Proton Beam Therapy Leads to Excellent Local Control Rates in Choroidal Melanoma in the Intermediate Fundus Zone

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• PURPOSE: To evaluate long-term outcomes of proton beam radiotherapy in the treatment of choroidal melanoma of the intermediate zone of the fundus.
• DESIGN: Retrospective interventional single-center study.
• METHODS: The study was a retrospective analysis with long-term follow-up of 62 patients with a minimum tumor-to-disc and tumor-to-fovea distance of 2 mm of choroidal melanoma in the intermediate zone of the fundus. Mean values of tumor prominence, largest basal diameter, and tumor distances to the optic disc and fovea were 7.6, 12.8, 5.2, and 4.6 mm, respectively. All patients were irradiated with a total proton dose of 60 cobalt gray equivalents.
• RESULTS: After proton beam radiotherapy, 71.0% of the patients received subsequent endoresection of the tumor. Only 18 patients (29.0%) did not require additional tumor resection and were analyzed as a separate group. For the total of patients, the median follow-up time was 70.3 months. The 5-year Kaplan-Meier rates of local tumor relapse, enucleation, and distant metastasis were 3.9%, 3.7%, and 13.4%, respectively. Cataract surgery was the most frequent secondary treatment in our cohort.
• CONCLUSIONS: In this study we demonstrate the effectiveness of proton beam irradiation in tumor control and preservation of the globe in the analyzed patients. The rate of metastasis was not higher than previously described. Nevertheless, consecutive tumor surgery is frequently required to maintain the eye in patients with large-sized choroidal melanomas. In conclusion, proton beam radiotherapy allows preservation of the eye in mid-zone choroidal melanomas. (Am J Ophthalmol 2014;158:1184–1191. © 2014 by Elsevier Inc. All rights reserved.)

NUCLEATION FOR CHOROIDAL MELANOMA HAS BEEN replaced by radiotherapy as an accepted treatment standard. The most popular techniques used for radiotherapy of choroidal melanoma are brachytherapy and proton beam therapy. There are currently more than 30 years of experience with proton beam irradiation.1 The advantage of using protons for irradiation is the fact that the proton energy can be modulated to cover target tissue of any shape and at any depth with a nearly uniform dose owing to its physical characteristics, including minimal scatter and delivery of maximum dose at the end of the beam path, known as Bragg peak. Several investigators have demonstrated a noninferiority of proton beam irradiation with respect to metastasis and tumor-specific survival.2,3 While proton beam therapy has been advocated for central choroidal melanoma with close proximity to the disc and fovea, studies demonstrated that tumors exceeding 6 mm in height can be successfully treated with proton beam therapy if the inflammatory reaction after irradiation is met with surgical excision of the tumor tissue via a transscleral approach or endoresection.2

The present retrospective analysis presents the long-term outcomes in patients with proton beam irradiation for choroidal melanoma in the intermediate zone of the fundus at the Center for Ocular Oncology in Berlin.

METHODS AND MATERIALS

• PATIENTS AND DATA COLLECTION: This is a retrospective single-center study of patients with choroidal malignant melanoma treated with proton beam radiotherapy in Berlin. The study was approved by the institutional review board of the Charité–Universitätsmedizin Berlin, Germany, and was in accordance with the Declaration of Helsinki specifications. This study focuses on tumors in the intermediate zone of the fundus not attaching the ciliary body. The minimal distance of the unifocal lesion to both the optic disc and fovea was 2 mm. Consequently, exclusion criteria for this study were tumor invasion of the anterior eye segment, parapapillary location or location close to the fovea, and pretreatment of the tumor.

