Survival After Proton-Beam Irradiation of Uveal Melanomas

L. KODJIKIAN, MD, PHD, P. ROY, MD, PHD, F. ROUBEROL, MD, J. G. GARWEG, MD, P. CHAUVEL, MD, L. MANON, MD, B. JEAN-LOUIS, MD, R. E. LITTLE, SCD, A. J. SASCO, MD, DRPH, AND J. D. GRANGE, MD

• PURPOSE: To evaluate the independent prognostic factors for survival, metastasis, local recurrence, and enucleation in patients who had undergone proton-beam therapy for posterior uveal melanomas.
• DESIGN: Interventional case series.
• METHODS: In this retrospective study, 224 consecutive incident cases were treated at the Biomedical Cyclotron Centre (Nice, France) from June 1991 to December 1997. Overall, metastasis-free, local recurrence-free, and enucleation-free survival rates were calculated according to the Kaplan-Meier method using the log-rank test. The multivariate prognostic analysis was performed using the Cox proportional hazards model.
• RESULTS: The 5-year overall survival rate was 78.1% (SE: 3.7%). A largest basal tumor diameter (LTD) below 10 mm and female sex were independently associated with a better prognosis. The 5-year metastasis-free survival rate was 75.6% (SE: 3.6%). Only an LTD above 10 mm and ciliary body involvement were independently associated with metastasis. Ten patients (4.5%) had a local recurrence, which was correlated with the risk of metastasis ($P = .045$). The 5-year enucleation-free survival rate was 69.6% (SE: 4.0%). Once again, an LTD below 10 mm and female sex were predictive of a better prognosis.
• CONCLUSION: Our results with proton-beam therapy correspond to those reported in the literature. This treatment strategy is safe and yields predictably good results. In addition to the two independent prognostic factors for survival and metastasis, namely LTD and ciliary body involvement, sex also had a significant impact in our case series, but the clinical relevance of this finding is unknown. (Am J Ophthalmol 2004;137:1002–1010. © 2004 by Elsevier Inc. All rights reserved.)

Biosketch and/or additional material at www.ajo.com
Accepted for publication Jan 2, 2004.

From the Department of Ophthalmology, Croix-Rousse Hospital, and Laboratory Biomaterials and Matrix Remodelling, Claude Bernard University, Lyon, France; Department of Ophthalmology, Inselspital, University of Bern, Bern, Switzerland; Department of Biostatistics, Lyon-Sud Hospital, Pierre-Bénite, Department of Radiotherapy, Biomedical Cyclotron, Comprehensive Cancer Center A. Lacassagne, Nice; and International Agency for Research on Cancer, and Institut National de la Santé et de la Recherche Médicale, Lyon, France.

This study was presented at the 23rd Meeting of the Jules Gonin Club, September 1, 2002, Montreux, Switzerland.

Inquiries to Laurent Kodjikian, MD, PhD, Croix-Rousse Hospital, Department of Ophthalmology, 103 Grande rue de la Croix-Rousse, 69004 Lyon, France; fax: +33-472-071-708; e-mail: kodjikian.laurent@wanadoo.fr

MELANOMAS OF THE UVEA ARE THE MOST COMmonly occurring type of primary intraocular tumor in adults,[1] and may arise in either the anterior (that is, iridial) or the posterior (that is, ciliary body or choroidal or both) portions of this tract. Conservative treatment of uveal melanomas includes brachytherapy using different sources of radiation, transscleral local resection, transpupillary thermotherapy, argon-laser photocoagulation, and external-particle radiotherapy.[2] Proton-beam therapy was first instigated for the handling of uveal melanomas in 1975 by Gragoudas and associates.[3] Several retrospective[4–9] and prospective studies conducted by the Collaborative Ocular Melanoma Study (COMS) Group[10,11] have yielded no evidence in favor of any particular therapeutic strategy (that is, radiation or enucleation). However, external-beam irradiation with accelerated proton particles offers several theoretical advantages over plaque therapy, including an optimal and uniform delivery of radiation to the entire tumor, minimal radiation damage to the surrounding normal tissue and no handling of radioactive elements by the ophthalmologist. We have used this mode of treating uveal melanomas since 1991, when it first became available in our region.

In the present retrospective, interventional case series study, we wished to determine the independent prognostic factors for overall survival, metastasis-free survival, local recurrence-free survival and enucleation-free survival in patients treated for posterior uveal melanomas by proton-beam therapy.

