±10.2) [29-81]
Gender: Male/Female ratio	20/23 (47/53%)	64/65 (50/50%)
Previous primary cancer	1 (Burkitt lymphoma)	1 (Hodgkin's lymphoma)
Dysplastic nevus syndrome	1 (2%)	0
Ocular melanocytosis	2 (5%)	5 (4%)
Affected Eye (Right/Left)	15/28 (35/65%)	55/74 (43/57%)
Baseline Symptoms • Loss of vision • Metamorphopsia • Flashes of light • Pain • Floaters • None	 • 29 (67%) • 6 (14%) • 4 (9%) • 0 • 1 (2%) • 13 (30%)	 • 94 (73%) • 28 (22%) • 44 (34%) • 1 (1%) • 17 (13%) • 11 (8%)

SD = Standard Deviation, UM = Uveal Melanoma.

Table 2: Baseline tumor characteristics comparing the juvenile and adult control uveal melanoma groups

Baseline tumor characteristics	Juvenile UM group (N=43)	Adult control UM group (N=129)	p-value
LTD (±SD) [range]	17.0 mm (±4.3) [8-24]	16.7 mm (±4.2) [8-23]	p=0.80*
Height (±SD) [range]	6.9 mm (±3.9) [2-20]	6.8 mm (±2.8) [2-14]	p=0.93*
Location of anterior tumor margin • Iris • Ciliary body • Anterior choroid • Posterior choroid	• 9 (21%) • 7 (16%) • 9 (21%) • 18 (42%)	• 23 (18%) • 24 (18%) • 28 (22%) • 54 (42%)	p=0.97†
Distance to the optic disc • Infiltration • In contact • >0 mm & <3.6 mm • ≥3.6mm	• 0 • 7 (16%) • 9 (21%) • 27 (63%)	• 12 (9%) • 23 (18%) • 27 (21%) • 67 (52%)	p=0.19†
Distance to the macula • In contact • >0mm & <3.6mm • ≥3.6mm	• 10 (23%) • 10 (23%) • 23 (54%)	• 43 (33%) • 35 (27%) • 51 (40%)	p=0.26†
Rupture of Bruch's membrane	5 (12%)	44 (34%)	**p=0.02**
Extrascleral extension	0	8 (6%)	p=0.19
TNM stage‡ • 1 • 2 • 3 • 4	• 4 (9%) • 13 (30%) • 9 (21%) • 17 (40%)	• 4 (3%) • 44 (34%) • 31 (24%) • 50 (39%)	p=0.99†

* = two-sample t-test, † = Chi-squared test ‡ = TNM staging of uveal melanoma according to the 7th ed. of the American Joint Committee on Cancer cancer staging 2010.[19] TNM = Tumor size, Nodes, Metastasis, SD = Standard Deviation, UM = Uveal Melanoma, LTD = Largest Tumor Diameter.

Table 3
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Table 3: Details of the juvenile uveal melanoma patients having developed metastases

Gender	Age at diagnosis (years)	UM location	Tumor size (mm): LTD x Height	Metastatic free survival after PBRT (years)	Metastatic survival (years)	Vital status
F	20	Ciliary body and anterior choroid	21.0 x 8.5	12	<1	Dead
F	20	Ciliary body and anterior choroid	16.8 x 8.5	2	<1	Dead
F	20	Anterior and posterior choroid	15.6 x 6.8	7	8	Alive
M	20	Anterior and posterior choroid	19.0 x 4.6	5	<1	Dead
M	18	Posterior choroid	19.0 x 9.0	14	<1	Dead
M	20	Ciliary body and anterior choroid	23.0 x 10.0	2	<1	Dead

UM = Uveal Melanoma, LTD = Largest Tumor Diameter, PBRT = Proton Beam RadioTherapy, F = Female, M= Male

Table 4
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Table 4: Subgroup analysis for metastatic occurrence in function of age.