From 1998 until 2005, a total number of 62 patients met the inclusion criteria and received proton therapy. Fourty-four
out of 62 tumors (71.0%) were regarded as large-sized, with a prominence of at least 6 mm, and were treated with a combination of primary irradiation and consecutive tumor endoresection performed during the interval between postirradiation day 10 and postirradiation day 30. No additional surgery was performed in 18 patients (29.0%) presenting only small and medium-size tumors and who were pooled in a separate group. The regular treatment for small to medium-size tumors without close proximity to the central ocular structures is ruthenium brachytherapy. Thus, the proton beam–treated group of small and medium-size tumors was rather small. There were no patients with extraocular growth or metastatic disease at the time of diagnosis.

The following clinical data were extracted from the patients’ medical records: treatment type, age, sex, affected eye, tumor location, tumor height, largest basal diameter, fluorescein angiography, and presence of subretinal fluid. Furthermore, side effects of radiation, such as cataract formation or secondary glaucoma, were assessed. Cataract was defined as the first occurrence of lens opacity before or after irradiation. Glaucoma was defined as persistent intraocular pressure of more than 20 mm Hg. Patients with optic nerve damage or with a local therapy at the present time owing to a known history of glaucoma were regarded as glaucoma patients, as well. Visual field was not done to detect abnormalities for diagnosis. Similarly, preexisting sight-threatening ocular diseases and previous surgical interventions were evaluated, as well as visual acuity prior to radiotherapy and during the follow-up. Follow-up visits were usually planned 6, 12, 18, and 24 months after radiotherapy and then annually. Follow-up data that were acquired by the end of December 2010 were considered for this study.

- **TREATMENT PROTOCOL:** A 68-megaelectron-volt proton beam at the Helmholtz-Zentrum Berlin was used to deliver the irradiation dose. Eye position and tumor margins were demarcated by tantalum marker clips prior to radiotherapy. During treatment the patient’s head was immobilized using an individually manufactured mask, and positioned by means of 3D digital radiography with a precision of about 0.3 mm. Irradiation was applied in 4 fractions of 15 cobalt gray equivalents on 4 consecutive days. A total dose of 60 cobalt gray equivalents was homogeneously distributed over the planned target volume, comprising the clinical target volume plus 1 mm of safety margin (ie, the 90% isodose level) in the surrounding area.

- **ENDORESECTION OF THE TUMORS:** In cases with large tumors, endoresection was performed as previously described. In short, after posterior vitreous detachment, decalin was used to attach the retina. Subsequently, the tumor tissue was endoresected with a cutter-probe with the intraocular pressure elevated to prevent excessive hemorrhage from the tumor ground. After endolaser of the margins of the coloboma left behind after complete resection of all tumor tissue, the intraocular pressure had slowly been reduced to normal. An exchange of the decalin with silicone oil was performed at the end of the procedure.

- **OUTCOME MEASURES:** Case-dependent prescription of the therapeutic regime called for a division of patients into 2 groups, 1 of which presented with smaller tumors that did not require any additional surgical therapy after proton beam irradiation (n = 18). In contrast, patients with more prominent tumors who received local endoresection after proton beam irradiation were evaluated within the other group (n = 44).

Local tumor control was defined as no evidence of tumor recurrence within the follow-up. Tumor recurrence was assumed if an increase in tumor volume of more than 25% was observed over 2 examination intervals at least 6 months after radiotherapy. Either a tumor growth at the margins of the lesions that was observed from fundus photography or an increase of the tumor prominence of about 1 mm or more upon ultrasound examination was considered recurrent or tumor progression. A pseudo-increase in size that was caused by tumor exudation or hemorrhages on the tumor surface was not considered as treatment failure but as a sign of radiation retinopathy.

Endpoints for survival analysis were enucleation, tumor recurrence, occurrence of metastatic disease, and tumor-related death. Secondary enucleation was performed only as a last resort in blind painful eyes.

- **STATISTICAL ANALYSIS:** For time-to-event analysis the Kaplan-Meier method was applied. A P value below .05 was considered statistically significant. Computations were performed with IBM SPSS Statistics release 20.0 (SPSS Inc, Chicago, Illinois, USA).

