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Clinical Investigation: Central Nervous System Tumor

Outcomes of Proton Radiation Therapy for Peripapillary Choroidal Melanoma at the BC Cancer Agency

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Summary

We report our experience with proton beam therapy in the treatment of peripapillary choroidal melanomas by means of a retrospective analysis of 59 patients treated between 1995 and 2007 at the only Canadian proton therapy facility. This article shows that excellent control and toxicity rates can also be achieved at smaller proton centers, which is of importance as newer centers come online and may provide this treatment option for localized choroidal melanomas. These results also raise caution for larger (T3) peripapillary tumors, because this group appears to have worse local control and distant metastasis rates.

Purpose: To report toxicity, local control, enucleation, and survival rates for patients with peripapillary choroidal melanoma treated with proton therapy in Canada.

Methods and Materials: We performed a retrospective analysis of patients with peripapillary choroidal melanoma ($\leq$2 mm from optic disc) treated between 1995 and 2007 at the only Canadian proton therapy facility. A prospective database was updated for follow-up information from a chart review. Descriptive and actuarial data are presented.

Results: In total, 59 patients were treated. The median age was 59 years. According to the 2010 American Joint Committee on Cancer TNM classification, there were 20 T1 tumors (34%), 28 T2 tumors (48%), and 11 T3 tumors (19%). The median tumor diameter was 11.4 mm, and the median thickness was 3.5 mm. Median follow-up was 63 months. Nineteen patients received 54 cobalt gray equivalents (CGE) and forty patients received 60 CGE, each in 4 fractions. The 5-year actuarial local control rate was 91% (T1, 100%; T2, 93%; and T3, 59%) ($p = 0.038$). There was a suggestive relationship between local control and dose. The local control rate was 97% with 60 CGE and 83% with 54 CGE ($p = 0.106$). The metastasis-free survival rate was 82% and related to T stage (T1, 94%; T2, 84%; and T3, 47%) ($p < 0.001$). Twelve patients died, including eleven with metastases. The 5-year actuarial rate of neovascular glaucoma was 31% (23% for T1–T2 and 68% for T3, $p < 0.001$), and that of enucleation was 0% for T1, 14% for T2, and 72% for T3 ($p < 0.001$). Radiation retinopathy (74%) and optic neuropathy (64%) were common within-field effects.

Conclusions: Proton therapy provides excellent local control with acceptable toxicity while conserving the globe in 80% of cases. These results are consistent with other single-institution series using proton radiotherapy, and toxicity rates were acceptable. T3 tumors carry a higher rate of both local recurrence and metastasis.

Keywords: Proton therapy, Choroidal melanoma, Peripapillary, Local control, Survival

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Introduction

Choroidal melanoma is a relatively uncommon malignancy, with an incidence rate of 4.3 per million each year in the United States (1). After the results of the large randomized Collaborative Ocular Melanoma Study (COMS) trial, eye-sparing treatments such as episcleral plaque brachytherapy, proton beam treatment, and stereotactic radiotherapy (SRT) have largely replaced enucleation in the treatment of localized choroidal melanomas (2–4). The principal advantage of radiotherapy is eye conservation and retention of useful vision in many patients, without sacrificing local control or survival.

Brachytherapy does not achieve adequate coverage of peripapillary choroidal melanomas because a tumor located next to the optic nerve hinders placement of the temporary plaque onto the sclera. Placement of a radioactive plaque adjacent to the optic nerve results in an excessively high risk of long-term sequelae including blindness (5).

Several strategies have been used to circumvent these limitations, including notched plaque radiotherapy, charged particle radiotherapy, and stereotactic radiosurgery (3, 4, 6–9). The dosimetric characteristics of protons allow for a relatively uniform dose to be delivered to the entire tumor, as well as a sharp reduction in dose outside the treated area, as compared with high-energy photon radiotherapy.

Since August 1995, the BC Cancer Agency, in conjunction with the University of British Columbia Eye Care Centre and TRIUMF (TRI-University Meson Facility), has been operating the only proton therapy facility in Canada to treat patients with ocular melanomas. Indications for proton therapy include large tumors and peripapillary tumors unsuitable for brachytherapy. This is the first report of toxicity, local control, and survival rates for patients with peripapillary choroidal melanomas treated with proton therapy in Canada.