Subgroup by age (years)	Number of patients in this group	Number of patients with metastases (%)	90% Confidence Intervals [%]
0-15	14	0	[0-16]
16-20	29	6 (21%)	[11-35]
21+	129	36 (28%)	[22-35]

Table 5
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Table 5: Tumor and radiation related complications following proton beam radiotherapy in juvenile and adult control uveal melanoma patients

Tumor and radiation related complications	Juvenile UM group (N=43)	Adult control UM group (N=129)
Local UM recurrence	1 (2%)	2 (2%)
Retinal ischemia requiring laser treatment	16 (37%)	20 (16%)
Neovascular glaucoma	8 (19%)	24 (19%)
Phthisis bulbi	2 (5%)	5 (4%)
Scleral melt	1 (2%)	3 (2%)
Chronic inflammation	1 (2%)	0
Pseudophakic bullous keratopathy	1 (2%)	0
Complication treatments		
Enucleation for local melanoma recurrence	1 (2%)	0
Enucleation for other complications	4 (9%)	21 (16%)
Other interventions • Strabismus surgery • Glaucoma surgery • Retinectomy/tumorectomy • Scleral graft • Phacoemulsification • Laser for conjunctival telangiectasia • Vitrectomy for massive vitreal hemorrhage	9 (21%) • 1 • 2 • 1 • 1 • 8 • 2 • 1	17 (13%) • 0 • 1 • 1 • 0 • 12 • NA • 3

UM = Uveal Melanoma, NA = data Not Available.

Table 6
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Table 6: Ocular status of the juvenile uveal melanoma patients at baseline and at the first and last control visit after proton beam radiotherapy

Ocular parameter	Baseline	6 months after PBRT	Last control visit (excluding 5 enucleated eyes)
Mean BCVA • NLP • ≤0.10 • >0.10	0.5 (±0.4) [0-1.25] • 0 • 5 (12%) • 38 (88%)	0.4 (±0.4) [0-1.5] • 2 (5%) • 11 (25%) • 30 (70%)	0.2 (±0.4) [0-1] • 7 (18%) • 15 (40%) • 16 (42%)
Mean IOP in mmHg	14.4 (±6.4) [7-43]	14.1 (±4.7) [2-25]	14.0(±6.8) [2-43]
Lens opacities • Absent • Present • Pseudophakic	 • 42 (98%) • 1 (2 %) • 0	 • 33 (77%) • 10 (23%) • 0	 • 17 (45%) • 15 (39%) • 6 (16%)
Retinal detachment • None • 1 quadrant • ≥2 quadrants	 • 18 (42%) • 12 (28%) • 13 (30%)	 • 27 (63%) • 7 (16%) • 9 (21%)	 • 30 (79%) • 2 (5%) • 6 (16%)
Vitreous or subretinal hemorrhage (Yes/No)	1/42	3/40	1/37

PBRT= Proton Beam RadioTherapy, BCVA = Best Corrected Visual Acuity, NLP = No Light Perception, IOP = IntraOcular Pressure

Table 7: Ocular status of the adult control uveal melanoma patients at baseline and at the first and last control visit after proton beam radiotherapy (PBRT).

Ocular parameter	Baseline	6 months after PBRT	Last control visit (excluding 21 enucleated eyes)
Mean BCVA • NLP • ≤0.10 • >0.10	0.6 (±0.4) [0-1.5] • 0 • 25 (19%) • 104 (81%)	0.4 (±0.4) [0-1.5] • 6 (5%) • 52 (40%) • 71 (55%)	0.3 (±0.4) [0-1.25] • 19 (21%) • 22 (24%) • 51 (55%)
Mean IOP in mmHg	14.0 (±3.4) [7-28]	15.7 (±8.0) [4-66]	16.3 (±8.1) [0-46]
Lens opacities • Absent • Present • Pseudophakic	 • 112 (87%) • 16 (12%) • 1 (1%)	 • 86 (67%) • 42 (32%) • 1 (1%)	 • 33 (36%) • 48 (52%) • 11 (12%)
Retinal detachment • None • 1 quadrant • 2 quadrants	 • 60 (47%) • 32 (25%) • 37 (28%)	 • 74 (57%) • 16 (12%) • 39 (31%)	 • 79 (86%) • 2 (2%) • 11 (12%)
Vitreous or subretinal hemorrhage (Yes/No)	17/112	7/122	7/85