METHODS

• PATIENTS AND TUMORS: Two hundred twenty-four consecutive patients with posterior uveal melanomas were

0002-9394/04/$30.00
doi:10.1016/j.ajo.2004.01.006

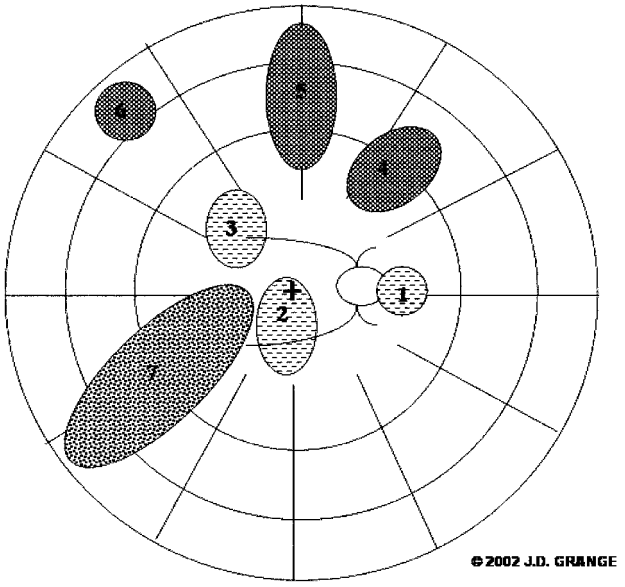

FIGURE 1. Classification of tumor location.

referred to our clinic (Department of Ophthalmology, the Croix-Rousse Hospital, Claude Bernard University, Lyon, France) between June 1, 1991, and December 31, 1997. After proton-beam therapy, each individual was monitored until April 1, 1998 for this study.

During the visit before irradiation, the best-corrected visual acuity of each patient was determined. All patients underwent slit-lamp examination of the anterior segment, which included a measurement of the intraocular pressure. Direct ophthalmoscopy with a three-mirror Goldmann contact lens was used to locate the tumor and estimate its degree of pigmentation, to detect rupturing or penetration of the Bruch membrane and assess the extent of any associated retinal detachment. Fundus photography, fluorescein angiography, and standardized A-scan and B-scan ocular ultrasonography were also performed to determine the largest basal diameter of the tumor (LTD) and its apical height.

Tumors were located in basically seven regions of the uvea (Figure 1): (1) the optic disk; (2) the macula; (3) the posterior pole, outside the macula and optic disk; (4) the peripheral choroid only; (5) the peripheral choroid with extension to the ciliary body; (6) exclusively within the ciliary body; and (7) the posterior pole and peripheral choroid. Categories 1, 2, and 3 represent a "posterior" location; 4, 5, and 6 an "anterior" one; and 7, both. Locations 5 and 6 represent the tumors involving the ciliary body, called "ciliary body location."

Tumors were staged on the basis of their apical height and LTD. Four groups were identified according to the TNM (tumor/node metastasis) classification of malignant tumors (systematized nomenclature of medicine ICD-O C69.3,4)[12]: T1a tumors ($\leq$ 2 mm in height and $\leq$ 7 mm in LTD); T1b tumors ($>$ 2 mm and $\leq$ 3 mm in height and $>$ 7 mm and $\leq$ 10 mm in LTD); T2 tumors ($>$ 3 mm and $\leq$ 5 mm in height and $>$ 10 mm and $\leq$ 15 mm in LTD); and T3 tumors ($>$ 5 mm in height and $>$ 15 mm in LTD). This international classification is almost equivalent to that used by the COMS group, with T1 tumors corresponding to its "small" ones, T2 to its "medium-sized" ones, and T3 to its "large" ones.[13–15]

• **TREATMENT AND FOLLOW-UP:** After positioning four or five tantalium rings around the tumor, which was localized by transillumination or ophthalmoscopy and scleral pressure, proton-beam therapy was administered on four consecutive days, a total dose of 52 Gy protons (60 CGE [Cobalt Gray equivalent]), being delivered at a dose rate of 50 to 60 Gy/min. Proton-beam irradiation requires a cyclotron, which is available at only a few institutions around the world. All patients included in this study underwent radiotherapy at the Antoine Lacassagne Cyclotron Biomedical Centre (Nice, France) and were treated by the same physician (P.C.).

Protons penetrating a mass of tissue induce ionization, which reaches a peak (the Bragg peak) at the precise point of immobilization. The proton-beam is generated using variable initial energies, which permit successive Bragg peaks to take shape at various tissue depths. The summit of these successive peaks forms a plateau of maximum ionization. The objective of the irradiation strategy is to modulate the proton beam in such a way that the plateau of the Bragg peaks falls exclusively within the confines of the tumor mass.

After radiotherapy, all patients were regularly monitored by the same physician (J.D.G.). They were examined every 4 months during the first year, every 6 months during the second year, and annually thereafter. The procedure adopted at the initial check-up was repeated on each subsequent occasion. This strategy permitted the detection of a local recurrence, which was defined as a documented tumor growth appearing after a stable period of remission. Screening for metastasis involved biannual physical examination and abdominal ultrasonography in all cases. If any abnormality was detected, a total body computed tomography (CT) scan was performed. Doubtful cases were confirmed by histology (core needle biopsy) or cytology (fine-needle aspiration) of liver metastases. No chest radiography was performed systematically. Nevertheless, if any clinical abnormality (pulmonary symptoms, neurologic symptoms, bone pain, subcutaneous nodules, lymph nodes, and so forth) or any metastases were detected, wherever located, ancillary screening was performed including total body CT scan.

