PROTON BEAM RADIOTHERAPY OF CHOROIDAL MELANOMA: THE LIVERPOOL-CLATTERBRIDGE EXPERIENCE

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Purpose: To report on outcomes after proton beam radiotherapy of choroidal melanoma using a 62-MeV cyclotron in patients considered unsuitable for other forms of conservative therapy.

Methods and Materials: A total of 349 patients with choroidal melanoma referred to the Liverpool Ocular Oncology Centre underwent proton beam radiotherapy at Clatterbridge Centre for Oncology (CCO) between January 1993 and December 2003. Four daily fractions of proton beam radiotherapy were delivered, with a total dose of 53.1 proton Gy, and with lateral and distal safety margins of 2.5 mm. Outcomes measured were local tumor recurrence; ocular conservation; vision; and metastatic death according to age, gender, eye, visual acuity, location of anterior and posterior tumor margins, quadrant, longest basal tumor dimension, tumor height, extraocular extension, and retinal invasion.

Results: The 5-year actuarial rates were 3.5% for local tumor recurrence, 9.4% for enucleation, 79.1% for conservation of vision of counting fingers or better, 61.1% for conservation of vision of 20/200 or better, 44.8% for conservation of vision of 20/40 or better, and 10.0% for death from metastasis.

Conclusion: Proton beam radiotherapy with a 62 MeV cyclotron achieves high rates of local tumor control and ocular conservation, with visual outcome depending on tumor size and location. © 2005 Elsevier Inc.

INTRODUCTION

Choroidal melanoma can cause visual handicap, loss of the eye, and metastatic disease, which is invariably fatal (1). For many years, the standard form of therapy was enucleation, but this has been replaced whenever possible by a variety of therapies aimed at destroying the primary tumor while conserving the eye, ideally with useful vision. Such “conservative” methods include: brachytherapy, using isotopes such as iodine-125 or ruthenium-106; proton beam radiotherapy; stereotactic radiotherapy; local resection, which can be transscleral or transretinal; and transpupillary thermotherapy (1).

Proton beam radiotherapy of uveal melanomas was first developed in Boston and is now performed in more than a dozen centers around the world (2). In Boston and some other centers, it is used for all patients; however, it is more expensive and time-consuming than brachytherapy and can also cause side effects in extraocular structures, such as eyelids, lacrimal gland, and the tear ducts. We therefore use proton beam radiotherapy selectively, when other methods are considered less likely to be successful (3). We mostly select proton beam radiotherapy for small, posterior tumors, because with such tumors we feel that it achieves local tumor control more reliably than brachytherapy while delivering smaller doses of radiation to the optic nerve and fovea. We also select proton beam radiotherapy when the tumor is too large for ruthenium plaque brachytherapy, if the patient is highly motivated to retain the eye, and if local resection is not possible.

Several centers have already reported their results with proton beam radiotherapy of uveal melanoma (4–10). However, our selection criteria are different. Furthermore, the Clatterbridge Centre for Oncology (CCO) proton beam is highly conformal in comparison to other units, and differences in treatment technique have evolved at different centers.

The aim of this study was to determine ocular outcomes such as visual acuity, local tumor control, ocular retention,
and survival after proton beam radiotherapy of choroidal melanoma at our center.

METHODS AND MATERIALS

Patients and data collection

Patients were included in the study prospectively and consecutively if they were treated for choroidal melanoma between 1993, when the Liverpool Ocular Oncology Centre was established, and December 2003. They were excluded if: (1) the tumor had previously been treated by other methods; (2) the tumor did not extend posterior to ora serrata; or if (3) the tumor was bilateral (1 patient) (11). They were not excluded because of poor general health, diffuse or extraocular spread, proximity to optic disc or fovea, or status of the fellow eye. Our criteria for diagnosing a choroidal tumor as melanoma included: (1) thickness greater than 2.0 mm; (2) serous retinal detachment; (3) confluent orange pigment; (4) history of recent visual symptoms; and (5) tumor growth, documented photographically.

