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# Visual Outcomes after Proton Beam Irradiation for Choroidal Melanomas Involving the Fovea

Avni V. Patel, MD, MBA,[1] Anne Marie Lane, MPH,[1] Margaux A. Morrison, MPH,[2] Alexei V. Trofimov, PhD,[3] Helen A. Shih, MD,[3] Evangelos S. Gragoudas, MD,[1] Ivana K. Kim, MD[1]

***Purpose:*** To report visual outcomes in patients undergoing proton beam irradiation of tumors located within 1 disc diameter of the fovea.

***Design:*** Retrospective review.

***Participants:*** Patients with choroidal melanoma involving the fovea treated with proton beam therapy between 1975 and 2009.

***Methods:*** Three hundred fifty-one patients with choroidal melanomas located 1 disc diameter (DD) or less from the fovea and more than 1 DD away from the optic nerve were included in this study. In a subgroup of 203 of the patients with small and medium choroidal melanomas, the effect of a reduced dose of radiation, 50 Gy (relative biological effectiveness [RBE]) versus 70 Gy (RBE), on visual outcomes was analyzed. The Kaplan-Meier method and Cox regression analysis were performed to calculate cumulative rates of vision loss and to assess risk factors for vision loss, respectively.

***Main Outcome Measures:*** Visual acuity and radiation complications, which included radiation maculopathy, papillopathy, retinal detachment, and rubeosis, were assessed.

***Results:*** Three hundred fifty-one patients were included in this study with a mean follow-up time of 68.7 months. More than one-third of patients (35.5%) retained 20/200 or better vision 5 years after proton beam irradiation. For those patients with a baseline visual acuity of 20/40 or better, 16.2% of patients retained this level of vision 5 years after proton beam irradiation. Tumor height less than 5 mm and baseline visual acuity 20/40 or better were associated significantly with a better visual outcome ($P < 0.001$). More than two-thirds (70.4%) of patients receiving 50 Gy (RBE) and nearly half (45.1%) of patients receiving 70 Gy (RBE) retained 20/200 or better vision 5 years after treatment, but this difference was not significant. Approximately 20% of patients with these smaller macular tumors retained 20/40 vision or better 5 years after irradiation.

***Conclusions:*** The results of this retrospective analysis demonstrate that despite receiving a full dose of radiation to the fovea, many patients with choroidal melanoma with foveal involvement maintain useful vision. A radiation dose reduction from 70 to 50 Gy (RBE) did not seem to increase the proportion of patients who retain usable vision. *Ophthalmology 2015;■:1–9 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.*

Choroidal melanoma is the most common primary intraocular malignancy among adult patients and is one of the few potentially fatal ocular diagnoses. Treatment options for choroidal melanomas include enucleation, laser photocoagulation, transpupillary thermotherapy, and irradiation. Over the past few decades, radiotherapy has become used more widely in the care of these tumors.[1–4] Achieving local tumor control, while preserving the eye and maintaining some useful vision, is the primary goal of radiotherapy in the management of uveal melanoma. Two major radiotherapy methods currently are used: external beam radiation therapy, most commonly with protons, and radioactive plaques, which are placed over the sclera in the area of the tumor.[2,4–6] As charged particles, protons can provide highly localized radiation dose distributions, and by doing so may reduce ocular morbidity.[3]

Radiation maculopathy and papillopathy are common sequelae of radiation treatment and are the predominant causes of visual loss in patients after radiotherapy. Radiation maculopathy is the main contributor to vision loss in patients who have tumors with foveal involvement.[7] The clinical manifestations of radiation maculopathy include capillary closure, telangiectasia, microaneurysm formation, hemorrhages, exudates, macular edema, and nerve fiber layer infarctions.[8] Previous studies have shown that the risk of radiation maculopathy and papillopathy are determined primarily by the radiation dose to the macula and optic nerve, respectively.[9,10] Additionally, underlying



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vascular disorders may enhance the risk of radiation maculopathy.[10] In patients who received plaque radiation, a significant dose-response relationship was shown between the dose of radiation to the fovea and the development of radiation maculopathy.[11] It is commonly assumed that patients with choroidal melanoma involving the fovea are destined to sustain severe vision loss after irradiation, but actual visual outcomes in patients with choroidal melanoma involving the fovea are not well described.

The primary goal of this study was to review visual outcomes in patients undergoing irradiation with proton beam therapy for tumors located within 1 disc diameter (DD) of the fovea. In addition, we examined whether a dose reduction from 70 to 50 Gy (relative biological effectiveness [RBE]) had any effect on visual outcomes in patients with this tumor location. In a previous randomized study, we demonstrated that although a dose reduction from 70 to 50 Gy (RBE) did not provide a significant visual benefit, there was a trend toward a decreased incidence of radiation papillopathy.[12] However, in the prior study, visual outcomes were evaluated in a subset of patients who had tumors located within 4 DD of the fovea or optic nerve. In the present study, to determine better the effects of radiation to the fovea on visual function, we restricted our analyses to patients with tumors in very close proximity to the fovea only. We believe these data are essential to guiding treatment decisions in these patients.

