Proton Irradiation for Peripapillary and Parapapillary Melanomas

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Objective: To examine ocular outcomes and survival after proton irradiation in patients with peripapillary and parapapillary melanomas ineligible for the Collaborative Ocular Melanoma Study.

Methods: A total of 573 patients who received proton irradiation from January 4, 1985, through December 24, 1997, for tumors located within 1 disc diameter of the optic nerve, and therefore ineligible for the Collaborative Ocular Melanoma Study, were evaluated. Cumulative rates of vision loss in the treated eye, eye loss, melanoma-related mortality, and tumor recurrence were estimated using the Kaplan-Meier method.

Results: Most (53.4%) tumors abutted the optic disc; median distance from the tumor to the macula was 0.5 disc diameters. By 5 years after proton therapy, radiation papillopathy had developed in 56.8% and maculopathy in 60.4% of patients. Of 450 patients with a baseline visual acuity of 20/200 or better in the treated eye, vision was retained in 54.9% at 2 years after irradiation. This decreased to 20.3% by 5 years after treatment, although 56.2% had visual acuity of counting fingers or better. Five- and 10-year rates of local recurrence were 3.3% and 6.0%, respectively. Enucleation rates were 13.3% at 5 years and 17.1% at 10 years after treatment. Melanoma-related mortality rates were similar to those in our larger cohort of patients (24.0% at 15 years).

Conclusions: Proton irradiation should be considered for treating patients with tumors contiguous to the optic disc. Although visual acuity is compromised, some preservation is possible (counting fingers or better in many patients). Eye conservation is likely, with low rates of tumor recurrence and no increased risk of metastasis.

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Patients diagnosed with tumors located near the optic nerve experience complications when treated with radiotherapy because irradiation of the nerve is unavoidable. These complications may lead to vision loss or loss of the eye. When these tumors are contiguous to or encircling the optic nerve, plaque radiotherapy is difficult. One type of external beam radiotherapy, proton beam irradiation, is well-suited to treating tumors located near critical structures because the treatment planning program allows irradiation of the tumor without localization of the posterior margin. With anterior localization and fundus photography, complete coverage of a tumor of any shape is possible. The proton beam also delivers a homogeneous dose to the tumor, and because of its sharp edge, reduces radiation exposure to surrounding sensitive tissues. Complete loss of vision, once thought to be inevitable in most cases of parapapillary and peripapillary tumors, is avoidable with proton therapy.

We examined ocular outcomes and survival in patients who received proton irradiation for peripapillary (surrounding the optic nerve) and parapapillary (≤1 disc diameter [DD] from the optic nerve) tumors, tumors ineligible for treatment in the Collaborative Ocular Melanoma Study (COMS), to determine whether proton therapy is a suitable treatment option with an acceptable radiation-complications profile.

METHODS

Patients who had tumors located within 1 DD of the nerve and who were treated with protons from January 4, 1985, through December 24, 1997, were included in this analysis. 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 (MEEI), Boston. Ocular and

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survival outcomes were ascertained by active surveillance at the MEEI or regular contact with patients’ local ophthalmologists and other specialists. Radiation papillopathy or maculopathy was diagnosed if hemorrhage, exudate, edema, or other microvascular changes involving the optic nerve or macula were present on ophthalmologic examination or fundus photography. Other signs of papillopathy included nerve fiber layer infarcts, pallor, or neovascularization of the disc. In addition, for mortality surveillance, the Social Security Death Index was used to identify deaths in the cohort. Cause of death was confirmed by biopsy in 59.4% of cases, and by computed tomography, magnetic resonance imaging, or other imaging studies in an additional 25.0%. Medical records and death certificates were obtained to determine cause of death in all but 1 of the remaining cases (death was reported by next of kin). Median follow-up was 96.3 months (range, 9.9-172.9 months). Kaplan-Meier techniques were used to determine cumulative rates of melanoma-related mortality, tumor recurrence, vision loss, enucleation, and complications, such as radiation maculopathy and papillopathy.

Five hundred seventy-three patients had parapapillary or peripapillary tumors. Of these, 306 patients had tumors touching the optic nerve, 240 patients had tumors involving the macula, and 128 patients had tumors that involved both structures. The median age of patients was 60 years (range, 14-91 years). Median tumor dimensions were 4.2 mm (range, 1.0-17.1 mm) and 13 mm (range, 6-24 mm) for height and diameter, respectively. The majority of patients had relatively good vision at the time of diagnosis; the median baseline visual acuity was 20/63 and varied between 20/16 and no light perception.