As a rule, proton beam radiotherapy was selected if: (1) the posterior tumor margin extended close to optic disc so that we felt that plaque radiotherapy could not be administered reliably without causing optic neuropathy; (2) the tumor extended close to fovea so that we felt there was a better chance of conserving central vision with proton beam radiotherapy than with other methods; or (3) the tumor height exceeded 5.5 mm and other forms of conservative treatment were inappropriate.

Preoperative and follow-up assessments included: (1) measurement of Snellen visual acuity, using spectacles or pinhole, if necessary; (2) full ophthalmologic examination; (3) B-scan ultrasonography; and (4) color photography. Follow-up assessments alternated between our center and the referring ophthalmologist until the probability of complications was considered to be low (i.e., <1%), when patients were discharged to their ophthalmologist for annual review. The referring ophthalmologists were asked to send us a report every time the patient was seen and were encouraged to refer the patient back to us if any problems arose. If no follow-up information was automatically received, this was requested by mail. Data regarding patient demographics, ocular and tumor characteristics, primary treatment, and all outcomes were collected prospectively. In patients with local tumor recurrence or enucleation, the charts were reviewed retrospectively. The tenets of the Helsinki Declaration were followed. Institutional ethical committee approval for outcomes analysis was not required.

Treatment protocol

Marker insertion: A 180° conjunctival peritomy was performed. Any rectus muscle overlying the tumor was disinserted after placing two 6-0 Vicryl sutures in the muscle tendon and measuring the knot-to-limbus distances. To rotate the eye, two bridle sutures were placed in the sclera, 4 mm from limbus and about 20 mm apart. The tumor margins were identified by transpupillary transillumination, or if this was not possible, by binocular indirect ophthalmoscopy with indentation. Four tantalum markers were sutured to the sclera with 5-0 Mersiline sutures. They were positioned as close as possible to the anterior, lateral, and posterior tumor margins, preferably over normal choroid; however, if the posterior marker could not be placed close to the posterior tumor border, it was attached to the sclera anterior to the tumor and used only for modeling ocular dimensions. Using calipers, measurements were taken from each marker to tumor border, each other marker, and limbus. If the marker-to-tumor distances could not be measured with calipers, as was often the case with small, posterior tumors, these were estimated ophthalmoscopically, holding the markers with forceps and indenting the eye, using the optic disc to judge a distance of 1.5 mm. The rectus muscles were reattached with 6-0 Vicryl sutures, taking care to ensure that the knot-to-limbus distances were the same as before muscle disinsertion. The conjunctiva was closed with 7-O Vicryl sutures.

Postoperatively, patients were treated with chloramphenicol drops for 1 week and fluorometholone drops for 12 weeks.

Simulation, eye planning, and treatment

The patients were simulated and treated at the CCO Douglas Cyclotron. First, the simulation and treatment procedures were explained to the patients and accompanying relatives. A face mask and dental bite were prepared for each patient to immobilize the head precisely. This was done with the patient seated in a dedicated treatment chair, which had precise x, y, z movements of 0.2-mm resolution.

The simulation procedures included: (1) evaluation of several candidate gaze directions, from which the optimum was selected, that is, the one giving minimal radiation to optic nerve, lens, fovea, and lacrimal gland; (2) measurement of any ocular torsion, when the eye was in the selected treatment position; (3) detection of any visual limitations that might have prevented steady gaze during treatment, in which case a more suitable gaze direction was selected; and (4) assessment of whether to retract the eyelid or treat through the closed lid, in which case eyelid thickness, shape, and position were measured. The patients were asked to gaze at a small, red light positioned at the selected polar and azimuthal angles. Bilateral X-ray Polaroid films were taken at each selected gaze direction. The results were transferred to the EYEPLAN eye planning program (Harvard, MA) with our modifications (M. Sheen, CCO, Wirral, UK), with further information on ocular features such as eye length, scleral thickness, limbus, and tantalum marker positions with respect to tumor margins and limbus. The position and shape of both the eye and tumor were modeled, and the optimum gaze angle was finalized. The required range and modulation for each treatment were calculated, with standard lateral and distal safety margins of 2.5 mm. In fields without eyelid involvement, a distal margin of 2 mm was used. In recent years, a notch was used to reduce radiation doses to optic nerve and fovea when treating posterior tumors.