BCVA = Best Corrected Visual Acuity, NLP = No Light Perception, IOP = IntraOcular Pressure

Table 8-online only pdf
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Summary of the 10 available series reporting on juvenile uveal melanoma:

Reference	Number of patients	UM Location	Treatment	Mortality (%)	Mean Follow-up (years)
***Petrovic 2013**	43	9 iris 7 CB 9 Anterior Choroid 18 Posterior Choroid	Proton beam radiotherapy	7	13
***Kaliki 2012** [11]	122	30 Iris 10 CB 13 Anterior Choroid 69 Posterior choroid	NA	8	5.25
***Vavvas 2010** [9]	17	1 CB 16 Choroid	Proton beam radiotherapy	0	16
†Pogrzebielski 2006 [7]	11	6 Iris 2 Iris and CB 3 Choroid	Surgical resection Surgical resection Enucleation/Brachytherapy	0	5
†Singh 2000 [10]	63	16 Iris 13 CB 34 Choroid	39 Enucleation 9 Brachytherapy 3 Surgical resection	6.4	4.5
Gailloud 1992 [8]	11	3 CB 8 Choroid	Proton beam radiotherapy	NA	1.9
Shields 1991 [6]	40	5 Iris 35 Choroid	24 Enucleation 7 Surgical resection 3 Brachytherapy 6 No treatment	2.5	5.7
Barr 1981 [5]	78	36 Iris 42 CB/Choroid	Enucleation and Surgical resection	22	16
Leonard 1975 [12]	7	2 Iris 5Choroid	2 Iridectomy 5 Enucleation	0	3
Verdaguer 1965 [4]	7	2 Iris 2 CB 3 Choroid	2 Iridectomy 5 Enucleation	0	3
Apt 1962 [3]	46	19 Iris 27 CB/Choroid	NA	15	NA

* matched control group; †historical control group; data not available (NA), UM = Uveal Melanoma, CB = Cilary Body.

Table 9: Review of the literature: children less than 16 years old who died from metastatic disease

Reference	Sex/Age (years)	Tumor size	Tumor location	Treatment	Metastatic occurrence (years)
Apt, 1962 [3]	F/2 M/11	NA NA	Iris Choroid	Enucleation Enucleation	6 NA
Barr, 1981 [5]	NA/3 NA/<16 NA/<16 NA/5 NA/2	NA NA NA NA NA	Choroid Choroid Choroid Iris Iris	Enucleation Enucleation Enucleation NA NA	NA
Colombo, 1935 [20]	F/3	NA	Choroid	Enucleation	0.5
Cury, 1959 [21]	M/5 M/11	16x17 mm 12x16 mm	CB Choroid	Enucleation Enucleation	NA
Fenske, 1964 [56]	F/11	NA	Iris	Enucleation	6
Rosembaum, 1988 [22]	M/5	NA	Iris, CB	Enucleation	0.8
Broadway, 1991 [23]	M/Congenital	40x50 mm	Choroid	Enucleation	Present at birth
Grabowska, 2011 [24]	M/1	15 mm (H)	Iris	Enucleation	0.5