The date and cause of death or the date on which metastasis was detected were documented. This irradiation and monitoring strategy has been followed for the past 20 years at our clinic.[16]

• **STATISTICAL METHODS:** Overall patient survival time was calculated from the date of onset of proton-beam therapy to the time of death. Observations relating to patients still alive on April 1, 1998 were censored after this date. Metastasis-free survival time was calculated from the date of onset of proton-beam therapy to that on which metastasis was detected or to the time of death. Enucleation-free survival time was calculated from the date of onset of proton-beam therapy to that of enucleation or to the time of death. Data relating to survival, metastasis, local recurrence and enucleation were analyzed to reveal possible associations with age, sex, Bruch membrane rupture, LTD, or tumor location. For the analysis of prognostic factors, patients were stratified according to age (younger or older than 60 years), LTD (below or above 10 mm), and tumor location with or without ciliary body involvement.

Survival and time-to-event rates, together with the SEs, were calculated according to the Kaplan-Meier method.[17] For the multivariate analysis, which was used to evaluate the independence of prognostic factors, the Cox proportional hazards model was adopted, the significance of each parameter being estimated by the likelihood-ratio test.[18] Relative risks were calculated with 95% confidence intervals. The Fisher exact test was used for comparisons when appropriate. A *P* value below .05 was considered to be statistically significant.

RESULTS

• **PATIENT AND TUMOR CHARACTERISTICS:** Data relating to patient and tumor characteristics are presented in Table 1. Patient age at the time of diagnosis ranged from 19 to 85 years (median 61 years). The distribution of tumors between posterior and anterior uveal tracts was comparable. Melanomas involving the ciliary body represented 16.5% of all tumors. Eighty-three percent of the tumors fell into the T2 and T3 (medium-sized and large) categories.

• **OVERALL SURVIVAL:** The median overall survival time to death was 40 months (1,217 days). The follow-up time for patients who were still alive at the study end point was 41 months. Twelve patients were lost to follow-up after a median time of 33 month (992 days) and a minimum period of 12 months, nine of these having been initially referred from abroad. The 5-year Kaplan-Meier overall survival rate was 78.1% (SE: 3.7%; Figure 2). Thirty-two patients (14.3%) died before the study end point. Among these deaths, 30 were tumor-related and two were not.

In a multivariate model including age, sex, LTD, tumor location, and BMR (Table 2), LTD was found to be independently associated with overall survival ($P < .05$). When LTD was greater than 10 mm, the relative risk of mortality was 3.3 times higher than when it was less than 10 mm. In this multivariate model, apical height was statistically significant only when LTD was excluded, owing to the high correlation between these two variables. The staging category, which depends upon both LTD and apical height, was not significant in the Cox model, but

TABLE 1. Characteristics of 224 Consecutive Patients With Malignant Uveal Melanomas Who Underwent Proton-Beam Therapy

Variables	No.	Proportion (%)
Patient characteristics		
Age (yr)		
<40	28	12.5
≥40 and <60	77	34.4
≥60	119	53.1
Sex: Male/female	104/120	46.4/53.6
Tumor characteristics		
Tumor location*		
Posterior	113	50.4
(1) Tumor involving the optic disk	33	14.7
(2) Tumor involving the macula	24	10.7
(3) Tumor located at the posterior pole, outside the macula and optic disk	56	25.0
Anterior	97	43.3
(4) Tumor located in the peripheral choroid	60	26.8
(5) Tumor located in the peripheral choroid and extending to the ciliary body	27	12.0
(6) Tumor located exclusively within the ciliary body	10	4.5
Posterior and anterior		
(7) Tumor located at the posterior pole and in the peripheral choroid	12	5.4
Ciliary body involvement = (5) + (6)	37	16.5
Staging (according to the TNM classification)		
T1a	4	1.8
T1b	34	15.2
T2	67	29.9
T3	119	53.1
Apical height of tumor (mm)		
≤3	40	17.9
>3 and ≤5	65	29.0
>5	119	53.1
Largest basal diameter of tumor (LTD, mm)		
≤10	145	64.7
>10 and ≤15	64	28.6
>15	15	6.7
Bruch membrane rupture	68	30.0

TNM = tumor/node-metastasis.
*Information lacking for two cases.

