

Author Manuscript

Faculty of Biology and Medicine Publication

This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Published in final edited form as:

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

Authors: Petrovic A, Bergin C, Schalenbourg A, Goitein G, Zografos L

Journal: Ophthalmology

Year: 2014 Apr

Volume: 121

Issue: 4

Pages: 898-904

DOI: 10.1016/j.optha.2013.10.032

In the absence of a copyright statement, users should assume that standard copyright protection applies, unless the article contains an explicit statement to the contrary. In case of doubt, contact the journal publisher to verify the copyright status of an article.

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

2

3 **Authors:** Aleksandra Petrovic, MD¹

4 Ciara Bergin, PhD¹

5 Ann Schalenbourg, MD¹

6 Gudrun Goitein, MD²

7 Leonidas Zografos, MD¹

8 **Affiliation:**

9 1. Department of Ophthalmology, University of Lausanne, Jules-Gonin Eye Hospital, FAA,
10 Lausanne, Switzerland.

11 2. Paul Scherrer Institute, Villigen, Switzerland

12

13 **Running head:** Proton therapy for juvenile uveal melanoma

14

15 **Corresponding author:** Aleksandra Petrovic

16 Address: Jules-Gonin Eye Hospital, Avenue de France 15, Lausanne CH-1004, Switzerland

17 Tel: +41 21 626 8111

18 Fax: +41 21 626 8889

19 Email: aleksandra-p@hotmail.com

20

21 **Financial support:** No funding received

22 No conflicting relationships exist for any author.

23 Word count: 2677

24 Abstract: 345

25 Tables: 9

26 Figures: 3

27 **ABSTRACT:**

28 **Objectives**

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

31 **Design**

32 Retrospective case-factor matched control study.

33 **Participants and controls**

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

36 **Methods**

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

42 **Main outcome measures**

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

46 **Results**

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

52 27 % (n=35) of matched patients developed metastases, there were 2 cases of local recurrence
53 and 16% (n=21) underwent enucleation due to complications. A visual acuity of >0.10 was
54 maintained in most cases, without any significant differences before or after treatment observed
55 between both groups.

56 **Conclusions**

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

62

63 **INTRODUCTION:**

64 Uveal melanoma (UM) is the most common primary ocular malignancy in adults, with an overall
65 incidence of about 6 new cases per million per year.^{1,2} In 1962, Apt was the first to report on a
66 series of 46 UM patients less than 20 years old, which he labeled “juvenile melanoma”.³ The
67 second cohort, published by Verdaguer in 1965, used 21 years as the upper age limit.⁴ Ever since,
68 series of juvenile UM patients have used this same age as the cut-off point; which has the
69 additional benefit of agreeing with the American Pediatric Academy definition of a child.
70 Juvenile UM is rare, with only one UM patient in a hundred being less than 21 years old.⁵⁻⁷ As a
71 consequence, to the best of our knowledge, there are only ten retrospective series reporting on
72 juvenile UM patients.³⁻¹² In most of these reports, young patients were treated with enucleation,
73 brachytherapy or surgical resection. Following our publication in 1992,⁸ only one other study has
74 described the clinical profile and prognosis of juvenile UM eyes (n=17) treated with proton beam
75 radiotherapy (PBRT).⁹
76 While all reports concluded that young patients tended to have a lower metastatic rate, very little
77 information is available on eye retention probability or visual acuity.^{8,9} The first aim of this study
78 is to compare the long term metastatic and survival rates for a group of juvenile and matched
79 control adult patients following PBRT for UM. The second aim is to examine whether
80 ophthalmologic outcomes such as the eye retention probability, complications requiring surgery
81 or visual function of these juvenile patients differ from their adult counterparts.