### RESULTS

SIXTY-TWO PATIENTS MET THE INCLUSION CRITERIA OF our retrospective study. The mean age was 57.7 years (standard deviation [SD] 13.6 years). Twenty-nine patients were female, 33 were male. The overall range for tumor prominence was 1.7–12.6 mm (mean 7.6 mm, SD 2.9 mm), and it was 6.6–21.5 mm (mean 12.8 mm, SD 3.4 mm) for the largest tumor diameter. The respective fovea and disc distances ranged from 2.0 both to 10.1 mm and 11.3 mm with a mean distance of 4.6 mm to the fovea (SD 2.2 mm) and 5.2 mm to the optic disc (SD 2.1 mm). For the proton beam radiotherapy alone group (n = 18) the mean values of tumor height and largest tumor diameter were 3.9 mm (SD 2.0 mm) and 10.6 mm (SD 3.0 mm), respectively. The mean tumor-to-fovea distance was 3.7 mm, and the tumor-to-disc distance was centered at 3.9 mm (both SD 1.9 mm). In the endoresection group (n = 44) we found a mean tumor height of 9.1 mm (SD 1.5 mm), a mean largest tumor diameter of 13.7 mm
and mean distances to the fovea and the disc of 5.1 and 5.3 mm (SD 2.2 and 2.3 mm), respectively. None of the patients demonstrated extraocular growth. Diabetes mellitus was present in 2 patients who were part of the endoresection group (3.2% of the cohort). One patient in each treatment group demonstrated glaucoma at pretreatment diagnosis. The median follow-up time was 77.2 months in the proton beam radiotherapy alone group and 64.4 months in the endoresection group. Nine eyes in the first group (50.0%) and 39 eyes in the latter group (88.6%) showed an exudative retinal detachment at presentation.

**TUMOR REGRESSION:** In the proton beam radiotherapy alone group, a slight tendency toward an initial swelling of the tumor could be observed in 3 patients during the first year after proton beam radiotherapy (Figure 1), followed by a continuous decrease in median tumor prominence up to the end of follow-up, which was valid for all of the patients in this group. Five years after proton beam radiotherapy, the tumor volume, as determined by the largest tumor diameter and prominence, was reduced to about 65% of the volume at the initial presentation. In the surgical group, there were no alterations of the tumor height owing to the almost complete surgical excision of the tumor tissue.

**SURVIVAL AND LOCAL TUMOR CONTROL:** For the total of 62 patients, metastasis-free survival was estimated at a rate of 86.6% and 81.8% 5 and 10 years after proton beam radiotherapy, respectively (Figure 2). Of 10 patients who developed metastasis, 8 died before completion of the 5-year follow-up (1 in the proton beam radiotherapy alone group, 7 in the endoresection group, Figure 3). Another 2 patients died of other causes, and 12 patients terminated the follow-up without known reason. Metastasis-related mortality was thus estimated at 10.6% and 16.9% within 5 and 10 years, respectively. Patients with smaller tumors who were treated by proton beam radiotherapy alone had a trend to a lower rate of metastasis-induced death compared to patients with large tumors and concomitant surgical therapy (Figures 4).

Local tumor control was estimated at 96.1% both after 5 and after 10 years. In total, 2 local recurrences developed during follow-up, 1 in each treatment group (Figures 5).

**FUNCTIONAL OUTCOME:** Both initial visual acuity and final visual outcome (Figures 6) were better in the proton beam radiotherapy alone group, where the visual acuity on
The visual acuity on presentation was high (20/16–20/50 Snellen or 0.1–0.4 logMAR) in 15 patients (83.3%), medium (20/63–20/160 Snellen or 0.5–0.9 logMAR) in 2 patients (11.1%), and low (20/200 Snellen or 1.0 logMAR and worse) in 1 patient (5.6%). The final visual acuity in this group was high in 9 (50.0%), medium in 3 (16.7%), and low in 6 patients (33.3%). In the endoresection group the visual acuity on presentation was high in 26 patients (59.1%), medium in 14 patients (31.4%), and low in 4 patients (8.5%).