NA = data Not Available, F = Female, M = Male, CB = Ciliary Body, H = Height

Figure 1

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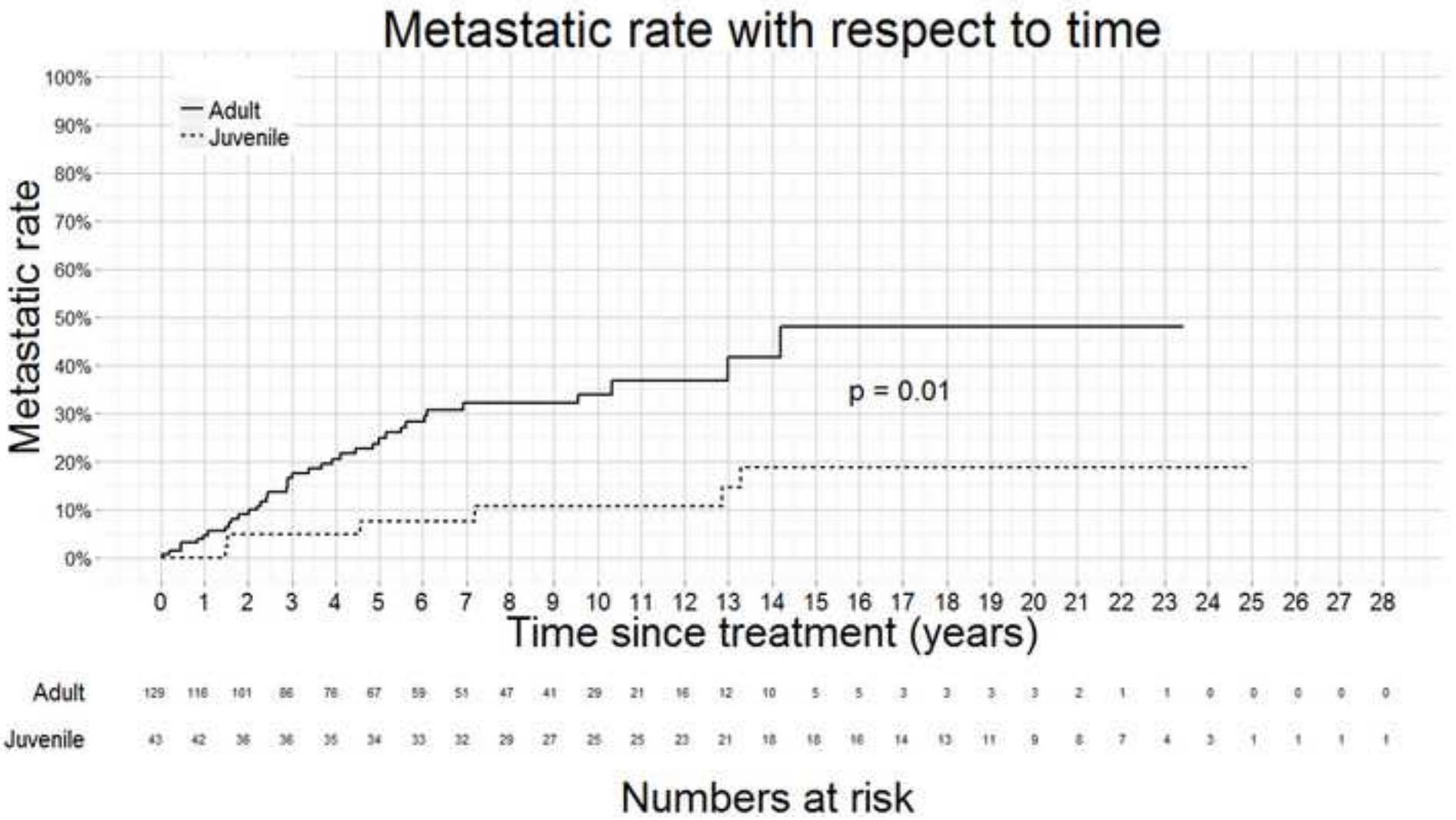