Methods and Materials

Patients were referred to the ocular oncology clinic at the Eye Care Centre in Vancouver by ophthalmologists based primarily in Western Canada. Demographic and tumor data were prospectively recorded into a database. Patients with peripapillary choroidal melanoma, defined as less than or equal to 2 mm from the optic disc, treated between March 1995 and December 2007 with proton therapy were retrospectively selected for this study. Patients with nonmelanoma tumors or re-treatment of plaque failures were excluded.

Before proton treatment, all patients had full systematic ocular examinations by a dedicated ocular oncologist (K.P.). This included slit-lamp examination, visual acuity, intraocular pressure measurement, direct and indirect ophthalmoscopy, fundus photography, fluorescein angiography, and A- and B-mode ultrasound for tumor measurements. Staging investigations included chest radiography, liver enzyme levels, and liver ultrasounds to exclude overt metastases. The patients were also assessed by one of two radiation oncologists (T.P. or R.M.) at the BC Cancer Agency to confirm eligibility.

Visual acuity and intraocular pressures were recorded prospectively. Slit-lamp examination and gonioscopy were performed to look for new iris and angle vessels at each visit. Tumor measurements were regularly recorded with ultrasonography and funduscopy. Treatment-related complications were documented prospectively.

The prospective database was updated for this report based on review of charts at the ocular oncology clinic and the BC Cancer Agency. Follow-up information for out-of-province and international patients was obtained from referring ophthalmologists through written and/or telephone contact. Tumors were retrospectively classified into T stage according to the 2010 American Joint Committee on Cancer's TNM cancer staging manual, based on tumor thickness and diameter at diagnosis (10). This study was reviewed and approved by the Research Ethics Board of the University of British Columbia.

Treatment procedure

The proton therapy treatment procedure is similar to that described by other authors (3, 7). Up to six tantalum clips, each measuring 2 mm, were surgically implanted on the sclera around the tumor edges after localization by transillumination and indirect ophthalmoscopy. This procedure was done with the patient under general anesthesia approximately 1 week before the planned treatment date. The distance between each clip and tumor edge was recorded intraoperatively.

The treatment was simulated by use of a thermoplastic head shell and bite block for immobilization (Fig. 1). Once installed on the positioning chair, the patient was asked to fixate on a small flashing target. Clip positions were captured by use of orthogonal x-ray images. Treatment was planned by use of EYEPLAN software, developed originally by Goitein and Miller (11) for dosimetry based on three-dimensional reconstruction of the eye, ocular structures, and tumor. Tumor borders were delineated by the ocular oncologist and verified by the radiation oncologist. Various gaze angles were assessed by the ophthalmologist and medical physicist to select the optimal angle that minimized irradiation of normal tissues. A brass collimator was custom-made for each patient to shape the treatment beam with a 2.5-mm margin to beam edge.

Orthogonal films were taken before each treatment to verify positioning of the clips relative to the treatment plan, and patient position adjustments were made if necessary. Treatment was delivered in 4 fractions on 4 consecutive days at the TRIUMF cyclotron facility on the University of British Columbia campus. T stage was not a determinant in dose; instead, the dose was initially 60 cobalt gray equivalents (CGE) for all patients until 1997. The dose was reduced to 54 CGE from 1997 to 2001 because of a clinical impression of a high rate of secondary glaucoma. The dose was reverted back to 60 CGE from 2001 onward because of the clinical concern of loss of tumor control observed on follow-up. The proton beam energy was set at 74 MeV, with a practical range in tissue of 34.3 mm, defined by the 90% isodose curve. A 2.5-mm margin was used for the distal and proximal end of the defined target. The beam-on time for each treatment session was approximately 90 seconds. The eye position was closely monitored for movement while the radiation beam was on, and the treatment was interrupted if necessary. After completion of the treatment, the patient was regularly evaluated for tumor response, toxicity, and visual acuity by the ocular oncologist.

Statistical analyses

Estimates of local control, metastasis-free survival, and overall survival were calculated according to the actuarial method of