FIGURE 4. Kaplan-Meier curves for disease-specific death in patients with choroidal melanoma in the intermediate fundus zone (Left). Cumulative result in all patients (Right). Separate results for patients with proton beam radiotherapy alone (black) and those with additional endoresection (gray).

FIGURE 5. Kaplan-Meier curves for local tumor relapse in patients with choroidal melanoma in the intermediate fundus zone (Left). Cumulative results in all patients (Right). Separate results for patients with proton beam radiotherapy alone (black) and those with additional endoresection (gray).

FIGURE 6. Box-Whisker plots of visual acuity in patients with choroidal melanoma in the intermediate fundus zone depending on the treatment modality according to the initial tumor size (Left). Distribution of visual acuity after proton beam therapy followed by adjuvant. Kaplan-Meier curves for distant metastasis in patients with choroidal melanoma in the intermediate fundus zone. Cumulative result in all patients tumor resection (Right). Distribution of visual acuity after proton beam radiotherapy alone. Visual acuity was measured as decimal and is described as logMAR. In agreement with MARAN protocol, counting fingers was added as 1.9 logMAR, hand motion as 2.0 logMAR, and light perception as 2.1 logMAR. For a description of the graphical elements used, see legend to Figure 1.
and low in 27 patients (61.4%). Secondary glaucoma occurred in 23.5% (4/17) and 18.6% (8/43) of the patients in the proton beam radiotherapy alone and the endoresection group, respectively (Figures 7).

SECONDARY TREATMENTS: Cataract was present in 33 out of 62 cases at diagnosis (53.2%): 11 out of 18 patients (61.1%) in the proton beam radiotherapy alone group and 22 of 44 (50.0%) in the endoresection group (Figure 8). One patient was pseudophakic prior to irradiation. Three patients in the proton beam radiotherapy alone (16.7%) and 40 patients in the endoresection group (90.9%) underwent phacoemulsification with intraocular lens implant to the posterior chamber. In the endoresection group cataract surgery was the most common additional therapy that typically took place within the first year after proton beam therapy (mean time 9.8 months, SD 10.6 months, range 0.3–57.0 months), only exceeded by vitrectomy (100% of patients in this group). In the proton therapy alone group, cataract surgery, if any, was performed after 52.9–57.8 months. Enucleation was performed in 1 case each per group. The indications for late enucleation in this study were phthisis bulbi in 1 patient after 20.5 months and recurrent tumor growth in the other after 38.7 months.

Secondary irradiation owing to recurrent tumor growth was performed in a single patient in the endoresection group. Surgical intervention for proliferative vitreoretinopathy or nonresorbing exudative detachment during follow-up was needed in 4 out of 62 patients (6.5%). Twenty-two patients (35.5%) ended follow-up with residual silicone oil tamponade. All secondary interventions took place between the first and the fifth year of follow-up. Thereafter, the retinal and tumor situation was considered stable.

DISCUSSION

THE MANAGEMENT OF PATIENTS WITH MEDIUM- AND large-size uveal melanoma in the intermediate zone of the fundus is challenging. Proton beam brachytherapy for large tumors has been reported with or without additional surgical resection of the tumor tissue. However, a long-term follow-up of these patients was lacking so far. The intention of this study was to present the outcomes of all
patients with choroidal melanomas in the intermediate fundus zone who met the inclusion criteria irrespective of treatment with proton beam therapy alone or additional enucleation. Thus patients were secondarily divided into 2 groups, 1 without additional surgery after proton beam radiotherapy (mostly smaller tumors) and the second with additional tumor resection. As tumors up to 6 mm in prominence would normally be treated with ruthenium brachytherapy in our department, there are fewer patients in this group. Matched-pair analysis was not feasible owing to the lack in patients with large tumors treated without subsequent resection.

