PROTON BEAM RADIOTHERAPY OF IRIS MELANOMA

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Purpose: To report on outcomes after proton beam radiotherapy of iris melanoma.
Methods and Materials: Between 1993 and 2004, 88 patients with iris melanoma received proton beam radiotherapy, with 53.1 Gy in 4 fractions.
Results: The patients had a mean age of 52 years and a median follow-up of 2.7 years. The tumors had a median diameter of 4.3 mm, involving more than 2 clock hours of iris in 32% of patients and more than 2 hours of angle in 27%. The ciliary body was involved in 20%. Cataract was present in 13 patients before treatment and subsequently developed in another 18. Cataract had a 4-year rate of 63% and by Cox analysis was related to age \( (p = 0.05) \), initial visual loss \( (p < 0.0001) \), iris involvement \( (p < 0.0001) \), and tumor thickness \( (p < 0.0001) \). Glaucoma was present before treatment in 13 patients and developed after treatment in another 3. Three eyes were enucleated, all because of recurrence, which had an actuarial 4-year rate of 3.3% (95% CI 0–8.0%). Conclusions: Proton beam radiotherapy of iris melanoma is well tolerated, the main problems being radiation-cataract, which was treatable, and preexisting glaucoma, which in several patients was difficult to control.

INTRODUCTION

Iris melanomas account for approximately 3–5% of all uveal melanomas (1). Without treatment, they can grow, seed throughout the anterior chamber, invade the drainage angle to cause secondary glaucoma, and spread extraocularly. Approximately 5–10% of patients die of metastatic disease within 10 years of treatment (2, 3).

The standard form of treatment for iris melanoma is iridectomy, with iridocyclectomy being performed if the tumor extends to angle or ciliary body (4). The surgical iris defect tends to cause photophobia, and cylectomy can cause lens subluxation, hypotony, and ptihesis. To prevent local tumor recurrence, iridocyclectomy can be performed with adjunctive plaque radiotherapy or a full-thickness corneo-scleral excision followed by a tectonic graft (5). Primary brachytherapy has been advocated for patients with extensive iris melanoma, and good results have been reported (6, 7).

Proton beam radiotherapy has been used for the treatment of ciliary body and choroidal melanomas for several decades, with excellent rates of local tumor control (8, 9). However, to our knowledge this modality has not previously been advocated for the treatment of iris melanomas. In 1994, it occurred to one of us (B.D.) that in view of the limitations of surgical resection and plaque radiotherapy of iris melanomas there was scope for treating iris melanomas with proton beam radiotherapy.

The aim of the present study was to evaluate the early results of proton beam radiotherapy of iris melanoma, measuring outcomes in terms of visual acuity and ocular complications.

PATIENTS AND METHODS

Patients were included in the study if (1) they were managed at the Liverpool Ocular Oncology Centre and Clatterbridge Centre for Oncology between 1994, when the first patient was treated, and September 15, 2004, when the study was closed; (2) the tumor was diagnosed as a melanoma, either clinically or histologically; (3) the primary treatment consisted of proton beam radiotherapy; and (4) at the time of our initial examination the tumor was considered to originate in iris. Patients were excluded from the study if they had previously received other treatment or if they were followed-up for less than 6 months.

Pretreatment assessment included: (1) measurement of Snellen visual acuity by an ophthalmic nurse, using spectacle or pinhole

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correction if necessary; (2) slit-lamp examination, with measurement of longitudinal and transverse tumor diameters, performed before mydriasis; (3) gonioscopy, measuring the circumferential extent of increased pigmentation in the angle, in clock hours; (4) binocular indirect ophthalmoscopy; (5) high-frequency B-scan echography, performed with the 20-MHz probe (Innovative Imaging Inc., Sacramento, CA), using a waterbath filled with 2% hypromellose; and (6) systematic inquiry. Informed consent was obtained from the patients, who were informed of the risks and benefits of proton beam radiotherapy and other forms of treatment. All patients were provided with an audiocassette tape recording of their consultation to help them remember what they were told. Ethics committee approval was not required for this study.