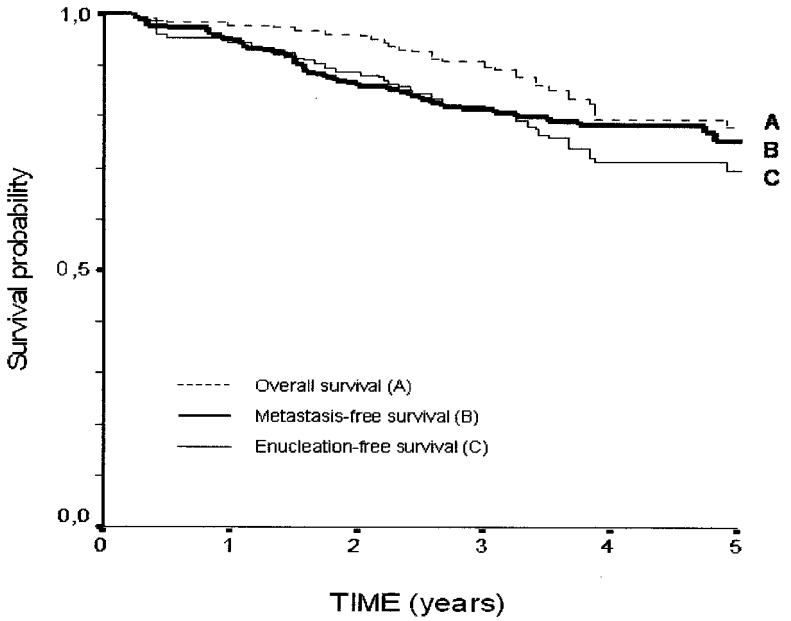

FIGURE 2. Kaplan-Meier curves of overall survival, metastasis-free survival, and enucleation-free survival for 224 patients who underwent treatment by proton-beam therapy for malignant uveal melanomas.

TABLE 2. Overall Survival Analysis of 220 Incident Cases of Uveal Melanoma

Factor	Category	No. of Patients	Relative Risk*	95% CI	*P* Value†
Age (yr)	<60	102	1.00		
	≥60	118	1.43	0.69–2.99	.331
Sex					
Male		104	1.00		
Female		116	0.48	0.23–1.02	.048
Largest basal tumor diameter (mm)	≤10	144	1.00		
	>10	76	3.32	1.56–7.08	.001
Location	Not involving ciliary body	183	1.00		
	Involving ciliary body	37	1.63	0.69–3.83	.279
Bruch membrane rupture	No	154	1.00		
	Yes	66	1.25	0.54–2.88	.613

CI = confidence interval.

*The relative risks of death were determined according to age group, sex, largest basal tumor diameter, tumor location, and Bruch membrane rupture (Cox model). Four cases were excluded owing to an absence of information with respect to Bruch membrane rupture (n = 2) and tumor location (n = 2).

†Likelihood ratio test for heterogeneity.

was negatively related to survival in the Kaplan-Meier analysis. Thus, the larger the melanoma volume, the worse the prognosis. Sex was also associated with outcome, which was more favorable for women than for men (P = .048). In contrast to the univariate survival analysis, tumors involving the ciliary body were not independently associated with prognosis in the multivariate survival model. This circumstance may relate to the large volume of the ciliary body melanomas, 49% of which (18/37 patients) had an LTD above 10 mm and 84% (31/37 patients) an apical height above 5 mm. Thus, 84% were classified as T3 and 100% as T2 or T3. Tumors involving the ciliary body tend to be diagnosed later in life than those affecting other regions of the uvea because they remain asymptomatic longer, and they thus attain a larger size before detection. The multivariate analysis revealed

TABLE 3. Metastasis-free Survival Analysis of 220 Incident Cases of Uveal Melanoma

Factor	Category	No. of Patients	Relative Risk*	95% CI	*P* Value†
Age (yr)	<60	102	1.00		
	≥60	118	1.28	0.68–2.42	.440
Sex					
Male		104	1.00		
Female		116	0.57	0.30–1.06	.071
Largest basal tumor diameter (mm)	≤10	144	1.00		
	>10	76	2.89	1.52–5.49	.001
Location	Not involving ciliary body	183	1.00		
	Involving ciliary body	37	2.28	1.13–4.63	.030
Bruch membrane rupture	No	154	1.00		
	Yes	66	1.21	0.59–2.46	.607

CI = confidence interval.

*The relative risks of death were determined according to age group, sex, largest basal tumor diameter, tumor location, and Bruch membrane rupture (Cox model). Four cases were excluded owing to an absence of information with respect to Bruch membrane rupture (n = 2) and tumor location (n = 2).

†Likelihood ratio test for heterogeneity.

tumor size to predominate over location for overall survival. Finally, age was generally not a useful prognostic factor. However, all 28 patients who were younger than 40 years were still alive at the end of the study, with a median follow-up time of 40 months (1,202 days) and a minimum follow-up of 3 months.

• **METASTASIS-FREE SURVIVAL:** In 40 patients (17.9%) metastasis developed before the study end point, thus yielding a 5-year metastasis-free survival rate of 75.6% (SE: 3.6%; Figure 2). Among the 32 patients who died during the study period, 30 had developed metastasis, the median survival time after its detection being 303 days (range 0 to 1,035 days). At the time when the uveal melanomas were diagnosed in this study, there was no evidence of metastasis in any of the patients. The minimal time period between the diagnosis of the uveal melanoma and the detection of the metastasis was 3 months.

In a multivariate model including age, sex, LTD, tumor location and BMR, only an LTD greater than 10 mm and a ciliary body location were independently associated with metastasis (Table 3). Sex had a bearing on metastasis-free survival only in the univariate analysis, not in the multivariate one.