Local anesthetic drops were applied before each fraction, instilling artificial tears as required. Four daily fractions were administered, on consecutive days, with a total dose of 53.1 proton Gy, having an assumed relative biological effect (RBE) of 1.1. If necessary, the eyelids were retracted or positioned using surgical tape. The treatment time per fraction was 30 s, with setup and preparation times of between 5 and 15 min. After treatment, anti-inflammatory drops were prescribed if needed.

Adjunctive therapy

During the latter part of the study period, transpupillary thermotherapy (TTT) was administered to the tumor, initially as a treatment for exudative maculopathy and, more recently, prophylactically before the onset of exudation. The phototherapy was applied in the conventional method, except that the safety margins were omitted (12). In addition, some juxtapapillary tumors were
treated with TTT to enable the radiation safety margin to be reduced, thereby lessening any chances of optic neuropathy.

Six patients with exudative retinal detachment underwent secondary local resection of the irradiated tumor, using techniques described previously (13).

Outcome measures

Visual acuity was measured using the Snellen Chart, with the patient’s usual spectacle correction, using a pinhole if necessary. If the patient was unable to count fingers centrally, then the test was repeated with the examiner’s hand in each quadrant. Minimum visual conservation time of 20/40 or better was measured from the time of treatment to the last date when this level of vision was documented. A similar protocol was followed for measuring visual conservation time of 20/200 or better and counting fingers or better.

Local treatment failure was diagnosed if (1) there was unequivocal expansion of any tumor margin on comparing the ophthalmoscopic appearances with previous color photographs or (2) definite increase in tumor height on echography, if necessary confirmed by sequential examination. When such regrowth was observed, treatment was by further appropriate conservative therapy, if possible; otherwise, enucleation was performed. Time to tumor recurrence was measured to the date of diagnosis of this complication. Time to enucleation was measured similarly.

Mortality was investigated only for patients resident in the United Kingdom, because these were flagged at the National Cancer Registry of the Office of National Statistics, which automatically notified us of the date and cause of any deaths. If no such notification was received, patients were assumed to be alive at the close of the study in September 2004.

Statistical methods

All outcomes analyses were based on data computerized by September 15, 2004. The follow-up period was measured to the latest date at which ocular status was known. The results were analyzed with SPSS software (Version 11.0, SPSS Inc., Chicago, IL). Cox’s univariate proportional hazards model was used to identify associations between baseline variables and time to measured outcome. Kaplan-Meier estimates were used to draw survival curves for time to this outcome. Statistical significance was taken to mean \( p < 0.05 \).

RESULTS

Description of patient population and treatment

The 349 patients (188 male, 161 female) had a mean age of 57.7 years (standard deviation, 13.9; range, 19–85). The tumor affected the right eye in 50.4% of patients. The initial visual acuity was 20/20 or better in 30.7%, 20/25–20/40 in 30.1%, 20/50–20/160 in 24.9%, and 20/200 or worse in 14.3%. The visual acuity in the fellow eye was ≥20/20 in 65.9%, 20/25–20/40 in 24.1%, 20/50–20/160 in 5.2%, and ≤20/200 in 4.3%. Two patients (0.6%) were monocular.

The anterior tumor margin was in postequatorial choroid in 68.5%, preequatorial choroid in 20.3% and anterior to ora serrata in 11.2%. The posterior tumor margin was more than 2 disc diameters from disc and fovea in 25.5%, 1–2 disc diameters from disc or fovea in 19.2%, ≤1 disc diameter from disc or fovea in 40.1%, and involved optic disc in 15.2%. The distance from tumor to disc center had a median of 3.0 mm (range, 0–22.0 mm) and was ≥2.0 mm in 36.7%, 2.1–4.0 mm in 29.5%, 4.1–6.0 mm in 16.3%, and >6.0 mm in 17.5. The center of the tumor was superior in 20.1%, supranasal in 11.5%, nasal in 5.2%, inferonasal in 8.3%, inferior in 11.2%, inferotemporal in 13.5%, temporal in 12.3%, and superotemporal in 18.1%. In the tumors extending anterior to ora serrata, 7 reached pars plana, 17 involved pars plicata, and 15 reached the anterior chamber. The extent of ciliary body involvement was 1 clock hour in 4 patients, 2 clock hours in 20 patients, 3 hours in 7 patients, and 4 hours in 2 patients. Retinal invasion or perforation was apparent in 18 eyes (5.1%); extraocular extension in 7 eyes (2.0%). The median tumor diameter was 10.1 mm (range, 2.0–21.6) and the median tumor height was 3.0 mm (range, 0.9–13.0 mm).