Figure 2

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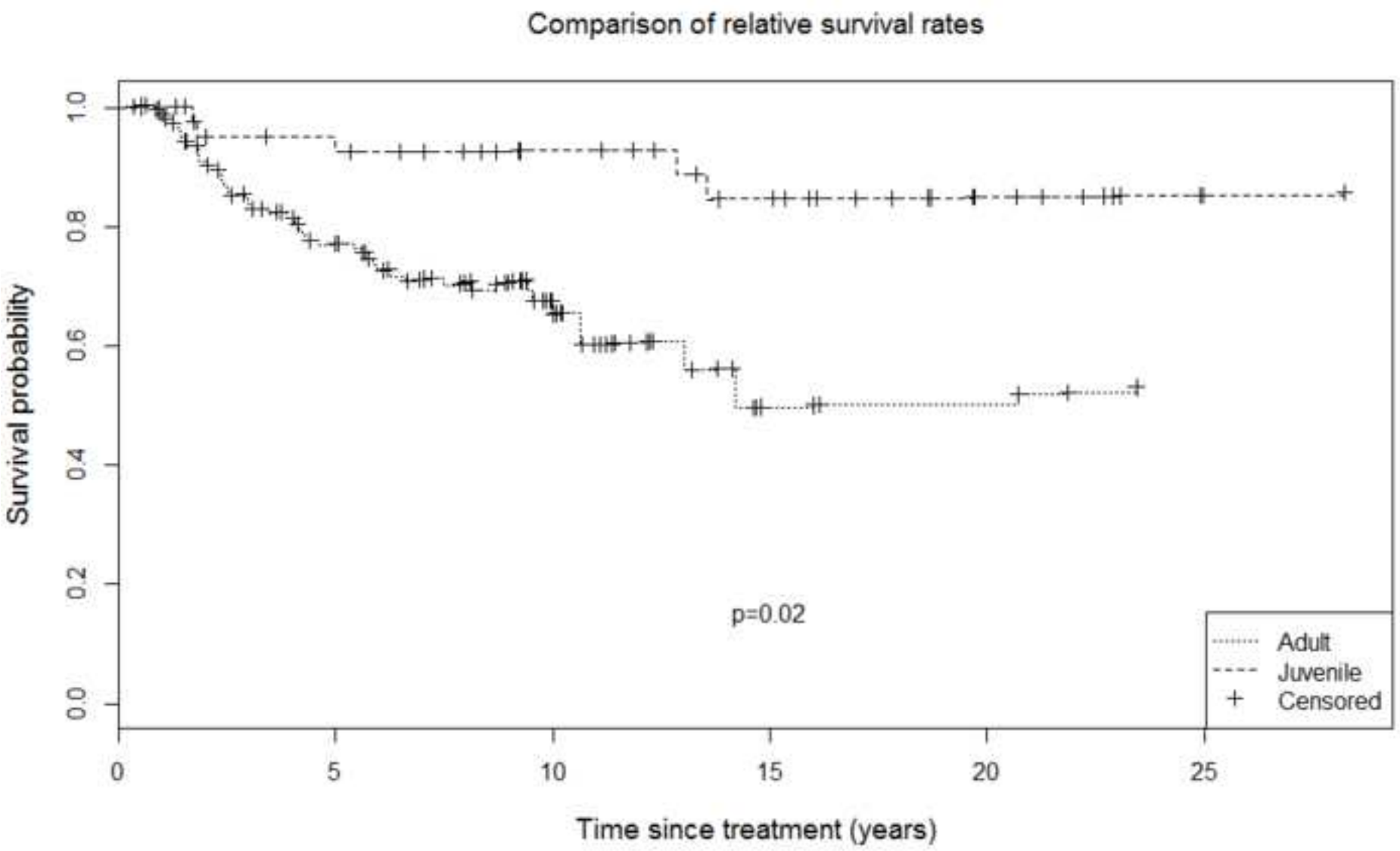

