International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Outcomes of Proton Therapy for the Treatment of Uveal Metastases

Sophia C. Kamran, MD,* John M. Collier, PhD,† Anne Marie Lane, MPH,‡ Ivana Kim, MD,‡ Andrzej Niemierko, PhD,§ Yen-Lin E. Chen, MD,† Shannon M. MacDonald, MD,† John E. Munzenrider, MD,† Evangelos Gragoudas, MD,‡ and Helen A. Shih, MD†

**Harvard Medical School; †Department of Radiation Oncology, Massachusetts General Hospital; ‡Retina Service, Massachusetts Eye and Ear Infirmary; and §Division of Biostatistics, Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts*

Received May 2, 2014, and in revised form Jul 15, 2014. Accepted for publication Aug 2, 2014.

Summary

This retrospective review investigated the use of proton therapy in providing local control of uveal metastases with minimization of normal tissue injury. Proton therapy was found to be an effective treatment, with modest localized symptoms. Visual function declined over time, but the high rate of local control, prevention of morbid disease symptom progression, and an efficient and cost-effective delivery system support proton therapy as a favorable option for palliation of uveal metastases.

Purpose/Objective(s): Radiation therapy can be used to treat uveal metastases with the goal of local control and improvement of quality of life. Proton therapy can be used to treat uveal tumors efficiently and with expectant minimization of normal tissue injury. Here, we report the use of proton beam therapy for the management of uveal metastases.
Methods and Materials: A retrospective chart review was made of all patients with uveal metastases treated at our institution with proton therapy between June 2002 and June 2012. Patient and tumor characteristics, fractionation and dose schemes, local control, and toxicities are reported.
Results: Ninety patients were identified. Of those, 13 were excluded because of missing information. We report on 77 patients with 99 affected eyes with available data. Patients were 68% female, and the most common primary tumor was breast carcinoma (49%). The median age at diagnosis of uveal metastasis was 57.9 years. Serous retinal detachment was seen in 38% of treated eyes. The median follow-up time was 7.7 months. The median dose delivered to either eye was 20 Gy(relative biological effectiveness [RBE]) in 2 fractions. Local control was 94%. The median survival after diagnosis of uveal metastases was 12.3 months (95% confidence interval, 7.7-16.8). Death in all cases was secondary to systemic disease. Radiation vasculopathy, measured decreased visual acuity, or both was observed in 50% of evaluable treated eyes. The actuarial rate of radiation vasculopathy, measured decreased visual acuity, or both was 46% at 6 months and 73% at 1 year. The 6 eyes with documented local failure were successfully salvaged with retreatment.
Conclusions: Proton therapy is an effective and efficient means of treating uveal metastases. Acutely, the majority of patients experience minor adverse effects. For

Reprint requests to: Helen A. Shih, MD, Department of Radiation Oncology, Massachusetts General Hospital, 30 Fruit St, Boston, MA 02114. Tel: (617) 724-9627; E-mail: hshih@partners.org

Presented in a poster format at the 55th Annual Meeting of the American Society for Radiation Oncology (ASTRO), Atlanta, GA, September 22-25, 2013.

Conflict of interest: H.A.S. is an editor of this journal. The authors report no other conflict of interest.

Int J Radiation Oncol Biol Phys, Vol. 90, No. 5, pp. 1044–1050, 2014
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2014.08.003

longer-term survivors, the risk of retinal injury with vision loss increases significantly over the first year. © 2014 Elsevier Inc.

Introduction

Uveal metastases are the most common intraocular tumor (1, 2), with the choroid as the most common site of involvement (3). Autopsy studies reveal an incidence of 4% to 12% of choroidal metastases in asymptomatic individuals with solid primary tumors (4). Typical symptoms include vision loss or visual field deficits, photophobia, and floaters (5). The most common primary tumors to give rise to intraocular metastases are lung and breast carcinoma (5). Untreated uveal metastases will cause gradual vision loss (6), and with continued progression, they will grow into the orbit, causing significant morbidity of pain, proptosis of the affected eye, and complete vision loss (7). Although uveal metastases are not typically fatal, they can be a source of significant morbidity if untreated, and therefore the goals of therapy include local control and improvement of quality of life.