82 **METHODS:**

83 **Patients**

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

91 **Treatment and Follow-up**

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

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

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

112 **Statistical analysis**

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

127 **Search of Literature**

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

133 **RESULTS:**

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

144 Six of 43 juvenile patients developed liver metastases (14%) between 2 and 14 years after
145 radiotherapy, five of whom had died less than a year later (12%) (**Table 3**). The surviving patient
146 was treated with immunotherapy, Fotemustine® chemotherapy and radiofrequency, and is in
147 remission, eight years after the biopsy proven presence of ganglion and liver metastases. The
148 primary uveal tumors of these patients were classified¹⁹ as T3 (N=2) or T4 (N=4) and half of
149 them involved the ciliary body. A baseline retinal detachment of at least 2 quadrants was present
150 in four of these patients, which persisted until the last visit for three of them. No juvenile
151 patients with a T1 or T2 tumor developed metastases. On the other hand, in the adult control
152 group, 35 patients developed metastases (27%), all of whom died less than 3 years later. Ten of
153 these 35 adults had a T2 tumor, the remainder presenting a T3 (N=6) or a T4 (N=19) tumor.
154 Kaplan-Meier curves comparing the metastatic rates in both groups (**Figure 1**) show a statistically
155 significant difference, with a metastatic rate in juvenile patients of 8% at 5 years (95% Confidence
156 Interval (CI) [0-16], n=34), 11% at 10 years (95% CI [0-20], n=25) and 19% at 15 years (95% CI
157 [3-32], n=18), whereas the adult controls had a metastatic rate of 24% at 5 years (95% CI [16-33],
158 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

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

187 While the eye retention rate was higher in the juvenile UM group, a comparison of the Kaplan-
188 Meier eye retention curves did not demonstrate a statistically significant difference (p=0.08)
189 (**Figure 3**). An eye retention rate of 90% at 5, 10 and 15 years (95% CI [80-100]; n=31, 24, 18
190 respectively) was observed in the juvenile group, where all but one enucleation took place within
191 the first 5 years following proton therapy. In the adult group the eye retention rate was 86%
192 (95% CI [80-93]), 77% (95% CI [68-88]) and 67% (95% CI [50-90]) at 5, 10 and 15 years
193 respectively.

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

203 **DISCUSSION:**

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

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

219 Examining risk factors for metastases within the juvenile UM group, showed that increasing age
220 proved to be a significant risk factor, which has previously been reported by Kaliki et al.¹¹ In
221 contrast to the traditional 21st birthday of political majority, Swiss pediatricians stop following
222 their patients after their 16th birthday, considering that most of them by then have reached
223 biological maturity. Respecting this distinction, the juvenile group was split into children
224 (<16years) and young adults (16-21years), and the difference in vital prognosis of -mostly
225 prepubescent- children compared to the adults became even more evident; here no UM children
226 developed metastases. On reviewing the literature, including all case reports, it was found that
227 approximately 470 cases of juvenile UM have been reported worldwide.¹⁹⁻⁵⁷ Of these, only 14
228 children (<16 years; 3%) were reported to have died from metastatic disease,^{3,5,19-23,55} (**Table 9**,
229 available at <http://aaojournal.org>) though it should be noted that not all juvenile series specify
230 the age at UM diagnosis of their patients having died from metastases.

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

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

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

246 This case-matched control study is the first to compare eye retention rates after conservative
247 radiotherapy between juvenile and adult control patients with UM. Though in the former group
248 88% of patients kept their eye against only 76% in the latter, this difference was not statistically
249 significant. No significant differences in visual outcome or other ocular parameters were found
250 between juvenile and adult eyes, indicating that following PBRT, juvenile UM eyes do not require
251 a different follow-up and/or management than adult eyes.

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

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

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

265

266

267 **REFERENCES**

- 268 1. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in
269 incidence, treatment and survival. *Ophthalmology*
270 2011;118:1881-5.
- 271 2. Egan KM, Seddon JM, Glynn RJ, et al. Epidemiologic aspects
272 of uveal melanoma. *Surv Ophthalmol* 1988;32:239-51.
- 273 3. Apt L. Uveal melanomas in children and adolescents. *Int*
274 *Ophthalmol Clin* 1962;2(2):403-10.
- 275 4. Verdaguer J Jr. Prepuberal and puberal melanomas in
276 ophthalmology. *Am J Ophthalmol* 1965;60:1002-11.
- 277 5. Barr CC, McLean IW, Zimmerman LE. Uveal melanoma in
278 children and adolescents. *Arch Ophthalmol* 1981;99:2133-6.
- 279 6. Shields CL, Shields JA, Milite J, et al. Uveal melanoma in
280 teenagers and children. A report of 40 cases. *Ophthalmology*
281 1991;98:1662-6.
- 282 7. Pogrzebielski A, Orłowska-Heitzman J, Romanowska-Dixon B.
283 Uveal melanoma in young patients. *Graefes Arch Clin Exp*
284 *Ophthalmol* 2006;244:1646-9.
- 285 8. Gailloud C, Zografos L, Bercher L, et al. Uveal melanomas
286 in patients less than 20 years of age [in German]. *Klin Monbl*
287 *Augenheilkd* 1992;200:428-30.
- 288 9. Vavvas D, Kim I, Lane AM, et al. Posterior uveal melanoma
289 in young patients treated with proton beam therapy. *Retina*
290 2010;30:1267-71.
- 291 10. Singh AD, Shields CL, Shields JA, Sato T. Uveal melanoma
292 in young patients. *Arch Ophthalmol* 2000;118:918-23.
- 293 11. Kaliki S, Shields CL, Mashayekhi A, et al. Influence of
294 age on prognosis of young patients with uveal melanoma: a
295 matched retrospective cohort study. *Eur J Ophthalmol*
296 2013;23:208-16.
- 297 12. Leonard BC, Shields JA, McDonald PR. Malignant melanomas
298 of the uveal tract in children and young adults. *Can J*
299 *Ophthalmol* 1975;10:441-9.