• **LOCAL RECURRENCE-FREE SURVIVAL:** Ten patients (4.5%) had a local recurrence with a median time of 7 months (range 4 to 18 months). In eight of these (80%), the initial melanoma was classified as being T3, whereas only 50% of the 224 melanomas of our series were classified T3. Four patients presented with location 1 (Figure 1), two patients with location 2, one patient with location 4, one patient with location 5, and two patients with location 7. Among the 224 patients, 57 presented with a peripapillary or perimacular location (Table 1), and six of these 57 (10.5%) had therefore a local recurrence. Consequently, local recurrences were more frequent in melanoma of peripapillary/perimacular location ($P = .019$). Two types of recurrences were identified: marginal recurrence in one case (10%) of a peripapillary tumor and total increase in tumor size in nine cases (90%). Recurrences were treated by enucleation in six patients, by a secondary proton beam therapy in two, and by ruthenium-106 brachytherapy in one; death occurred before any secondary treatment in one patient.

Four of the patients manifested metastasis, but only one of these died of this cause during the observation period. Twenty-one percent (n = 44) of patients without and 40% (n = 4) with local recurrences manifested metastasis ($P = .045$). Local recurrence was thus significantly associated with the risk of metastasis and subsequent death.

• **ENUCLEATION-FREE SURVIVAL:** During the study period, we observed at least one ocular complication in 127 patients (57%): maculopathy (n = 100; 45%), optic neuropathy (n = 17; 8%), vascular occlusion (n = 36; 16%), retinal detachment (n = 11; 5%), and neovascular glaucoma (n = 31; 14%). This led to enucleation in 22 patients (9.8%), which was performed after a median follow-up period of 18 months (range 4 to 47). Enucleation was performed for either painful blindness with neovascular glaucoma (14 patients), local recurrence of the tumor

TABLE 4. Enucleation-free Survival Analysis of 220 Incident Cases of Uveal Melanoma

Factor	Category	No. of of Patients	Relative Risk*	95% CI	*P* Value†
Age (yr)	<60	102	1.00		
	≥60	118	1.48	0.81–2.70	.194
Sex					
Male		104	1.00		
Female		116	0.44	0.24–0.81	.006
Largest basal tumor diameter (mm)	≤10	144	1.00		
	>10	76	3.96	2.15–7.28	<.001
Location	Not involving ciliary body	183	1.00		
	Involving ciliary body	37	1.17	0.56–2.45	.678
Bruch membrane rupture	No	154	1.00		
	Yes	66	1.36	0.72–2.58	.350

CI = confidence interval.

*The relative risks of death were determined according to age group, sex, largest basal tumor diameter, tumor location, and Bruch membrane rupture (Cox model). Four cases were excluded owing to an absence of information with respect to Bruch membrane rupture (n = 2) and tumor location (n = 2).

†Likelihood ratio test for heterogeneity.

(six patients), or complete retinal detachment associated with visual loss (five patients). In three patients, two causes were operative. The 5-year enucleation-free survival rate was 69.6% (SE: 4.0%; Figure 2). Histopathology revealed six of the tumors to be epithelioid, eight to be spindle cell type, seven to be of mixed cell type, and one to be completely necrotic. Local recurrences were not linked to a particular histopathologic type. Seventeen of the 22 patients (77.3%) were still alive at the study end point.

In the multivariate analysis, an LTD below 10 mm and female sex were predictive of a better enucleation-free survival (Table 4).

DISCUSSION

OUR CASE SERIES INCLUDED A LARGE NUMBER OF UVEAL melanoma patients who were monitored for a sufficient length of time after proton-beam therapy to permit not only a calculation of survival rates but also an assessment of the prognostic factors using a multivariate model.

North American centers mostly use clinical examination, liver function test, and chest radiograph for screening, even though imaging of the liver as an additional measure has been recommended by investigators interested in metastatic melanoma. In some European countries, imaging of the liver has been routine for the last decade and is used alone. This strategy has been followed for the past 20 years at our clinic. In a recent study, whose purpose was to assess the value of routine imaging and liver function tests in detecting metastases from uveal melanoma, two patients (4.3%) only had extrahepatic (pulmonary) metastases and they were both symptomatic.[16] In other words, all 27 entirely asymptomatic patients of this series presented with liver metastases associated sometimes with metastases at other sites. One might argue that the two reported cases with pulmonary metastases had become symptomatic because screening based on abdominal ultrasonography and physical examination had led to a delay in diagnosis. But the fact that the median size of largest metastasis, tumor burden, and disease-free interval of patients who did or did not develop symptoms were overlapping suggests that some patients are more prone to develop manifestations than others. We finally agree with the arguments of Eskelin and associates,[16] that screening with abdominal ultrasonography and physical examination is the recommended diagnostic strategy, and that chest radiography has to be abandoned as a follow-up examination.