The use of proton beam radiation for uveal metastases has been in practice at Massachusetts General Hospital in collaboration with Massachusetts Eye and Ear Infirmary since 1975. Over time, the practice has evolved with dose reduction from 28 Gy(relative biological effectiveness [RBE]) to 20 Gy(RBE) divided in 2 fractions. To date, there is limited published literature on the outcomes of uveal metastases treated with proton beam therapy, specifically with evaluation of treatment details such as dose and target volume effects. Here, we present our results in patients with uveal metastases treated with proton beam therapy.

Methods and Materials

This institutional review board—approved retrospective study reviewed all records of patients treated with proton beam therapy for uveal metastases between June 2002 and June 2012. Patients included in the study were >18 years with a diagnosis of uveal metastasis from any primary site.

A detailed review of electronic medical records and chart records was completed. Data collected included patient characteristics, primary tumor characteristics, primary tumor treatment, uveal metastasis information, uveal metastasis treatment information, and ophthalmologic follow-up data including tumor response and adverse events as defined by visual acuity and radiation vasculopathy, other new adverse effects or worsening of existing symptoms, and other potential findings on direct examination. Adverse effects were based on patient report and clinical documentation. Adverse effects were classified for their lack of presence before treatment and arising after treatment to differentiate potential radiation treatment effect from symptoms related to disease. Treatment adverse events were defined as toxicity or deficit determined by formal evaluation, namely radiation vasculopathy, radiation papillopathy, and resulting decrease in visual acuity at any point after treatment, not to be scored more than once per patient. Follow-up was defined from the completion of treatment. The diagnosis of choroidal metastasis was based on ophthalmic examination, including fundoscopy and ultrasonography. Biopsy was not routinely performed, and it was assumed that the choroidal metastasis originated from the known primary tumor.

Planning and treatment

All patients were treated definitively for their uveal metastases with proton radiation therapy. This involved creating a model of the patient's eye using software that was initially developed at our center and subsequently further advanced by others (8) (Eyeplan, Clatterbridge Cancer Center, NHS Foundation Trust, UK). Integrated data into the eye model included the tumor location, shape, and size, based on clinical examination, fundus photographs, and ultrasound measurements of both eye and tumor. Beam selection and patient gaze direction were determined by use of Eyeplan with both ophthalmologist and radiation oncologist working collaboratively with the medical physicist. Patients were positioned for treatment sitting upright with a thermoplastic mask and dental mold used for immobilization of the head. The patient's eye was positioned for treatment by the patient's voluntary fixation on a spot positioned to achieve the desired eye gaze position, typically in such a manner that the proton beam was directed on the sclera to avoid the anteriormost eye structures as much as possible without compromising target coverage. If the patient was not able to fixate on the light source with the eye being treated, setup was achieved by use of the contralateral eye for achieving the desired placement of the eye being treated. Optimal gaze direction was selected based on providing full-dose coverage to the tumor while minimizing dose to critical normal tissues, including the macula, optic disc, retina, lens, ciliary body, limbus, lacrimal gland, canthi, and eyelids. Treatment planning used 4-mm lateral margins to the field edge. Beam modulation delivered dose with 3-mm proximal and 4-mm distal margins. The net target coverage was by the 90% isodose. Dose prescription was typically in 2 fractions, most commonly 14 Gy(RBE) or 10 Gy(RBE) per fraction for a total of 28 or 20 Gy(RBE), respectively. There was some dose variation, as detailed in Table 1. Each treatment required a radiation oncologist present to verify the setup based on incident light field on the eye to be treated.