## Methods

A waiver of informed consent and Health Insurance Portability and Accountability Act authorization was granted by the institutional review board of the Massachusetts Eye and Ear Infirmary for this medical records review.

Patients with choroidal melanoma involving the fovea (n = 351) treated with proton beam therapy at the Harvard Cyclotron Laboratory, Cambridge, Massachusetts, or the Francis H. Burr Proton Therapy Center at Massachusetts General Hospital, Boston, Massachusetts, between 1975 and 2009 were included in this study. Most patients (n = 326) were treated between 1975 and 1996. These patients were included in a previous analysis evaluating outcomes in more than 2000 patients treated with proton therapy for unilateral choroidal or ciliary body melanoma, or both.[13] Additionally, a small number of patients (n = 34) participated in a randomized clinical trial evaluating dose reduction.[12] Twenty-five patients included in the analysis were treated between 2005 and 2009, when a change in the dosing regimen for small to medium tumors near the fovea was implemented. The patients were identified through the Melanoma Registry of the Ocular Oncology Service at the Massachusetts Eye and Ear Infirmary, Boston, Massachusetts. Patients with choroidal melanomas located 1 DD or less from the fovea and more than 1 DD away from the optic nerve were included in this study. Patients with these tumor characteristics were selected for evaluation because they were more likely to have received at least 90% of the prescribed dose of radiation to the fovea and significantly less of the dose to the optic nerve. These criteria identified tumors at highest risk for radiation maculopathy while minimizing the risk of papillopathy. Thus, they were more likely to be at risk of vision loss resulting from radiation to the fovea than other vision-compromising conditions.

Patients were evaluated annually at a minimum at the Massachusetts Eye and Ear Infirmary or by their local ophthalmologist. The ophthalmologic examination at each visit included Snellen visual acuity testing, slit-lamp biomicroscopy, indirect ophthalmoscopy, and fundus photography. All patients were followed up for ocular outcomes, including visual acuity and radiation complications, which included radiation maculopathy, papillopathy, retinal detachment, and rubeosis.

Table 1. Patient Characteristics

| | |
|---|---|
| Mean age at treatment (range), yrs | 58.09 (14.62–91.47) |
| Female gender, no. (%) | 157 (44.7) |
| Male gender, no. (%) | 194 (55.3) |
| Diabetes, no. (%) | 29 (8.3) |
| Hypertension, no. (%) | 72 (29.4) |
| Mean largest tumor diameter (range), mm | 12.8 (5–23) |
| Mean largest tumor height (range), mm | 4.9 (0.6–14.3) |
| Tumors within 1 DD of the fovea, no. (%) | 343 (97.4) |
| Tumors involving the fovea, no. (%) | 90 (25.6) |
| Tumors >2 DD away from the nerve, no. (%) | 174 (49.6) |
| Mean follow-up (range), mos | 68.7 (0.8–264.7) |

DD = disc diameter.

The treatment planning protocol for proton therapy of uveal melanomas has been described previously.[3] A 3-dimensional treatment planning computer program is used with selection of visual fixation direction to minimize irradiation to the lens, fovea, and optic disc. Patient immobilization is achieved via a bite block and individually contoured plastic mask mounted into a frame on the head holder. Patients are set up radiographically and monitored during treatment with a video camera to ensure that they are fixating on a predetermined point. Determination of the radiation doses to the fovea for each patient is derived from the 3-dimensional treatment plan.

In addition to the analysis performed in this series of 351 patients with choroidal melanomas of any size located in close proximity to the fovea, a subgroup analysis of 203 patients with small and medium choroidal melanomas also was performed. In this subgroup analysis, 156 patients received a total dose to the tumor of 70 Gy (RBE) and 47 patients received a total dose of 50 Gy (RBE) delivered in 5 equal fractions over 5 to 10 days.

### Statistical Analysis

Cumulative rates of vision loss were calculated according to the Kaplan-Meier method. These rates of vision loss also were assessed by tumor height and by baseline visual acuity. Cox regression analysis was performed to assess risk factors for vision loss among these patients. The risk factors analyzed included tumor height, tumor diameter, distance of tumor from the optic nerve, age at treatment, history of diabetes, and baseline visual acuity. We also evaluated the effect of ocular complications from radiation

Table 2. Visual Acuity at Final Follow-up Examination

| Visual Acuity | Baseline | Last Follow-up |
|---|---|---|
| 20/40 or better | 178 (50.7) | 66 (18.8) |
| 20/50–20/100 | 122 (34.8) | 57 (16.2) |
| 20/125–20/800 | 51 (14.5) | 90 (25.6) |
| CF–NLP | 0 (0.0) | 138 (39.3) |

CF = counting fingers; NLP = no light perception.
Data are no. of patients (%).