Overall, we showed excellent results in our analysis of 62 consecutive patients with medium-size and large-size uveal melanoma in the intermediate fundus zone. In the present study the local tumor control was 96.1% after 5 and 10 years in all patients. In total, 2 local recurrences developed during follow-up, 1 of each in both treatment groups. Thus, there was no difference between the separated results of the 2 treatment approaches. Egger and associates reported a local control rate of up to 98.9% after 5 years in a group of 2435 patients with uveal melanoma with a 3% retreatment rate owing to recurrent tumor growth.

Regarding the aspect of eye preservation, we were able to avoid enucleation in 96.1% in both groups after 5 and 10 years. The main reasons for secondary enucleation were anterior location or ciliary body extension of the tumor, proximity to the optic disc or fovea, tumor size, extracocular extension, suspected local recurrence, and neovascular glaucoma. We have excluded tumors with extension into the ciliary body as well as close proximity to the central structures to assess whether the tumor volume alone affects the maintenance of the globe. Although our groups were of different size and patients received different treatments, there seemed to be no difference in preservation of the eye between medium-size and large tumors, if the latter group is treated with additional surgical tumor excision after proton beam radiotherapy. Similarly there was no significant difference with respect to metastasis; however, as expected, there was a trend toward the group with the large tumors.

In the present study the disease-specific survival 5 and 10 years after radiotherapy was 89.4% and 83.1%, respectively. This is comparable to other published results. Dendale and associates reported on a melanoma-specific survival rate of 79% after 5 years for a comparable group of patients with a median basal diameter of 13 mm, a median tumor thickness of 4.8 mm, and a median tumor-to-macula distance of 2.4 mm. Other proton beam centers have reported varying 5-year disease-specific survival rates of 75%. The mortality through metastases was estimated to be 10.6% and 16.9% within 5 and 10 years, respectively. Interestingly, both groups of patients with and without tumor resection after proton therapy in our cohort showed equal mortality risks. But the risk for developing metastases in the enucleation group was higher after 5 years.

Tumor-associated risk factors such as tumor basal diameter larger than 10 mm, and patient-associated factors like male sex and age older than 60 years, are 2 of the best parameters used to predict metastatic disease. Gragoudas and associates reported that 65% of patients developing metastases after proton beam therapy had a tumor diameter larger than 15 mm. These findings are in accordance to our data reporting higher rates of metastatic spread in large-sized tumors and larger basal diameters (surgical group), compared to the proton beam radiotherapy alone group with a mean basal diameter of only 10.6 mm.

As expected, our proton beam radiotherapy alone group seemed to be more successful than the combined therapy approach in larger tumors applying irradiation and adjuvant tumor resection, though this was not a significant effect. Nevertheless, these data cannot prove that tumor resection performed after proton beam irradiation increases the risk for metastasis, or prove that enucleation, when performed after sterilization of the tumor by proton beam irradiation, is not associated with an increased risk for metastatic disease despite the theoretical risk.

Functional outcome is a relevant endpoint for the patient. In the proton beam radiotherapy alone group, 83.3% of the patients presented with an initial visual acuity better than 20/50 (0.4 logMAR). At the end of the follow-up 33.3% had a poor visual acuity of 20/200 (1.0 logMAR) or worse. A total of 5.6% of these patients were seen with a poor visual acuity at first presentation. A low visual outcome is mostly related to radiation-induced retinopathy and optic neuropathy and their consequences. In comparison, patients with lower tumor prominence had better visual outcome and the development of visual acuity depended also on the following tumor resection. In the resection group 26 patients (59.1%) presented with an initial visual acuity better than 20/50. At the end of the follow-up 61.4% had a poor visual acuity of 20/200 or worse, while 9.1% of these patients were seen with a poor visual acuity at first presentation.