On September 15, 2004, when the analysis was performed, the follow-up had a median of 3.1 years (range, 0.01–11.49 years), exceeding 1 year in 299 patients, 2 years in 227 patients, and 5 years in 104 patients. Of the 336 patients treated more than 1 year before analysis, follow-up information exceeding 1 year was available in 91%. The corresponding figures at 2 years were 81% of 291 patients; at 5 years, 56% of 197 patients.

Adjunctive transpupillary thermotherapy at the time of the proton beam radiotherapy was given in 11 patients to prevent exudation (5 patients) to reduce symptomatic exudative retinal detachment (2 patients) and to reduce the radiation safety margin (4 patients). A further 23 patients received TTT as a treatment for exudation from the irradiated tumor. One patient received photodynamic therapy as a secondary treatment for macular edema. Six patients had transcleral local resection of the irradiated tumor as treatment for the exudative retinal detachment. Two patients had transretinal enucleation of the tumor for exudation.

Local treatment failure

By the close of the study, treatment failure occurred in nine eyes. The cumulative risk of local treatment failure at 5 years was 3.5% (95% confidence interval [CI], 1.21–5.83%). Cox univariate analysis showed the only significant predictive factors to be longest basal tumor dimension \( (p = 0.01; \text{risk ratio}, 1.24/mm; 95\% \text{ CI}, 1.05–1.47) \) and increased tumor height \( (p = 0.014; \text{risk ratio}, 1.31/mm; 95\% \text{ CI}, 1.06–1.63) \). Eight eyes with local recurrence were enucleated, one after unsuccessful TTT and one was conserved with a second course of proton beam radiotherapy. Figure 1 shows the Kaplan-Meier survival curve relating to local tumor recurrence.

Secondary enucleation

Twenty-five eyes were enucleated by the close of the study. The actuarial rate of enucleation was 1.6% (95% CI, 0.2–3.0%) at 1 year, 4.0% (95% CI, 1.6–6.1%) at 2 years, and 9.4% (95% CI, 5.4–13.5%) at 5 years. Cox univariate analysis found the factors associated with increased risk of enucleation to be ciliary body involvement \( (p < 0.0001, \)
risk ratio 2.57; 95% CI, 1.56–4.21); posterior tumor extension (\( p = 0.045 \); risk ratio, 0.67; 95% CI, 0.43–1.00); longest basal dimension (\( p < 0.0001 \); risk ratio, 1.30 per mm; 95% CI, 1.15–1.47); tumor height (\( p < 0.0001 \); risk ratio, 1.55 per mm; 95% CI, 1.34–1.80); and retinal invasion (\( p = 0.024 \); risk ratio, 4.07; 95% CI, 1.20–13.79). Figure 2 shows Kaplan-Meier survival curves of ocular conservation according to tumor height. The reasons for enucleation were neovascular glaucoma (9 patients) and local tumor recurrence (8 patients), with other reasons being retinal fibrosis (1 patient), retinal detachment (3 patients), bullous keratopathy (1 patient), and patient choice (1 patient).

Visual acuity

Conservation of visual acuity of counting fingers or better: In the 346 patients with visual acuity of counting fingers or better at treatment, conservation of such vision was achieved in 89.2% (95% CI, 85.6–92.8%) at 2 years, 79.1% (95% CI, 73.6–84.6%) at 5 years, and 72.9 (95% CI, 65.8–79.9%) at 8 years.