300 13. Zografos L, Perret C, Egger E, et al. Proton beam
301 irradiation of uveal melanomas at Paul Scherrer Institute
302 (former SIN). *Strahlenther Onkol* 1990;166:114.

303 14. Egger E, Zografos L, Munkel G, et al. Results of proton
304 radiotherapy for uveal melanomas. *Front Radiat Ther Oncol*
305 1997;30:111-22.

306 15. Therneau TM, Grambsch PM. Modeling Survival Data:
307 Extending the Cox Model. New York: Springer; 2000:268-83.

308 16. Pohar M et Stare J. Relative survival analysis in R.
309 *Comput Methods Programs Biomed* 2006;81: 272-8.

310 17. The Human Life-Table Database. Switzerland. <Tables used
311 from 1920 to 1998>. Max Planck Gesellschaft; 2013. Available
312 at: [http://www.lifetable.de/cgi-](http://www.lifetable.de/cgi-bin/Country.plx?Country=Switzerland)
313 [bin/Country.plx?Country=Switzerland](http://www.lifetable.de/cgi-bin/Country.plx?Country=Switzerland). Accessed May 30, 2013.

314 18. American Joint Committee on Cancer. AJCC Cancer Staging
315 Manual. 7th ed. New York: Springer; 2010:547-59.

316 19. Colombo G. Sarcoma melanotico della corioide con metastasi
317 palpebrale apigmentata in una bambina di anni tre. *Boll Ocul*
318 1935;14:839-51.

319 20. Cury D, Lucic H, Irvine AR Jr. Prepubertal intraocular
320 malignant melanoma. *Am J Ophthalmol* 1959;47:202-6.

321 21. Rosenbaum PS, Boniuk M, Font RL. Diffuse uveal melanoma in
322 a 5 year-old child. *Am J Ophthalmol* 1988;15:601-6.

323 22. Broadway D, Lang S, Harper J, et al. Congenital malignant
324 melanoma of the eye. *Cancer* 1991;67:2642-52.

325 23. Grabowska A, Abelarias J, Peralta J, et al. Uveal melanoma
326 in a 19-month-old child. *J AAPOS* 2011;15:606-8.

327 24. Shields CL, Kaliki S, Shah SU, et al. Iris melanoma:
328 features and prognosis in 317 children and adults. *J AAPOS*
329 2012;16:10-6.

330 25. Dimaras H, Parulekar MV, Kwok G, et al. Molecular testing
331 prognostic of low risk in epithelioid uveal melanoma in a
332 child. *Br J Ophthalmol* 2013;97:323-6.

333 26. Palazzi MA, Ober MD, Abreu HF, et al. Congenital uveal
334 malignant melanoma: a case report. *Can J Ophthalmol*
335 2005;40:611-5.

336 27. Greer CH. Congenital melanoma of the anterior uvea. *Arch*
337 *Ophthalmol* 1966;76:77-8.

338 28. Posnick JC, Chen P, Zuker R, et al. Extensive malignant
339 melanoma of the uvea in childhood: resection and immediate
340 reconstruction with microsurgical and craniofacial techniques.
341 *Ann Plast Surg* 1993;31:265-70.

342 29. Gambrelle J, Dayan G, Baggetto LG, et al Uveal melanoma in
343 an 18-year-old African black man [letter]. *Acta Ophthalmol*
344 *Scand* 2005;83:134-6.

345 30. Kanthan GL, Grigg J, Billson F, et al. Paediatric uveal
346 melanoma. *Clin Experiment Ophthalmol* 2008;36:374-6.

347 31. Jones ST. Choroidal malignant melanoma in a child. *Br J*
348 *Ophthalmol* 1967;51:489-91.

349 32. Fledelius H, Land AM. Malignant melanoma of the choroid in
350 an 11-month-old infant. *Acta Ophthalmol (Copenh)* 1975;53:160-
351 6.