The 5-year overall survival rate of 78.1% in our case series corresponds well with literature values relating to the same therapy, these being 80% for the Harvard Cyclotron team,[19] 85% for the Paul Scherrer Institute,[20] and 70.3% for the Loma Linda University Medical Center (for T2 and T3 melanomas).[21] These results are comparable to those obtained after brachytherapy, which range from 78% to 89.6%,[22,23] but better than those attained after enucleation, which are reported to be 84%, 68%, and 47% for small, medium-sized, and large tumors, respectively.[24] However, more recent data furnish no evidence in favor of any particular mode of therapy.[4,11,25,26] According to the

literature, the most relevant clinical risk factors for survival, irrespective of the treatment used, are a large tumor size, an anterior location, and an advanced patient age.[25,27] In our multivariate model, tumor size was likewise found to affect the outcome, since LTD was independently associated with mortality. However, ciliary body involvement was not independently associated with survival, owing to the high proportion of large tumors in this region. In our multivariate analysis, adjusting for confounding variables using the Cox proportional hazards model, the size of the tumor largely predominated over its location. Also in contrast with the literature,[25] age was not a significant prognostic factor in our series.

The incidence of, and prognostic factors for, metastasis in patients who have undergone enucleation or irradiation for uveal melanomas have been previously published.[25,26,28] The rate of metastasis (17.9%) and the 5-year metastasis-free survival rate (75.6%) determined for our case series correspond to values reported in the literature.[21,25,28] As found for overall survival, LTD was also the most relevant clinical risk factor for metastasis in our case series, which is consistent with previously published findings, relating not only to proton-beam therapy[25] but also to enucleation.[26] Moreover, in both our series and previous studies,[26,29] patients with ciliary body melanomas had a worse prognosis for metastasis, irrespective of tumor size, than did those with melanomas involving other regions of the uvea. Indeed, tumors involving the ciliary body are known to be more likely to harbor monosomy of chromosome 3 and trisomy of chromosome 8q, a situation that is associated with a very high risk for metastatic death.[30–32] Clearly, tumor genetics may represent an as yet unexplored confounder of prognosis. Against this background, the consistency of the results yielded by independent studies is thus somewhat surprising.

In our case series, 4.5% of patients (10/224) had local recurrences. This rate lies within the reported range for proton-beam irradiation of uveal melanomas, that is, 1.1.% to 9.4%,[33,34] which is moreover much lower than the 5-year values attained after brachytherapy with either cobalt ions (12% to 14%),[35,36] ruthenium-106 (19% to 41%),[37,38] or iodine-125 (4.2% to 15%).[39–42] One of the greatest advantages of proton-beam therapy, from which the low recurrence rates probably result, is that the radiation dose can be more accurately localized to the tumorous mass than is possible with brachytherapy. Local recurrence is an important issue, because it was associated with a higher risk of metastasis in our case series and thus with a poorer prognosis. Indeed, many authors have shown tumor recurrence to be a negative predictor of survival.[33,34,36,42] Within the framework of these findings, proton-beam therapy is now the recommended treatment for uveal melanomas, especially for tumors with an apical height above 5 mm or LTD exceeding 10 mm, or both, albeit that it is not yet universally available.[43] Because local recurrence and the risk of metastasis are associated with a poor prognosis, the tumors involved may share genetic features in common, such as monosomy for chromosome 3 or trisomy for chromosome 8q,[30–32] and thus be similarly resistant to treatment. Nine of 10 local recurrences manifested by total increase in tumor size, which is most likely from radio-resistance of the melanoma, whereas previous studies found a predominance of marginal recurrences,[33,34,43] which is usually from a planning failure. Our single marginal recurrence developed indeed from a peripapillary melanoma, considering safety margins were reduced to preserve the optic disk. Eight of these 10 melanomas were large tumors, which may have outgrown the local blood supply and become hypoxic, rendering them less sensitive to irradiation. In literature, recurrences occur more commonly among large tumors and tumors involving the ciliary body (multivariate analysis).[33,34,44] In our series, six melanomas with local recurrences (60%) were located in the posterior pole. Among these, five presented total increase in tumor size, which seems more related to the large volume of these tumors than to their location. The high proportion of ciliary body melanomas in published series, which contrast with the present one (only one case), may be related to the fact that many ciliary body ring melanomas are not initially diagnosed as such and recur outside of the treated area. The higher likelihood of recurrences may also refer to the fact that planning errors are more frequent because visualization of the tumor margins by transillumination is complex and that genetic alterations appear more commonly in ciliary body tumors.[34,44]

The overall rate of ocular complications (57%) and of enucleations (9.8%), with a 5-year enucleation-free survival rate of 69.6%, may well have to be included in the treatment decision. Five- and 10-year enucleation rates of 8% and 11%, respectively, have been reported for proton-beam therapy,[45] the corresponding ones for helium therapy being 17% and 22.4%,[46] and those for ruthenium-106-brachytherapy 11% and 18%.[38,47,48] Because 77% of our patients who underwent enucleation were still alive at the study end point, this undertaking did not appear to have a deleterious effect on an individual patient's survival. In our series, the leading risk factors for enucleation were an LDT above 10 mm and male sex, whereas the most common factors reported in the literature are tumor size and ciliary body involvement.[49] In our series, sex was only weakly correlated with overall survival and metastasis-free survival, but strongly so with enucleation-free survival. No obvious selection factor was revealed among the various patient or tumor characteristics. Because we cannot account for it on a pathophysiologic basis, its clinical relevance remains obscure.