Cox univariate analysis showed the most significant factor predicting loss of vision of counting fingers or better to be ciliary body involvement (\( p = 0.001 \); risk ratio, 1.80; 95% CI, 1.26–2.58), longest basal tumor dimension (\( p < 0.0001 \); risk ratio, 1.24/mm; 95% CI, 1.14–1.34), greater tumor height (\( p < 0.0001 \); risk ratio, 1.40/mm; 95% CI, 1.26–1.55), retinal invasion (\( p < 0.0001 \); risk ratio, 5.50; 95% CI, 2.44–12.38), and extraocular extension (\( p < 0.0001 \); risk ratio, 6.37; 95% CI, 2.28–17.83). Figure 3 shows Kaplan-Meier survival curves of conservation of vision of counting fingers or better according to tumor height.

Conservation of visual acuity of 20/200 or better

There were 301 patients with initial visual acuity of 20/200 or better. Visual acuity of 20/200 or better was conserved in 81.9% (95% CI, 77.2–86.6%) at 2 years, 61.1% (95% CI, 54.1–68.1%) at 5 years, and 41.7% (95% CI, 32.4–51.0%) at 8 years.

Cox univariate analysis showed that the variables predicting loss of visual acuity of 20/200 or better were: reduced initial visual acuity (\( p = 0.002 \); risk ratio, 1.15 per Snellen line; 95% CI, 1.05–1.26), tumor height (\( p = 0.001 \); risk ratio, 1.16/mm; 95% CI, 1.06–1.27), and retinal invasion (\( p < 0.0001 \); risk ratio, 5.00; 95% CI, 2.11–11.7). Figure 4 shows the Kaplan-Meier survival curves according to tumor height.
Conservation of good visual acuity of 20/40 or better

At the time of treatment, 212 patients had vision of 20/40 or better in the tumor-affected eye. Such vision was conserved in 63.5% (95% CI, 55.9–71.1%) at 2 years, 44.8% (95% CI, 35.3–54.4%) at 5 years, and 32.2% (95% CI, 21.1–43.2%) at 8 years.

Cox univariate analysis showed that the variables predicting loss of 20/40 vision were: reduced initial visual acuity \((p = 0.007; \text{risk ratio,} 1.37\text{ per Snellen line; 95% CI,} 1.09–1.71)\) and posterior tumor extension \((p = 0.001; \text{risk ratio,} 1.58; 95\% \text{ CI,} 1.22–2.05)\). Figure 5 shows Kaplan-Meier survival curves of conservation of vision of 20/40 or better, according to posterior tumor extension.

Death from metastatic disease

There were 285 patients resident in the United Kingdom. In these patients, the cumulative actuarial rates of metastatic death were 2.5% (95% CI, 0.7–4.4%) at 2 years, 10.0% (95% CI, 5.8–14.1%) at 5 years, and 14.1% (95% CI, 9.0–19.3%) at 8 years.

Cox univariate analysis showed that the variables predicting death from metastatic disease were longest basal tumor dimension \((p < 0.0001; \text{risk ratio,} 1.26/\text{mm; 95% CI,} 1.13–1.40)\), tumor height \((p = 0.005; \text{risk ratio,} 1.23/\text{mm; 95% CI,} 1.06–1.42)\), and extraocular tumor extension \((p = 0.026; \text{risk ratio,} 5.12; 95\% \text{ CI,} 0.1.21–21.69)\). Figure 6 shows Kaplan-Meier survival curves of time to metastatic death according to longest basal tumor dimension.

DISCUSSION

This study reports on ocular outcomes and patient survival after proton beam radiotherapy of choroidal melanomas at CCO in collaboration with the Liverpool Ocular Oncology Centre. The oncology service in Liverpool has a wide range of therapeutic modalities, which include ruthenium-106 and iodine-125 brachytherapy, transscleral and transretinal local resection, transpupillary thermotherapy, and photodynamic therapy. This study demonstrates the clinical benefits for patients who were deemed unsuitable for other forms of conservative treatment because of tumor size and location. For this reason, these patients represent a particularly challenging group, with 75% of tumors extending to within 2 disc diameters (3 mm) of the optic disc or...
fovea. The findings are interesting also because our proton beam has relatively sharp conformal dose characteristics, thereby enhancing its capability for avoiding critical structures.