Proton treatment plans were prepared according to information on a special form, which included: (1) a drawing of the shape and extent of the tumor; (2) the target area comprising the tumor and safety margins; (3) echographic measurements of distances from cornea to back of lens, cornea to retina, retina to outer sclera, and transverse ocular diameter (Fig. 1). Tantalum markers were not necessary. The treatment was delivered with the pupil dilated to reduce the tumor area. The eyelids were fully retracted, improving accuracy of radiation targeting. The circumferential safety margins were empirically adjusted to treat 1 clock hour (i.e., 3 mm) of iris or angle beyond any visible tumor or suspicious pigmentation. Wherever the angle was directly involved by the main body of the tumor, the safety margin extended 4 mm posterior to limbus, in case there was any ciliary body invasion. If the angle was involved only by lateral extensions from the tumor, then a radial safety margin of only 2 mm was used. The EYEPLAN eye therapy program (V.1 to 1.6b, Douglas Cyclotron, Clatterbridge Centre for Oncology) was used to contour the tumor and treatment areas, to estimate radiation doses delivered to adjacent healthy structures such as ciliary body and lens, and to provide data to a precision milling machine for a brass collimator to be made, customized for each tumor. The proton beam depth dose was measured before treatment to confirm that the radiation beam had the required accuracy in terms of dose and depth. The prescribed dose of radiation was 53.1 Gy (58.4 Gy $^{60}$Co-equivalent), which was delivered in 4 fractions over 4 consecutive days. Dosimetry checks were performed before each treatment. A thin-walled MARKUS...

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**Fig. 1.** Infero-temporal iris melanoma in the left eye of a 52-year-old man, referred after growth of the lesion. (top left) Multinodular tumor in December 1998, when the eye had a visual acuity of 20/13 and glaucoma was controlled with Alphagan and Timolol drops; (top right) beam’s eye view, with line showing collimator edge; (bottom left) lateral view, showing 90%, 50%, and 20% isodose curves; and (bottom right) appearance 5.5 years after treatment, when the eye was comfortable with visual acuity of 20/20, an atrophic tumor, no cataract, minimal conjunctival telangiectasia, and normal intraocular pressure after trabeculectomy in 2000.
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The latest recorded visual acuity was 20/17 (28%), 20/20 (30%), 20/30 (22%), 20/40 (7%), 20/60 (1%), 20/100 (2%), 20/200 (1%), Counting Fingers (2%), Hand Movements (2%), Light Perception (1%). Three eyes were enucleated. Figure 2 shows the last known visual acuity plotted against

**RESULTS**

The sample comprised 88 patients (56% female, 44% male). The age at treatment averaged 52.0 years (range, 21–76 years). The follow-up had a median of 2.7 years, exceeding 1 year in 72 patients, 2 years in 54 patients, and 4 years in 32 patients. The tumor was located in the right eye in 51% patients and the left eye in 49% patients. The visual acuity before treatment was 20/17 (40%), 20/20 (36%), 20/30 (15%), 20/40 (3%), 20/60 (1%), 20/80 (1%), 20/200 (1%), Counting Fingers (1%), and Light Perception (1%). Concurrent ocular abnormalities included cataract (15%), glaucoma (15%), uveitis (3%), amblyopia (1%), herpetic keratitis (1%), band keratopathy (1%), hyphema (1%), cellophane maculopathy (1%), age-related macular degeneration (1%), and keratoconjunctivitis sicca (1%). Important systemic disease included diabetes mellitus (1%), Behcet’s syndrome (1%), ovariain cancer (1%), thyroid cancer (1%), systemic hypertension (1%), multiple sclerosis (1%), and polymyalgia rheumatica (1%).

The posterior tumor margin was in iris (80%), pars plicata (14%), and pars plana (7%). The quadrant where the tumor was centered was superior (1%), superonasal (5%), nasal (3%), inferonasal (25%), inferior (13%), inferotemporal (44%), temporal (8%), and superotemporal (1%). The tumor involved 1 (26%), 2 (42%), 3 (26%), 4 (2%), 6 (2%), and 7 (1%) clock hours of iris. Angle spread was present in 59% of patients and included 1 (15%), 2 (17%), 3 (11%), 4 (6%), 5 (1%), 6 (5%), 7 (2%), 8 (1%), and 12 (1%) clock hours. The ciliary body involvement by tumor was 1 (6%), 2 (8%), 3 (7%), and 4 (1%) hours. Extraocular extension was present in 3 patients. The tumor diameter ranged from 1.8 mm to 11.7 mm with a median of 4.3 mm. The tumor thickness ranged from 0.5 mm to 5.0 mm, with a median of 1.4 mm. Trans-scleral biopsy before radiotherapy was performed in 2 patients and showed spindle-cell melanoma in each case.