An obvious limitation of our study is its retrospective nature, but because we did not aim at comparing therapies, this restriction is of minor bearing. The strength of the study lies in the circumstance that each of the 224 patients was irradiated according to the same therapeutic strategy

by the same clinician at a single center and subsequently monitored by the same ophthalmologist.

Our data consolidate previously published findings relating to proton-beam therapy and confirm that is a safe and predictable mode of treatment for white patients with posterior uveal melanomas.

REFERENCES

1. Shields J, Shields C. Intraocular tumors: a text and atlas. Philadelphia: WB Saunders, 1992.
2. Shields JA, Shields CL. Current management of posterior uveal melanoma. Mayo Clin Proc 1993;68:1196–1200.
3. Gragoudas ES, Goitein M, Koehler AM, et al. Proton irradiation of small choroidal malignant melanomas. Am J Ophthalmol 1977;83:665–673.
4. Seddon JM, Gragoudas ES, Albert DM, et al. Comparison of survival rates for patients with uveal melanoma after treatment with proton beam irradiation or enucleation. Am J Ophthalmol 1985;99:282–290.
5. De Potter P, Shields CL, Shields JA, Cater JR, Tardio DJ. Impact of enucleation versus plaque radiotherapy in the management of juxtapapillary choroidal melanoma on patient survival. Br J Ophthalmol 1994;78:109–114.
6. Augsburger JJ, Correa ZM, Freire J, Brady LW. Long-term survival in choroidal and ciliary body melanoma after enucleation versus plaque radiation therapy. Ophthalmology 1998;105:1670–1678.
7. Adams KS, Abramson DH, Ellsworth RM, et al. Cobalt plaque versus enucleation for uveal melanoma: comparison of survival rates. Br J Ophthalmol 1988;72:494–497.
8. Lommatzsch PK. Results after beta-irradiation (106Ru/106Rh) of choroidal melanomas: 20 years' experience. Br J Ophthalmol 1986;70:844–851.
9. Char DH, Castro JR, Quivey JM, et al. Uveal melanoma radiation. 125I brachytherapy versus helium ion irradiation. Ophthalmology 1989;96:1708–1715.
10. Diener-West M, Earle JD, Fine SL, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma. II: characteristics of patients enrolled and not enrolled. COMS report no 17. Arch Ophthalmol 2001;119:951–965.
11. Diener-West M, Earle JD, Fine SL, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma. III: initial mortality findings. COMS report no 18. Arch Ophthalmol 2001;119:969–982.
12. Hermanek P, Sobin L. Union Internationale Contre le Cancer. TNM classification of malignant tumours [translation]. Geneva: Springer-Verlag, 1988.
13. Collaborative Ocular Melanoma Study Group. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15. Arch Ophthalmol 2001;119:670–676.
14. Melia BM, Abramson DH, Albert DM, et al. Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years. COMS report no 16. Ophthalmology 2001;108:348–366.
15. Collaborative Ocular Melanoma Study Group. Factors predictive of growth and treatment of small choroidal melanoma: COMS report no. 5. The Collaborative Ocular Melanoma Study Group. Arch Ophthalmol 1997;115:1537–1544.
16. Eskelin S, Pyrhonen S, Summanen P, Prause JU, Kivela T. Screening for metastatic malignant melanoma of the uvea revisited. Cancer 1999;85:1151–1159.
17. Kaplan E, Meier P. Non-parametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457–481.
18. Cox D. Regression models and life-tables (with discussions). J Roy Statist Soc Series B 1972;34:187–220.
19. Krengli M, Munzenrider J, Suit H. Clinical experience with proton beam therapy at MGH, MEEI, and HCL: skull base sarcoma and uveal melanoma. In: Amaldi U, Larsson B, Lemoigne Y, editors. Advances in hadrontherapy. Amsterdam: Elsevier, 1997:95–102.
20. Egger E, Zografos L. Proton beam irradiation of uveal melanoma at PSI: latest results. In: Amaldi U, Larsson B, editors. Hadrontherapy in oncology. Amsterdam: Elsevier, 1994:145–149.
21. Fuss M, Loredo LN, Blacharski PA, Grove RI, Slater JD. Proton radiation therapy for medium and large choroidal melanoma: preservation of the eye and its functionality. Int J Radiat Oncol Biol Phys 2001;49:1053–1059.
22. Lommatzsch PK, Werschnik C, Schuster E. Long-term follow-up of Ru-106/Rh-106 brachytherapy for posterior uveal melanoma. Graefes Arch Clin Exp Ophthalmol 2000;238:129–137.
23. Grange J, Joschi G, Gerard J, et al. Results of 10 years' experience with contact beta-therapy with Ruthénium 106 applicators for uveal melanoma. Review of 207 cases and tribute to PK Lommatzsch [translation]. Ophtalmologie 1995;9:317–323.
24. Diener-West M, Hawkins BS, Markowitz JA, Schachat AP. A review of mortality from choroidal melanoma. II. A meta-analysis of 5-year mortality rates following enucleation, 1966 through 1988. Arch Ophthalmol 1992;110:245–250.
25. Gragoudas ES, Seddon JM, Egan KM, et al. Metastasis from uveal melanoma after proton beam irradiation. Ophthalmology 1988;95:992–999.
26. Seddon JM, Albert DM, Lavin PT, Robinson N. A prognostic factor study of disease-free interval and survival following enucleation for uveal melanoma. Arch Ophthalmol 1983;101:1894–1899.
27. Kroll S, Char DH, Quivey J, Castro J. A comparison of cause-specific melanoma mortality and all-cause mortality in survival analyses after radiation treatment for uveal melanoma. Ophthalmology 1998;105:2035–2045.
28. Gragoudas ES, Seddon JM, Egan KM, et al. Prognostic factors for metastasis following proton beam irradiation of uveal melanomas. Ophthalmology 1986;93:675–680.
29. Raivio I. Uveal melanoma in Finland. An epidemiological, clinical, histological and prognostic study. Acta Ophthalmol 1977;133(Suppl):1–64.
30. Li W, Gragoudas ES, Egan KM. Metastatic melanoma death rates by anatomic site after proton beam irradiation for uveal melanoma. Arch Ophthalmol 2000;118:1066–1070.
31. Sisley K, Rennie IG, Parsons MA, et al. Abnormalities of chromosomes 3 and 8 in posterior uveal melanoma correlate with prognosis. Genes Chromosomes Cancer 1997;19:22–28.
32. Prescher G, Bornfeld N, Hirche H, et al. Prognostic implications of monosomy 3 in uveal melanoma. Lancet 1996;347:1222–1225.
33. Egger E, Schalenbourg A, Zografos L, et al. Maximizing local tumor control and survival after proton beam radiotherapy of uveal melanoma. Int J Radiat Oncol Biol Phys 2001;51:138–147.
34. Gragoudas ES, Egan KM, Seddon JM, Walsh SM, Munzenrider JE. Intraocular recurrence of uveal melanoma after proton beam irradiation. Ophthalmology 1992;99:760–766.
35. Bacin F, Kwiatkowski F, Dalens H, et al. Long-term results of