RESULTS

 Ninety-six patients died of melanoma metastasis, and an additional 18 patients were diagnosed as having metastatic disease while under observation. Eighty-two patients died of nonmelanoma causes. Cumulative rates of melanoma-related mortality are shown in Figure 1. Most deaths occurred in the early years after receiving treatment, with one-half of all patient deaths observed within the first 5 years after therapy.

Cumulative rates of tumor recurrence were quite low, with definite regrowth of the tumor (documented at MEEI) occurring in 3.3% of patients by 5 years after radiation therapy and with 6.0% recurring at 10 years after therapy. Marginal recurrences occurred in 6 patients, whereas continued tumor growth in all dimensions was observed in 4 patients. Six eyes were enucleated because of definite regrowth. There were an additional 5 patients with suspected regrowth (not evaluated at the MEEI) who underwent enucleation at other institutions.

Sixty-six eyes (11.5%) underwent enucleation. The most common reason for enucleation was neovascular glaucoma, with 43 patients losing the eye because of this complication. Other complications that led to removal of the eye included complete retinal detachment and total loss of vision. By 1 year after proton therapy, 1.9% of patients required enucleation of the eye; this rate had increased to 13.3% by 5 years after radiation.

Signs of radiation vasculopathy (maculopathy and/or papillopathy) were detected in 60.2% of this cohort. Radiation papillopathy was found in 258 eyes (45.0%), and radiation maculopathy occurred in 276 eyes (48.2%). Both types of complications were more likely to be early-onset complications, developing 2 to 3 years after irradiation in most cases. Cumulative rates of radiation papillopathy and maculopathy were quite similar; by 3 years after proton therapy, the cumulative rate of both complications was approximately 49%, which increased to 61.1% for papillopathy and 68.0% for maculopathy by 10 years after treatment.

We evaluated vision loss in a subgroup of 450 patients (78.5%) with a pretreatment visual acuity of 20/200 or better and found that two-thirds had visual acuity less than 20/200 after irradiation. Similar to other outcomes, rates of vision loss increased steadily in the first 5 years after treatment, and long-term prognosis for retention of visual acuity better than 20/200 was poor (Figure 2). Despite the poor prognosis, some patients were able to maintain ambulatory vision for long periods after treatment, as illustrated in Figure 3.

To determine whether these outcomes were similar to those observed in patients with tumors located farther away from the optic nerve, we compared cumulative rates of each outcome in this COMS-ineligible patient series with rates in our larger cohort of patients with choroidal melanomas who followed the same treatment and follow-up protocols as COMS-ineligible patients during the study period. Ten-year rates of melanoma-related mortality were similar in the 2 groups: 21.3% in patients with tumors within 1 DD of the optic nerve compared with 23.5% in the larger cohort. Likewise, rates of
tumor regrowth did not differ with respect to proximity of the tumor to the optic nerve (Table).

In contrast, cumulative rates of all functional outcomes (complications, eye loss, and vision loss) were significantly higher in patients with tumors within 1 DD of the optic nerve than in those with tumors situated farther away from the disc. There were marked differences in the incidence of vision loss between the COMS-ineligible patients and all other patients in the cohort. Ten-year rates of vision loss, to worse than 20/200, were 91.0% and 56.7% for COMS-ineligible patients and all other patients treated with proton therapy, respectively. Higher rates of maculopathy and papillopathy were observed in the COMS-ineligible patients (68.0% and 61.1%, respectively) than in the remaining cohort (36.3% and 6.4%, respectively).

We previously evaluated the incidence of radiation papillopathy and maculopathy in a series of patients restricted to smaller tumors located within 4 DD of the optic nerve or macula. The 5-year rates of papillopathy, maculopathy, and vision loss were 34.8%, 64.3%, and 67.7%, respectively, and compare favorably with the rates of these conditions observed in the current series. Another end point previously evaluated in patients with parapapillary tumors was visual field defects secondary to radiation papillopathy. Although 31% of patients developed radiation papillopathy, the risk of developing visual field defects was not associated with papillopathy status.