352 33. Reeh MJ, Petersen P, Kobrin JG, Chenoweth RG. Malignant
353 melanoma of choroid developing in the eye of a three-year-old
354 boy. *Ann Ophthalmol* 1979;11:57-70.

355 34. Hill JC, Stannard C, Bowen RM. Ciliary body malignant
356 melanoma in a black child. *J Pediatr Ophthalmol Strabismus*
357 1991;28:38-40.

358 35. Gündüz K, Shields JA, Shields CL, Eagle RC Jr. Choroidal
359 melanoma in a 14-year-old patient with ocular melanocytosis.
360 *Arch Ophthalmol* 1998;116:1112-4.

361 36. Malik Rahman A, Augsburger JJ, Corrêa ZM. Iridociliary
362 melanoma associated with ocular melanocytosis in a 6-year-old
363 boy. *J AAPOS* 2008;12:312-3.

364 37. Fong A, Lee L, Glasson W. Pediatric choroidal melanoma in
365 a 13-year-old girl--a clinical masquerade. *J AAPOS*
366 2011;15:305-7.

367 38. Newman LP, Wolter JR. Malignant melanoma of the choroid in
368 a nine-year-old girl. *J Pediatr Ophthalmol* 1973;10:44-6.

369 39. Scheffer CH, Binkhorst PG, Hamburg A. Malignant melanoma
370 of the choroid in a 2-year-old infant. *Ophthalmologica*
371 1974;169:401-10.

372 40. Ellsworth RM. Juvenile melanoma of the uvea. *Trans Am Acad*
373 *Ophthalmol Otolaryngol* 1960;64:148-9.

374 41. Goder G. Malignant melanoblastoma of the uvea in childhood
375 with an unusual combination of findings [in German]. *Ber*
376 *Zusammenkunft Dtsch Ophthalmol Ges* 1961;64:445-8.

377 42. Rosenberg AJ. Malignant melanoma of the iris at age
378 fifteen: a clinico-pathologic study. *Trans Pac Coast*
379 *Otoophthalmol Soc Annu Meet* 1955;36:71-5.

380 43. Samuels SL. Juvenile melanoma of the iris. *Trans Am Acad*
381 *Ophthalmol Otolaryngol* 1963;67:718-22.

382 44. Desjardins L, Bondu G, Boutillier J, Dhermy P. Malignant
383 melanoma of the iris in a 16-year-old girl [in French]. *Bull*
384 *Soc Ophtalmol Fr* 1987;87:537-9.

385 45. Chaves E, Granville R. Choroidal malignant melanoma in a
386 two-and-one-half-year-old girl. *Am J Ophthalmol* 1972;74:20-3.

387 46. Ducasse A, Segal A, Favre F, et al. Melanoma of the uvea
388 in young patients. Apropos of 3 cases [in French]. *Bull Soc*
389 *Ophtalmol Fr* 1990;90:195-7.

390 47. Moragrega-Adame E, Rodriguez-Reyes A, Salcedo-Casillas G,
391 et al. Choroidal melanoma in a 6-year-old female:
392 ultrasonographic diagnosis. *Acta Clin Croat*
393 2012;51(suppl):103-6.

394 48. Singh AD, Shields JA, Eagle RC, et al. Iris melanoma in a
395 ten-year-old boy with familial atypical mole-melanoma (FAM-M)
396 syndrome. *Ophthalmic Genet* 1994;15:145-9.

397 49. Faraj H, Levy-Gabriel C, Lumbroso-Le Rouic L, et al.
398 Cavitary choroidal melanoma in a child [in French]. *J Fr*
399 *Ophtalmol* 2006;29:559-63.

400 50. Bürki E. On a sarcoma of the iris in an infant [in
401 German]. *Ophthalmologica* 1961;142:487-99.

402 51. Reese AB. Congenital melanomas. *Am J Ophthalmol*
403 1974;77:789-808.

404 52. Bronner MA. Malignant melanoma of the choroid in young
405 persons [in French]. *Bull Soc Ophtalmol Fr* 1973;73:377-9.

406 53. Haye C, Dufier P, Dhermy P. Melanoma of the choroid in
407 young patients [in French]. *Bull Soc Ophtalmol Fr* 1979;79:537-
408 8.

409 54. Russo A, Coupland SE, O'Keefe M, Damato BE. Choroidal
410 melanoma in a 7-year-old child treated by trans-scleral local
411 resection. *Graefes Arch Clin Exp Ophthalmol* 2010;248:747-9.

412 55. Fenske HD, Burr SP. A lethal iris melanoma in a child.
413 *Surv Ophthalmol* 1964;9:1-4.