In all patients, a dose of 90% or more of the radiation delivered was received by a median of 0% of retina, 24% of the ciliary body, 20% of the lens, and 37% of the lens periphery.

The latest recorded visual acuity was 20/17 (28%), 20/20 (30%), 20/30 (22%), 20/40 (7%), 20/60 (1%), 20/100 (2%), 20/200 (1%), Counting Fingers (2%), Hand Movements (2%), Light Perception (1%). Three eyes were enucleated. Figure 2 shows the last known visual acuity plotted against
the pretreatment acuity, with labels for patients with loss of 20/40. The causes of visual loss were cataract, with the patients waiting for surgery (4), glaucoma and cataract (2), local tumor recurrence (3), bullous keratopathy, in a patient who presented with band keratopathy caused by the tumor (1), amblyopia (1), and hyphema, which was drained with improvement of vision to 20/30 (1) (Table 1).

Cataract was first recorded after the radiotherapy in 18 patients. After excluding patients with pretreatment cataract, the cumulative incidence of cataract at 4 years was 63% (95% confidence interval [CI], 48–78%). Cox analysis showed that cataract was related to age at treatment \( (p = 0.048; \text{risk ratio, } 1.04 \text{ per year}; 95\% \text{ CI}, 1.00–1.08) \), initial visual loss \( (p < 0.0001; \text{risk ratio, } 3.10 \text{ per category (i.e., } 20/17–20/40, 20/60–20/200, 20/240–\text{Finger Counting, Hand Movements to Light Perception}), 95\% \text{ CI } 1.65–5.80) \), tumor thickness \( (p < 0.0001; \text{risk ratio, } 2.77 \text{ per mm}; 95\% \text{ CI, } 1.59–4.83) \), iris involvement \( (p < 0.0001; \text{risk ratio, } 1.91; 95\% \text{ CI, } 1.39–2.63) \), angle involvement \( (p = 0.008; \text{risk ratio, } 1.22; 95\% \text{ CI, } 1.05–1.41) \), and ciliary body involvement \( (p = 0.001; \text{risk ratio, } 1.80; 95\% \text{ CI, } 1.28–2.53) \). Figure 3 shows the actuarial rates of cataract according to tumor size. After cataract surgery, vision improved to 20/30 or better in all 4 patients with follow-up information and no other causes of visual loss.

Glaucoma was present in 13 patients before treatment and developed after the radiotherapy in another 3 patients. In 1 patient with secondary glaucoma before treatment, the intraocular pressure was controlled serendipitously when a drainage bleb developed after biopsy, which was performed before the radiotherapy. In the remaining patients the glaucoma was treated with a variety of medications and surgical procedures, with varying degrees of success. The glaucoma contributed to visual loss in 2 patients.

Other complications were mild and transient conjunctivitis (2 patients), corneal edema (1 patient, who had band keratopathy before treatment), mild superficial keratitis (2 patients), recurrent hyphema (3 patients, 1 of whom required evacuation of the blood), and loss of lashes (1 patient). Several patients had temporary conjunctival hyperemia soon after treatment, delayed conjunctival telangiectasia, pigment scatter on the iris surface or trabecular meshwork, and pupil distortion. No patients developed definite rubeosis or neovascular glaucoma, although in 3 patients a dilated iris vessel was recorded. Other than the patient with Behcet’s syndrome, no patients developed frank uveitis.

The three enucleations were all performed because of local tumor recurrence, which occurred only in these 3 patients. The cumulative incidence of local tumor recurrence and enucleation at 5 years was 6.3% (95% CI, 0–14%). Figure 4 shows ocular conservation according to tumor size. In 2 patients, the recurrent tumor arose from untreated diffuse, circumferential spread around the anterior chamber angle. The third patient, a 68-year-old woman, presented with an advanced tumor measuring 8.7 \( \times \) 8.6 mm \( \times \) 3.9 mm and received proton beam radiotherapy only because she was extremely reluctant to undergo primary enucleation. She developed recurrence 2 years after her radiotherapy and died of metastasis 4 months later.