Table. Cumulative Rates of Ocular Outcomes and Survival After Proton Therapy in Patients With Choroidal Melanomas

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate (95% Confidence Interval), %</th>
<th>Patients With Tumors Within 1 DD of Optic Nerve</th>
<th>All Other Patients (Tumors &gt;1 DD From the Optic Nerve)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma-related mortality</td>
<td>11.9 (9.3-15.1)</td>
<td>21.3 (17.6-25.7)</td>
<td>15.2 (12.9-17.9)</td>
<td>.29</td>
</tr>
<tr>
<td>Regrowth</td>
<td>3.3 (1.9-5.6)</td>
<td>6.0 (3.1-11.6)</td>
<td>3.0 (1.9-4.6)</td>
<td>.57</td>
</tr>
<tr>
<td>Eye loss</td>
<td>13.3 (10.3-16.9)</td>
<td>17.1 (13.1-22.0)</td>
<td>4.8 (3.4-6.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vision loss</td>
<td>79.7 (75.0-84.0)</td>
<td>91.0 (85.5-95.0)</td>
<td>39.7 (35.9-43.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maculopathy</td>
<td>60.4 (55.5-65.4)</td>
<td>68.0 (62.2-73.7)</td>
<td>29.0 (25.6-32.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Papillopathy</td>
<td>56.8 (51.9-61.7)</td>
<td>61.1 (55.6-66.6)</td>
<td>4.8 (3.4-6.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: DD, disc diameter.

a Patients treated at Massachusetts Eye and Ear Infirmary from January 4, 1985, through December 24, 1997.
b Log-rank test.
In this series of patients with peripapillary and parapapillary tumors, poorer outcomes were observed in terms of function and similar outcomes in terms of survival, compared with the remaining cohort of patients who received proton irradiation. In COMS-ineffligible patients, by 5 years after therapy, radiation maculopathy and papillopathy developed at 2 times (for maculopathy) to 10 times (for papillopathy) the rate of these complications observed in patients treated at MEEI for tumors located farther away from the optic disc. However, although poorer visual outcomes were demonstrated in patients with tumors on or near the optic nerve, total vision loss was uncommon. At 2 and 5 years after proton therapy, 81.8% and 56.2% of patients, respectively, retained visual acuity of counting fingers or better.

One of the weaknesses of this study is nonstandardization of visual acuity measurement and definitions of radiation maculopathy and papillopathy. However, more than two-thirds of patients included in this analysis returned to the MEEI for follow-up examinations in which a single method of visual acuity testing was performed using Early Treatment Diabetic Retinopathy Study charts. Similarly, standard definitions of characteristics of radiation vasculopathy were applied to identify cases at the MEEI. For patients not returning to the MEEI, standardized mail questionnaires were regularly sent to their local ophthalmologists to obtain these data, and photographs and angiograms were reviewed by a single physician (E.S.G.) in the Retina Service, whenever possible. These efforts and the fairly high rate of follow-up at MEEI may have reduced any effect that nonstandardization may have had on our results.

Alternative treatment modalities have been used to treat these tumors. Stereotactic radiotherapy was applied in a series of 28 patients with juxtapapillary choroidal melanoma, and 37% developed optic neuropathy less than 2 years after therapy. Increased rates (64%) were observed with evaluation of additional cases and longer follow-up. At the present time, brachytherapy is difficult to administer in cases of peripapillary and parapapillary tumors, although it has been used in some cases with additional transpupillary thermotherapy. Inadequate treatment may lead to an increase in tumor recurrences. Recurrences occurred in 10% of 141 patients with tumors overhanging the optic disc who were treated with plaque brachytherapy, and 23% of eyes were enucleated. Notched plaques and “slotted” eye plaques can accommodate the anatomy of the eye and improve coverage of the tumor. In the mentioned series, 89% of patients were treated with notched plaques, and a lower recurrence rate (6%) was observed in these cases. In contrast, 3.3% of patients developed local recurrences and 13.3% of patients underwent enucleation in our series using protons. Puusaari and colleagues have performed simulations of a collimating plaque, modified to reduce radiation exposure to the macula and optic nerve, but its utility for tumors contiguous to the nerve has yet to be evaluated.

The findings of this study suggest that proton therapy should be considered for patients with tumors encroaching or contiguous to the optic nerve. Eye conservation is possible in the vast majority of cases, with low rates of recurrence and metastasis. However, vision loss is still significant in this group of patients. Investigation of a reduction in total radiation dose or hyperfractionation in select patients, eg, patients with smaller tumors, may be worthwhile, but this would require a randomized clinical trial.

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REFERENCES