414 56. Greven CM, Stanton C, Yeatts RP, Shields CL. Diffuse iris
415 melanoma in a young patient. *Arch Ophthalmol* 1997;115:682-3.

416 57. Levasseur SD, Paton KE, Van Raamsdonk CD, et al. Mutation
417 of *GNAQ* in a cytologically unusual choroidal melanoma in an
418 18-month-old child [letter]. *JAMA Ophthalmol* 2013;131:810-2.

419 58. Kivelä T, Eskelin S, Mäkitie T, Summanen P. Exudative
420 retinal detachment from malignant uveal melanoma: predictors
421 and prognostic significance. *Invest Ophthalmol Vis Sci*
422 2001;42:2085-93.

423

Table 1: Patient characteristics and baseline symptoms

| Patient characteristics | Juvenile UM group (N=43) | Adult control UM group (N=129) |
|--|--|---|
| Mean age at diagnosis (\pm SD) [range] | 17.3 years (\pm 3.5) [9-21] | 50.4 years (\pm 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 | | |
| <ul style="list-style-type: none"> • Loss of vision • Metamorphopsia • Flashes of light • Pain • Floaters • None | <ul style="list-style-type: none"> • 29 (67%) • 6 (14%) • 4 (9%) • 0 • 1 (2%) • 13 (30%) | <ul style="list-style-type: none"> • 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 | Juvenile UM group (N=43) | Adult control UM group (N=129) | p-value |
|-----------------------------------|--------------------------|--------------------------------|---------------|
| tumor characteristics | | | |
| 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 | • 9 (21%) | • 23 (18%) | p=0.97† |
| • Ciliary body | • 7 (16%) | • 24 (18%) | |
| • Anterior choroid | • 9 (21%) | • 28 (22%) | |
| • Posterior choroid | • 18 (42%) | • 54 (42%) | |
| Distance to the optic disc | | | |
| • Infiltration | • 0 | • 12 (9%) | p=0.19† |
| • In contact | • 7 (16%) | • 23 (18%) | |
| • >0 mm & <3.6 mm | • 9 (21%) | • 27 (21%) | |
| • ≥3.6mm | • 27 (63%) | • 67 (52%) | |
| Distance to the macula | | | |
| • In contact | • 10 (23%) | • 43 (33%) | p=0.26† |
| • >0mm & <3.6mm | • 10 (23%) | • 35 (27%) | |
| • ≥3.6mm | • 23 (54%) | • 51 (40%) | |
| Rupture of Bruch's membrane | 5 (12%) | 44 (34%) | p=0.02 |
| Extrascleral extension | 0 | 8 (6%) | p=0.19 |
| TNM stage‡ | | | |
| • 1 | • 4 (9%) | • 4 (3%) | p=0.99† |
| • 2 | • 13 (30%) | • 44 (34%) | |
| • 3 | • 9 (21%) | • 31 (24%) | |
| • 4 | • 17 (40%) | • 50 (39%) | |

* = 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[Click here to download Table: table 3.docx](#)**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[Click here to download Table: table 4 corrected.docx](#)**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[Click here to download Table: table 5 corrected.docx](#)**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 | 9 (21%) | 17 (13%) |
| <ul style="list-style-type: none"> • Strabismus surgery • Glaucoma surgery • Retinectomy/tumorectomy • Scleral graft • Phacoemulsification • Laser for conjunctival telangiectasia • Vitrectomy for massive vitreal hemorrhage | <ul style="list-style-type: none"> • 1 • 2 • 1 • 1 • 8 • 2 • 1 | <ul style="list-style-type: none"> • 0 • 1 • 1 • 0 • 12 • NA • 3 |

UM = Uveal Melanoma, NA = data Not Available.