This is comparable to the results of Dunavolgyi and associates, who reported on 212 patients with large tumors of more than 7 mm with 3 mm tumor distance to sensitive structures. Before radiotherapy, 83.0% of the patients had a visual acuity of better than 20/200. This rate decreased considerably to 8.8% 5 years after radiotherapy. These data suggest that radiotherapy of the large tumors alone, together with the slow degradation of the tumor and inflammatory response (toxic tumor syndrome), may cause the degradation of visual acuity. Interestingly, the rate of patients with a poor visual acuity but without tumor resection is higher (91.2%) compared to our group after tumor resection (61.3%). Thus resection of the tumor after proton beam radiotherapy may result in a lower rate of patients with poor visual outcome. Randomized studies are required to confirm this hypothesis.

A significant source of visual loss is retinal detachment because of apoptotic photoreceptor cell death. Owing to the associated tumor pathology (eg, retinal detachment or edema and subsequent degeneration of the central
macula), visual outcome in patients treated by proton beam radiotherapy is difficult to predict for the group of patients analyzed in this study. Similarly, comparisons to other reports are difficult. Exudative retinal detachment is present in up to 75% of the cases in other studies. In our study a retinal detachment was present in the majority of the cases at the moment of diagnosis (77.4%), although only in half of the cases treated with proton beam radiotherapy alone and in 88.6% of the group receiving surgical excision. As to be expected, tumor exudation prior to irradiation depended on the tumor size.

After proton beam irradiation small amounts of subretinal fluid are likely to resolve, as was seen in our proton beam radiotherapy only group. Continuous exudation and increase in exudation was approached by surgical excision of the tumor tissue and subsequent vitreous tamponade. It is widely observed that owing to swelling of cells and fluid accumulation in the tissue early after proton beam therapy, the tumor size increases. Thus, in this initial phase endoresection was performed to avoid inflammatory reaction, as described as toxic tumor syndrome. Proliferative vitreoretinopathy was a feature of the surgical excision group; however, only 4 out of our cohort required additional treatment. For various reasons, 22 patients maintained their long-term tamponade at the last follow-up.

In about half of the patients (48.4% or 30/62) dose delivery to the lens could be reduced with regard to the respective tumor spread to a fraction of 4%-28% of the lens volume, and another 24.2% of the lenses (15/62) were completely kept dose free. Despite this, occurrence of cataract markedly increased after irradiation as an early treatment complication, presumably owing to the high radiosensitivity of the lens. The rate of cataract surgery (95.5%) was significantly higher, especially in our surgical group, compared to the proton beam radiotherapy alone group (57.1%), the latter of which is comparable with the documented high prevalence of cataract before therapy (53.2%). Cataract extraction was routinely performed to provide better visual access to the posterior pole and the vitreous base during the planned tumor excision. Another indication is to provide optimal visualization for postoperative tumor management. Augsburger and Shields were the first to report no positive improvement in visual acuity after cataract extractions in patients who had previously undergone cobalt-60 plaque therapy. This is probably similar for the patients after proton beam radiotherapy, as the macular and optic disc function after irradiation and endoresection determines the final visual acuity.

In conclusion, proton beam radiotherapy is a promising procedure for choroidal melanomas in the intermediate fundus zone independent of the tumor size. Depending on the expected complication profile in larger tumors, subsequent surgical tumor resection should be performed. In this study, endoresection did not increase the risk of metastasis when performed after sterilization of the tumor cells by proton beam radiotherapy. Proton beam radiotherapy and associated surgical treatments allowed for the prevention of enucleation. Further studies are needed on whether the results of proton beam radiotherapy, with or without concomitant surgery, justify this technique over other irradiation modalities.

REFERENCES


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**REPORTING VISUAL ACUITIES**

The AJO encourages authors to report the visual acuity in the manuscript using the same nomenclature that was used in gathering the data provided they were recorded in one of the methods listed here. This table of equivalent visual acuities is provided to the readers as an aid to interpret visual acuity findings in familiar units.

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