Our rates of local tumor failure are similar to those reported by other groups (6, 14, 15). Treatment failure was related to large tumor size. Large tumors are more likely to be associated with aggressive behavior and hence diffuse and subclinical lateral tumor extensions into surrounding choroid. Our impression, therefore, is that failure of local tumor control occurred because it was not possible to define clinically the tumor extent and not because of problems with treatment planning and administration.

Secondary enucleation was related to large tumor size, posterior tumor extension, ciliary body involvement, and retinal invasion. Others have reported similar correlations (7, 8, 10). Large tumor size was an adverse factor for two reasons: first, because it increased the risk of local tumor recurrence and, second, because it was associated with persistent exudative retinal detachment and neovascular glaucoma. Daftari et al. have attributed the neovascular glaucoma to extensive irradiation of anterior ocular structures and have suggested anterior segment sparing to reduce this complication (16). We have successfully treated exudative retinal detachment after proton beam radiotherapy by resecting the irradiated tumor and this has resulted in regression of the iris neovascularization. This finding suggests that it is the presence of bulky, irradiated tumor that causes exudative retinal detachment and neovascular glaucoma. Retinal invasion is not widely reported as an adverse risk factor; however, a Collaborative Ocular Melanoma Study report on brachytherapy identifies collar-stud shape as a poor prognostic feature and tumors with this configuration tend to invade the retina (17). Our experience suggests that retinal invasion and perforation are associated with recurrent vitreous hemorrhage and uveitis after radiotherapy.

Visual outcome was mostly related to tumor size and posterior tumor extension. Others, such as Gragoudas et al., have previously reported similar correlations (10). Comparisons between our study and other reports is limited by selection bias, as mentioned previously; furthermore, we prefer to report minimum visual conservation time, which we feel is (1) more precise than time to loss of vision and (2) correlates more closely with what is communicated to patients when they are counseled before treatment. The correlation between posterior tumor extension and visual loss can readily be explained by the higher doses of radiation delivered to optic nerve and fovea; however, our impression is that another important cause of visual loss is exudation from the irradiated tumor. This mechanism would account for the correlation between larger tumor size and visual loss, even when the optic nerve and fovea have not received any radiation. This hypothesis has encouraged us to administer transpupillary thermotherapy and photodynamic therapy as a treatment for macular exudates and edema. Char and associates have since published successful results with this approach (18). Successful preliminary results have led us to give such treatments prophylactically. This is the subject of an ongoing investigation.

The main purpose of this study was to evaluate the principal ocular results of our treatment; therefore, metastatic disease is only briefly reported. As with other studies, the rate of death from metastatic disease correlates with tumor size at the time of treatment (19). It is widely believed that large tumors are associated with poor survival because they are more malignant, with a greater tendency to metastasize. This hypothesis results in large tumors being treated more aggressively and urgently than small tumors, some of which are even left untreated until growth is documented. Recent studies show that metastasis correlates closely with monosomy 3, which develops at an early stage (20). We therefore treat small melanomas aggressively, because it is with such lesions that opportunities for preventing metastatic spread are greatest. It is for this reason that our sample includes some small tumors, which some others might have left untreated.

Several procedures mentioned in our study are still under investigation, including treatment through the closed eyelid, notched beams, adjunctive transpupillary thermotherapy or phototherapy, and treatment of retinal detachment and neovascular glaucoma by local resection. We look forward to reporting on these in future articles.

In conclusion, proton beam radiotherapy achieves high rates of ocular conservation and local tumor control in patients considered unsuitable for other forms of conservative treatment. There is appreciable ocular morbidity, however, which correlates strongly with tumor size. There would seem to be scope for directing future efforts at preventing exudation from the irradiated melanoma, by closing leaking vessels with phototherapy or photodynamic therapy or by resecting the offending residual tumor.

REFERENCES

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