Table 6[Click here to download Table: table 6 corrected.docx](#)**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 | 0.5 (± 0.4) [0-1.25] | 0.4 (± 0.4) [0-1.5] | 0.2 (± 0.4) [0-1] |
| <ul style="list-style-type: none"> • NLP • ≤ 0.10 • > 0.10 | <ul style="list-style-type: none"> • 0 • 5 (12%) • 38 (88%) | <ul style="list-style-type: none"> • 2 (5%) • 11 (25%) • 30 (70%) | <ul style="list-style-type: none"> • 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 | | | |
| <ul style="list-style-type: none"> • Absent • Present • Pseudophakic | <ul style="list-style-type: none"> • 42 (98%) • 1 (2%) • 0 | <ul style="list-style-type: none"> • 33 (77%) • 10 (23%) • 0 | <ul style="list-style-type: none"> • 17 (45%) • 15 (39%) • 6 (16%) |
| Retinal detachment | | | |
| <ul style="list-style-type: none"> • None • 1 quadrant • ≥ 2 quadrants | <ul style="list-style-type: none"> • 18 (42%) • 12 (28%) • 13 (30%) | <ul style="list-style-type: none"> • 27 (63%) • 7 (16%) • 9 (21%) | <ul style="list-style-type: none"> • 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 | 0.6 (±0.4) [0-1.5] | 0.4 (±0.4) [0-1.5] | 0.3 (±0.4) [0-1.25] |
| <ul style="list-style-type: none"> • NLP • ≤0.10 • >0.10 | <ul style="list-style-type: none"> • 0 • 25 (19%) • 104 (81%) | <ul style="list-style-type: none"> • 6 (5%) • 52 (40%) • 71 (55%) | <ul style="list-style-type: none"> • 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 | | | |
| <ul style="list-style-type: none"> • Absent • Present • Pseudophakic | <ul style="list-style-type: none"> • 112 (87%) • 16 (12%) • 1 (1%) | <ul style="list-style-type: none"> • 86 (67%) • 42 (32%) • 1 (1%) | <ul style="list-style-type: none"> • 33 (36%) • 48 (52%) • 11 (12%) |
| Retinal detachment | | | |
| <ul style="list-style-type: none"> • None • 1 quadrant • 2 quadrants | <ul style="list-style-type: none"> • 60 (47%) • 32 (25%) • 37 (28%) | <ul style="list-style-type: none"> • 74 (57%) • 16 (12%) • 39 (31%) | <ul style="list-style-type: none"> • 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

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 5 Choroid | 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 = Ciliary Body.

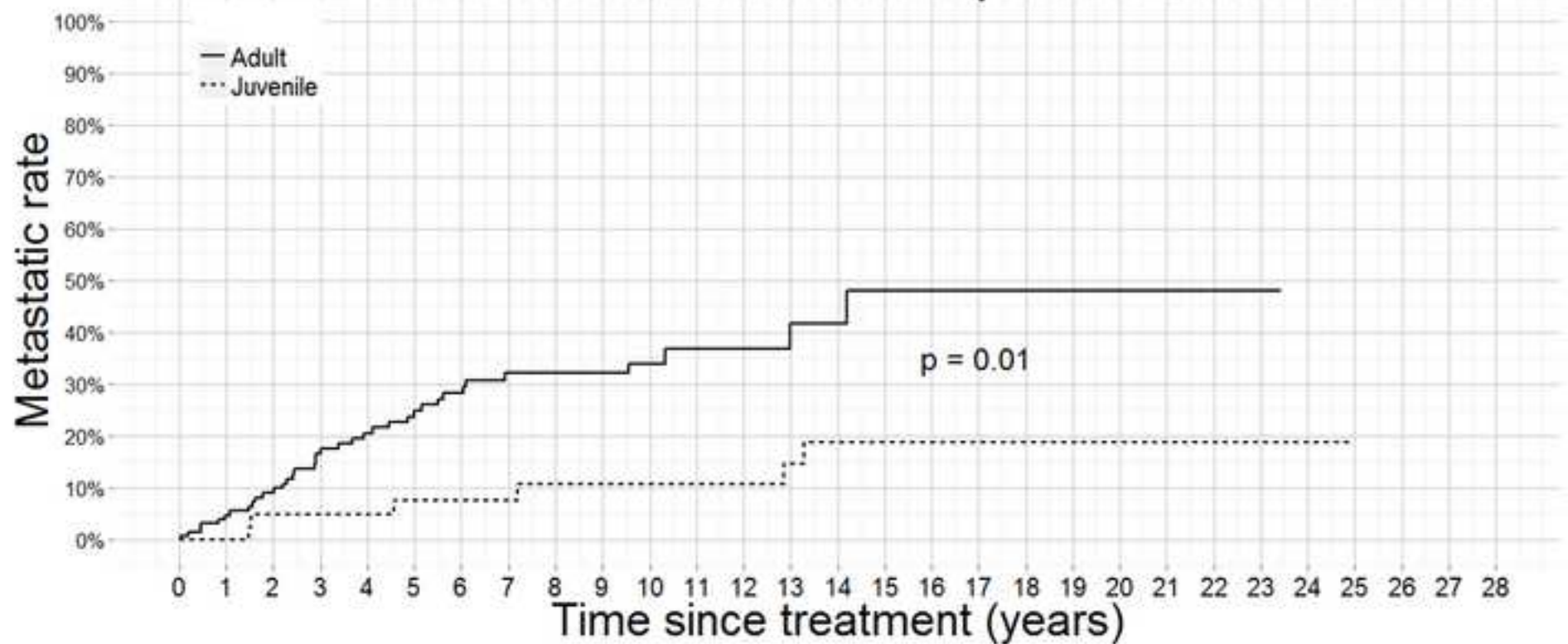
Table 9: Review of the literature: children less than 16 years old who died from metastatic disease

| 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
[Click here to download high resolution image](#)