Statistical analyses

The Kaplan-Meier method was used for actuarial analysis of overall survival and time to tumor progression. Survival

Table 1 Demographic, tumor, and treatment characteristics

Patient, clinical characteristic, or treatment	No. (%)
Sex	
Male	25 (32)
Female	52 (68)
Median age at diagnosis of primary, y	52
Median age at diagnosis of uveal metastasis, y	58
Primary cancers	
Breast	38 (49)
Lung	17 (22)
Renal cell	4 (5)
Thyroid	3 (4)
Colon	2 (3)
Esophageal	2 (3)
Other	11 (14)
Presence of extraocular metastases	
Yes	63 (82)
No	13 (17)
Unknown	1 (1)
Treatment received for primary disease	
Chemotherapy alone	6 (8)
Radiation alone	4 (5)
Surgery alone	9 (12)
Chemotherapy + surgery	13 (17)
Chemotherapy + radiation	9 (12)
Radiation + surgery	4 (5)
All 3 modalities	25 (32)
Unknown or no treatment	7 (9)
Prior whole brain irradiation	
Yes	8 (10)
No	34 (44)
Unknown	35 (46)
Eye(s) involved*	
Left eye	27 (35)
Right eye	28 (36)
Both	22 (29)
Primary presenting symptom	
Decreased vision/blurry vision	54 (70)
Blind spot	14 (18)
None	9 (12)
Retinal detachment at presentation†	
Yes	32 (42)
No	45 (58)
Total dose, Gy(RBE)†	
16	3 (3)
20	65 (66)
24	10 (10)
25	2 (2)
28	18 (18)
48	1 (1)

Abbreviation: RBE = relative biological effectiveness.
* Calculated per patient (n=77).
† Calculated per eye (n=99).

curves were compared using the log-rank test. A 2-sided *t* test and Fisher exact test were used to compare continuous and categorical patient and treatment characteristics among groups. *P* values <.05 were considered statistically significant. All calculations were performed with Stata (StataCorp 2011.Stata Statistical Software: Release 12. College Station, TX).

Results

Ninety patients with uveal metastases were identified who received proton therapy during our study period. Of these, 13 patients were excluded because of missing information, leaving 77 patients in our final study cohort. All of the uveal metastases were of the choroid. Sixty-eight percent of the cohort was female, and the most common primary tumor was breast carcinoma (49%), followed by lung carcinoma (17%) (Table 1). The median age at diagnosis of primary disease was 52.4 years, and the median age at diagnosis of uveal metastases was 57.9 years. The median interval between initial diagnosis of primary to uveal metastases was 64 months (range, 0-43 years). Most patients presented with ocular symptoms of decreased/blurry vision or perception of a blind spot; however, 9 patients were found to have a uveal metastasis on routine ophthalmologic examination and had no initial ocular symptoms (Table 1). One patient received a diagnosis uveal metastasis 43 years after a primary diagnosis of fibrosarcoma; there was no other intervening malignancy, and the uveal tumor was thought to be most consistent with a metastatic lesion despite the long interval. Extraocular metastases were present in 82% of patients at the time of diagnosis of a choroidal metastasis. Most patients were treated with chemotherapy, surgery, and radiation for their primary malignancy, followed by surgery and chemotherapy, and 10% of patients received prior brain irradiation.

In the study cohort, 71% of patients had unilateral eye lesions and 29% of patients had bilaterally affected eyes for a total of 99 treated eyes included in the analysis (Table 1). At the time of diagnosis, 38% of eyes had retinal detachment. The median dose of proton treatment was 20 Gy(RBE); the highest dose was 48 Gy(RBE) in 2 fractions to 1 eye. All patients were treated in 2 fractions, with the exception of 1 patient receiving 4 fractions of 5 Gy(RBE) each for a total of 20 Gy(RBE) to 1 eye, and a patient receiving 5 fractions of 5 Gy(RBE) each to both eyes for a total of 25 Gy(RBE) to either eye. The median time between diagnosis of uveal metastasis and proton beam irradiation was 28 days.