cobalt 60 curietherapy for uveal melanoma [translation]. J Fr Ophtalmol 1998;21:333–344.
36. Karlsson UL, Augsburger JJ, Shields JA, et al. Recurrence of posterior uveal melanoma after 60Co episcleral plaque therapy. Ophthalmology 1989;96:382–388.
37. Summanen P, Immonen I, Heikkonen J, et al. Survival of patients and metastatic and local recurrent tumor growth in malignant melanoma of the uvea after ruthenium plaque radiotherapy. Ophthalmic Surg 1993;24:82–90.
38. Foerster MH, Bornfeld N, Schulz U, Wessing A, Meyer-Schwickerath G. Complications of local beta radiation of uveal melanomas. Graefes Arch Clin Exp Ophthalmol 1986; 224:336–340.
39. Wilson MW, Hungerford JL. Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma. Ophthalmology 1999;106: 1579–1587.
40. Packer S, Stoller S, Lesser ML, Mandel FS, Finger PT. Long-term results of iodine 125 irradiation of uveal melanoma. Ophthalmology 1992;99:767–774.
41. Fontanesi J, Meyer D, Xu S, Tai D. Treatment of choroidal melanoma with I-125 plaque. Int J Radiat Oncol Biol Phys 1993;26:619–623.
42. Harbour JW, Char DH, Kroll S, Quivey JM, Castro J. Metastatic risk for distinct patterns of postirradiation local recurrence of posterior uveal melanoma. Ophthalmology 1997;104:1785–1793.
43. Gragoudas ES, Li W, Goitein M, et al. Evidence-based estimates of outcome in patients irradiated for intraocular melanoma. Arch Ophthalmol 2002;120:1665–1671.
44. Gragoudas ES, Lane AM, Munzenrider J, Egan KM, Li W. Long-term risk of local failure after proton therapy for choroidal/ciliary body melanoma. Trans Am Ophthalmol Soc 2002;100:43–48.
45. Egan KM, Ryan LM, Gragoudas ES. Survival implications of enucleation after definitive radiotherapy for choroidal melanoma: an example of regression on time-dependent covariates. Arch Ophthalmol 1998;116:366–370.
46. Char DH, Kroll SM, Castro J. Ten-year follow-up of helium ion therapy for uveal melanoma. Am J Ophthalmol 1998; 125:81–89.
47. Summanen P, Immonen I, Kivela T, et al. Radiation related complications after ruthenium plaque radiotherapy of uveal melanoma. Br J Ophthalmol 1996;80:732–739.
48. Seregard S, aft Trampe E, Lax I, Kock E, Lundell G. Results following episcleral ruthenium plaque radiotherapy for posterior uveal melanoma. The Swedish experience. Acta Ophthalmol Scand 1997;75:11–16.
49. Egan KM, Gragoudas ES, Seddon JM, et al. The risk of enucleation after proton beam irradiation of uveal melanoma. Ophthalmology 1989;96:1377–1383.