Metastatic rate with respect to time



| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|----------|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|---|---|---|---|---|---|
| Adult | 129 | 116 | 101 | 86 | 76 | 67 | 59 | 51 | 47 | 41 | 29 | 21 | 16 | 12 | 10 | 5 | 5 | 3 | 3 | 3 | 3 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Juvenile | 43 | 42 | 36 | 36 | 35 | 34 | 33 | 32 | 29 | 27 | 25 | 25 | 23 | 21 | 18 | 16 | 16 | 14 | 13 | 11 | 9 | 8 | 7 | 4 | 3 | 1 | 1 | 1 | 1 |

Numbers at risk

Figure 2
[Click here to download high resolution image](#)

Comparison of relative survival rates

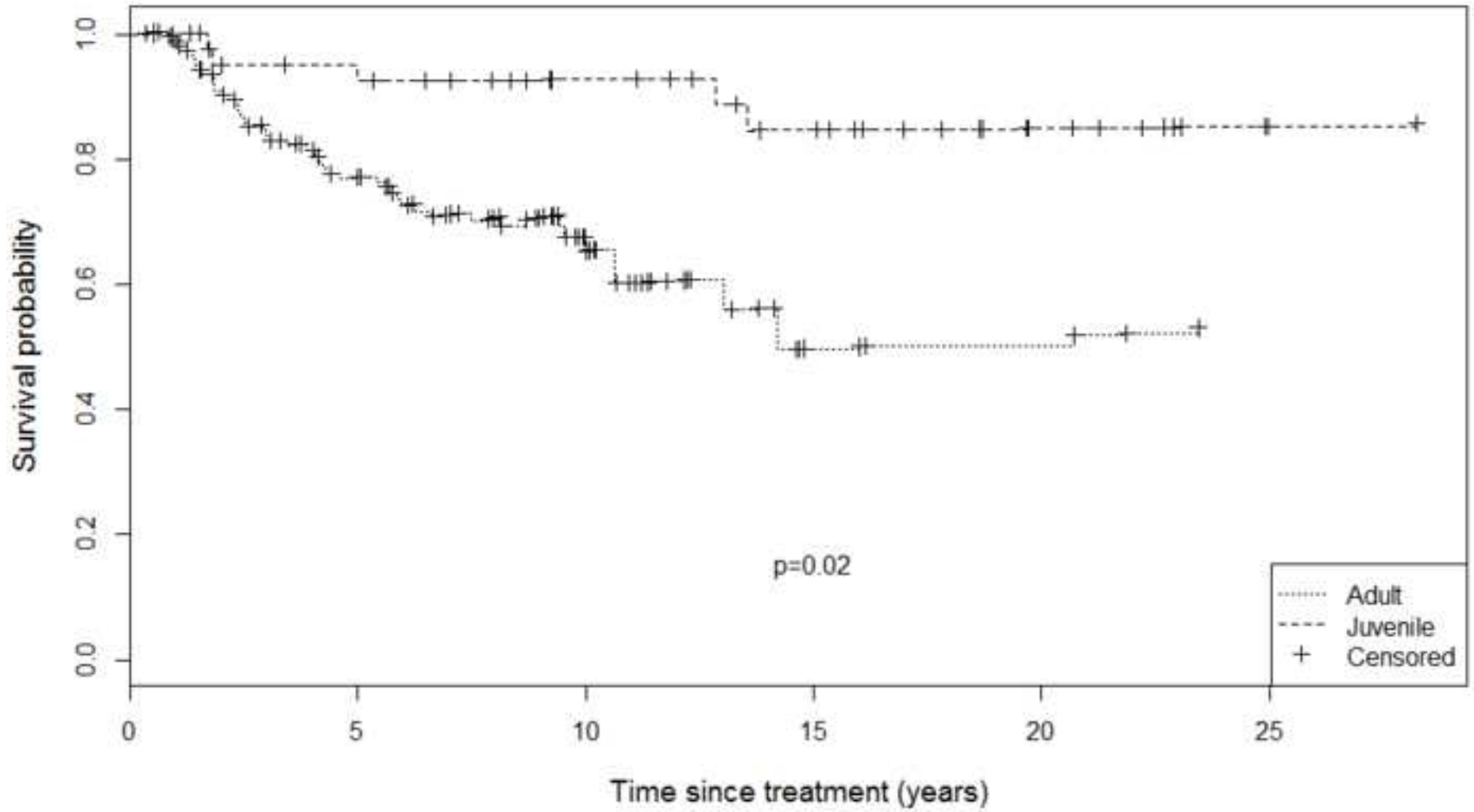


Figure 3
[Click here to download high resolution image](#)