The median follow-up time was 7.7 months. The median survival time was 12.3 months (95% confidence interval [CI], 7.7-16.8) (Fig. 1). Death was secondary to systemic disease in all cases. The median overall survival time for breast cancer patients was 15.7 months versus 7.4 months for lung cancer patients ($P=.09$). Potential treatment-related adverse effects were reported in 24 patients (31%) (Table 2) and included tearing, increased flashes or floaters, dry eye, pain, and blurry vision. All adverse effects were deemed minor. The pretreatment symptoms of blind spots resolved completely, and 38% of patients with decreased visual acuity before treatment had stable or improved visual

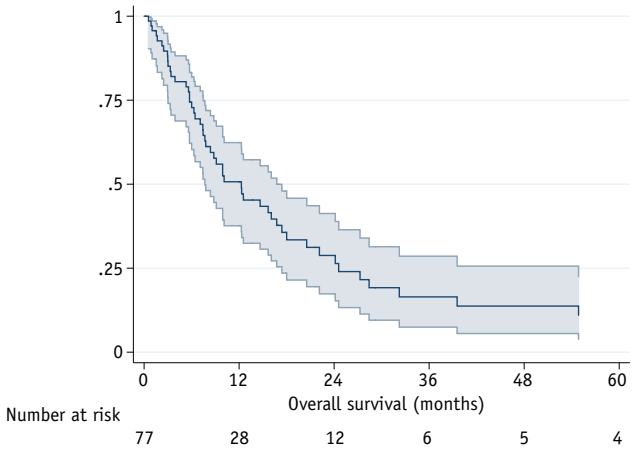

Fig. 1. Overall survival. Median survival was 12.3 months (95% confidence interval, 7.7-16.8). Death was secondary to systemic disease in all cases.

acuity after treatment. Radiation-related vasculopathy occurred in 7 eyes, and decreased visual acuity occurred in 30 of 68 treated eyes with complete follow-up information. The cumulative incidence of adverse events as defined by either vasculopathy or decreased visual acuity was 46% at 6 months and 73% at 1 year. One patient required enucleation 5 years after treatment because of a blind, painful eye as a result of neovascular glaucoma after receiving 28 Gy(RBE). The rate of mild adverse effects and objective radiation-related adverse events among patients who had received prior brain irradiation compared with the rate of adverse events among patients who had not received brain irradiation was not statistically significant (71% vs 61%, $P=.7$). There was no significant association between dose and treatment-associated adverse events ($P=.9$). Local failure occurred in 6 (6%) treated eyes, with 1 case of bilateral failure occurring 40 months after radiation therapy (Fig. 2). The actuarial cumulative incidence of local failure at 12 months was 8% (95% CI, 3%-22%). All failed lesions were retreated successfully with 20 Gy(RBE) delivered in 2 fractions. New uveal disease (outside the radiation field) occurred in 2% of treated eyes. There was no significant association between dose and local recurrence ($P=.8$). Tumor regression was demonstrated in 100% of treated eyes. There was no significant association between dose and improved or worsened visual acuity ($P=.9$).

Other technical factors related to the radiation treatment were assessed, including eye positioning during treatment, tumor size, dose to various eye structures (lens, limbus, ciliary body, retina, fovea, optic disc), absolute beam depth (range) and width in depth of treatment field (modulation), and beam distal and proximal margins to tumor. No association of any of these factors with local failure or toxicity was seen.

Table 2 Outcomes after proton therapy

	No. (%)
Local failure*	
Yes	6 (6%)
No	93 (94%)
New uveal metastases*	
Yes	2 (2%)
No	97 (98%)
Posttreatment adverse effects†,‡	
Yes	24 (31%)
No	53 (69%)
Retinal detachment resolution (n=13 eyes)	
Yes	6 (46%)
No	7 (54%)
Radiation vasculopathy*	
Yes	7 (7%)
No	92 (93%)
Visual acuity after treatment*	
Improved or stable	38 (38%)
Decreased	30 (30%)
Unknown	31 (31%)
Cumulative incidence of adverse events (vasculopathy and/or visual acuity)*	
6 weeks	27% (95% CI, 18%-39%)
6 months	46% (95% CI, 34%-60%)
10 months	59% (95% CI, 45%-74%)
12 months	73% (95% CI, 56%-87%)

Abbreviation: CI = confidence interval.
* Calculated per eye (n=99).
† Calculated per patient (n=77).
‡ All adverse effects were scored minor and included dry eye, pain, flashes, floaters, tearing, and blurry vision.

Discussion

Radiation therapy is an excellent treatment modality for uveal metastases because of its ease and efficient delivery (9, 10). It can be delivered with radioactive plaque brachytherapy (11) or with external beam radiation therapy (EBRT) using either photons (3, 4, 12-14) or protons (15).