One patient (mentioned above) died of metastatic disease. Two patients died of other causes, which were myocardial infarction and head injury respectively.

**DISCUSSION**

This prospective, noncomparative, interventional study found that proton beam radiotherapy of iris melanoma was well tolerated, the main complication being cataract. No

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*Abbreviations: CF = Counting Fingers; HM = Hand Motions; LP = Light Perception; EN = Enucleated.*
patients developed iris neovascularization, despite irradiation of iris and ciliary body. To our knowledge, there have not been any published studies on proton beam radiotherapy of iris melanoma. The main strengths of this study are the large number of cases, the length of follow-up, and the treatment at a single center.

We did not routinely confirm malignancy histologically or observe patients for tumor growth before treatment so that some of the tumors in our sample may have been benign (11). The tumor inactivity after treatment may therefore not have been the result of the radiotherapy; however, proton beam radiotherapy of ciliary body and choroidal melanomas has been shown to have extremely high rates of local tumor control, approaching 100%. There is no consensus about the clinical features distinguishing iris nevus from melanoma, with some authors diagnosing malignancy if the tumor diameter exceeds 3 mm and others believing that the tumor diameter and thickness should be at least 5 mm and 2 mm respectively. We have therefore categorized our tumors according to these dimensions, when reporting outcomes. We do not believe, however, that tumor size is necessarily the best predictor of its behavior, because small tumors can behave more aggressively than large lesions. More ominous features, in our opinion, are diffuse tumor growth and seeding, as shown by our patient with recurrence after treatment of a 3.3-mm tumor. It was not the purpose of this study to determine whether melanocytic iris tumors should be observed or treated. Such a question can be addressed only by a randomized, prospective study involving several hundred patients and decades of follow-up. In a series of 27 observed iris tumors, 70% subsequently showed tumor growth, 11% developed raised intraocular pressure, 1 patient had recurrent hyphema, and 1 patient was lost to follow-up (4).

Local tumor control relies on the clinical ability to measure circumferential spread around the angle. This can be difficult, as shown by the fact that 2 of the 3 recurrent tumors arose from angle infiltration that was clinically underestimated. There is scope for further studies aimed at improving the differentiation of melanoma cells from melanomacrophages, when assessing pigment in the angle or on the iris surface.

Approximately 20% of the tumors in this study involved both iris and ciliary body. Which of these tissues was primarily involved was decided at the initial examination according to where the tumor was more bulky or extensive; however, it is possible that some of the tumors originated in ciliary body. Excluding tumors involving ciliary body would have avoided this potential error but would have biased our results by omitting more aggressive iris melanomas.

One of the most remarkable findings of this study was the minimal nature of the complications after treatment. The most frequent complication in our study was cataract, which also accounted for 4 of the 9 patients with visual loss caused by the tumor or its treatment. Because this complication is eminently treatable, with only rare complications and good improvement of vision, the rates of loss of 20/40 and 20/200 visual acuity would have been appreciably lower if it had been possible for our referring ophthalmologists to perform cataract surgery without delay. Indeed, our data show good improvement in vision after cataract surgery in patients with no other causes of visual loss. Gragoudas and associates have reported improved vision with cataract extraction after proton beam radiotherapy of uveal melanoma, with no increase in mortality (12). Although results are likely to be similar in patients developing cataract after proton beam radiotherapy for iris melanoma, there would be scope for further studies once more such patients have undergone cataract surgery. Cataract can also occur after iridocyclectomy, in which case phacoevisulization is likely to be more difficult because of instability of the lens, unless a tension

![Fig. 3. Kaplan-Meier survival curves showing time to cataract according to tumor diameter. A: Diameter ≤ 3.0 mm (n = 16); B: Tumor diameter 3.1–5.0 mm (n = 45); C: Tumor diameter > 5.0 mm and thickness > 2.0 mm (n = 13); D: Tumor diameter > 5.0 mm and thickness ≥ 2.0 mm (n = 14). Log rank: p < 0.0001. Cataract at Day 1 indicates preexisting disease.](image)