Eye retention rate with respect to time

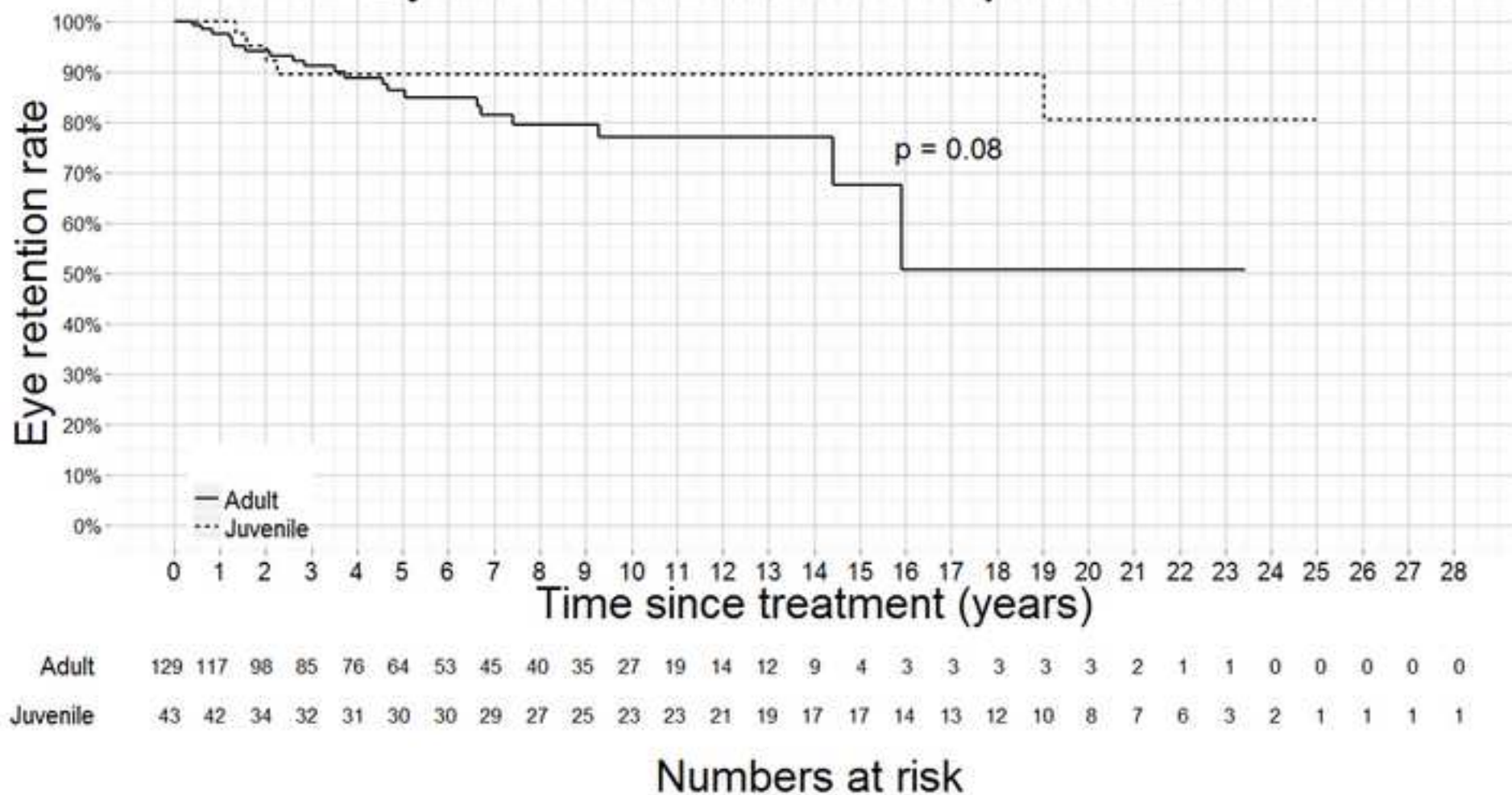


FIGURE LEGENDS

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.