Figure 3

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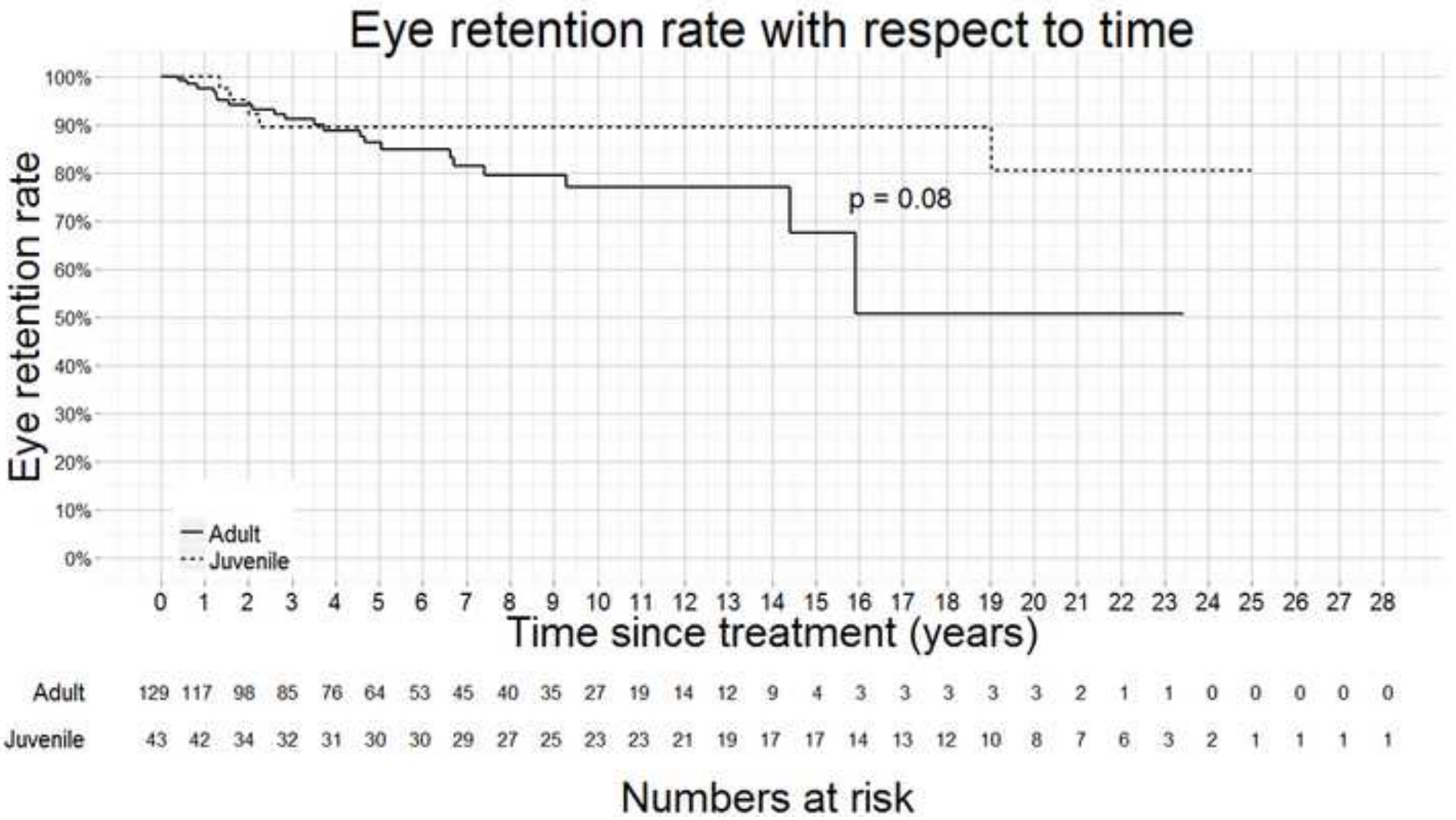

FIGURE LEGENDS

Figure 1: Kaplan-Meier metastatic rate curves comparing the juvenile and adult control uveal melanoma groups.

Figure 2: Relative survival rates comparing the juvenile and adult control uveal melanoma groups (Hakulinen method).

Figure 3: Kaplan-Meier eye retention curves comparing the juvenile and adult control uveal melanoma groups.