![Fig. 4. Kaplan-Meier survival curves showing ocular conservation according to tumor size (Subgroups A–D are as in Fig. 2).](image)
ring is used. In several patients, lens opacities were present before treatment. Many patients had glaucoma before treatment, and a few developed this problem after the radiotherapy. Glaucoma was a difficult problem to manage and merits a separate study to determine how it should be treated and whether it is ever an indication for primary enucleation. Three patients developed prominent iris blood vessels, which did not have the features of rubeosis and which might therefore represent telangiectasia or a collateral circulation. Corneal problems were minimal. No patients developed corneal stem cell deficiency. The single patient who developed loss of lashes adjacent to the tumor was treated in 1995 and was the sixth patient in our series to receive proton beam radiotherapy for iris melanoma. This problem, which can also occur after proton beam radiotherapy of choroidal melanomas, can usually be avoided by careful retraction of the eyelid. The median follow-up was only 2.7 years, because the number of patients increased during each year of the study. There is scope for further, long-term studies.

No patients in this series developed rubeosis or neovascular glaucoma, despite the fact that several received high-dose radiotherapy to extensive areas of healthy iris and ciliary body. Other workers have suggested anterior segment sparing to prevent neovascular glaucoma after helium ion irradiation of posterior uveal melanomas (13). This recommendation was based on a strong correlation between neovascular glaucoma and volume of lens and anterior chamber tissues in the radiation field (13). Our results from this study suggest that neovascular glaucoma following proton beam radiotherapy of posterior segment melanoma is more likely to be caused by angiogenic factors released by detached retina and bulky irradiated tumor, as suggested by Foss and colleagues (14).

It is not possible to perform meaningful comparisons between our study and previous investigations by other workers. Nevertheless, good results have been reported after plaque radiotherapy. Shields and colleagues reported the results of 125 iodine plaque radiotherapy of 14 nonresectable melanomas with custom designed plaque radiotherapy. Shields and colleagues reported the results of 125 iodine plaque radiotherapy of 14 nonresectable iris melanomas (6). After a mean follow-up of 26 months, local tumor control was achieved in 93% of cases, the main complications being cataract and posterior synechiae. Finger has reported the results of 103 Pd brachytherapy in 22 melanomas involving iris, ciliary body, or both (7). After a mean follow-up of 56 months (range 9 to 117) all eyes were retained, with 91% having visual acuities within 2 lines of pretreatment values. Secondary cataract occurred in 71% of eyes. The results achieved with plaque radiotherapy are probably similar to our own findings so that the choice between brachytherapy and charged particle radiotherapy will probably depend on which treatment is available to the ophthalmologist and, if both are present, as at our center, whichever method the patient finds most convenient.

Two relatively recent articles on iridocyclectomy give an impression of the results that might have been achieved with surgery in some of our patients. It must be emphasized that the samples in these two studies are not strictly comparable with our cases, because in both studies resection was restricted to tumors not involving more than 5 clock hours of the iris. Conway and associates reported 44 patients treated by iridectomy or iridocyclectomy (4). The mean follow-up was 10.4 years. More than 1 year postoperatively, 67% of patients had visual acuity of 20/40 or better, with cataract in 16%, troublesome photophobia in 25%, and local tumor control in 84%. Naumann and Rummelt reported the results of 68 iridocyclectomies, which were performed for a variety of tumors involving the angle (5). After a median follow-up of 6.3 years, cataract occurred in 32% of patients, with loss of 20/60 vision in 47% and enucleation in 6%. Our impressions based on these two studies and our own similar experience with more than 50 iridocyclectomies (unpublished data) suggest that ocular morbidity after resection of iris tumors is greater than that of plaque or proton beam radiotherapy, at least in the first few years after treatment. There is scope for multicenter studies comparing proton beam radiotherapy with other forms of management, ideally in a randomized, prospective fashion.

In conclusion, our preliminary data suggest that proton beam radiotherapy for iris melanoma was well tolerated, the main complication being cataract, which was eminently treatable. Preexisting glaucoma was a common problem, which was often difficult to control. Neovascular glaucoma did not occur despite extensive irradiation of iris and ciliary body. This study suggests that proton beam radiotherapy is a reasonable alternative to plaque radiotherapy or surgical resection.

REFERENCES