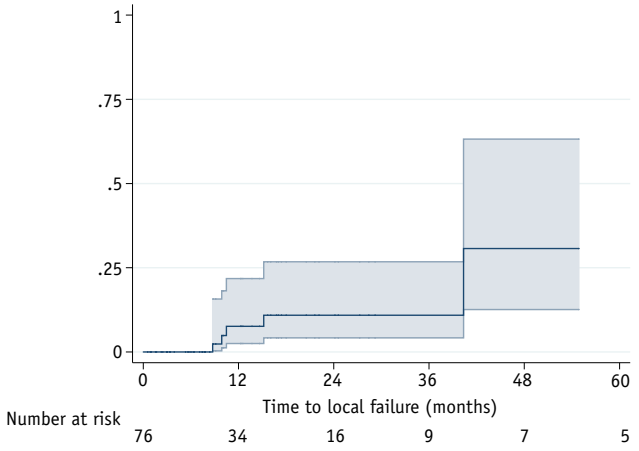

Fig. 2. Cumulative incidence of local failure. Local failure occurred in 6 (6%) treated eyes. These patients were retreated successfully with a second course of proton therapy to 20 Gy(RBE) delivered in 2 fractions.

Proton therapy has been limited but has become increasingly available because the number of new centers in the United States and worldwide has markedly increased in the last decade. Protons have been used at our institution for many years. Most patients at our center are treated in 2 fractions without pretreatment surgery for placement of markers to facilitate radiation treatment localization, as is often performed with treatment of primary uveal melanomas. A slightly larger target-to-aperture width is used (4 mm vs 3 mm) to compensate for the reliance on clinical setup. The decision to use 2 fractions of 10 Gy(RBE) each arose from our experience with treating primary uveal melanomas that also used significantly hypofractionated dose schedules of 10 to 14 Gy(RBE) per fraction to 50 to 70 Gy(RBE) with good tolerance and acceptable adverse effects, most significant being loss of vision (6, 16). In earlier practices of proton therapy for uveal metastases, the dose of 28 Gy(RBE) was used with good response (15). Our current data support that the interval dose reduction is acceptable with achievement of effective palliation with possibly reduced toxicity. This 2-day treatment is in contrast to alternatives of either 2 to 4 weeks of daily EBRT (10) or multiple surgeries to place and remove radioactive plaques (11, 17). The comparatively short course of treatment with proton therapy allows for a better quality of life for patients at a relatively inexpensive cost. Treatment of 1 patient with 2 fractions with protons costs approximately $13,000, compared with an alternative radiation therapeutic option of a 10- to 20-fraction course of photon radiation therapy costing in the range of $30,000 to $45,000 at our institution, depending on the use of technique from fluoroscopic simulation and treatment, 3-dimensional conformal radiation planning and delivery, or stereotactic radiation therapy, priced all at 10 fractions. Owing to the dose concentration within the Bragg peak and lack of exit dose with protons, a highly localized and uniform radiation dose can be easily delivered to the tumor with minimization of radiation exposure to surrounding nontarget tissues, including essentially no dose delivered to the brain (6). Proton therapy is simple and fast to deliver, with minimal discomfort during delivery.

In our retrospective study, we found that the majority of the cohort had breast carcinoma as the primary cancer, followed by lung cancer. This is similar to most studies examining uveal metastases (4, 5, 12, 15, 18). Most patients in our study received 20 Gy(RBE). The median survival time was 12.3 months after the diagnosis of uveal metastasis, the median survival time for breast cancer patients being 15.6 months, although this was not statistically significant. In our study, 94% of uveal metastases were successfully irradiated with no local failure. Retinal detachments resolved in 44% of treated eyes with follow-up data, with perhaps more experiencing resolution but unaccounted for because of lack of follow-up data, which were available for only 18 eyes reported with retinal detachment. Retinal detachment typically reduces with time (6, 19). Our study supports the effectiveness of proton therapy. Our results are comparable with those from a previous proton beam study from our institution, which examined patients who were treated with proton therapy between December 1989 and September 2000, with a local control rate of 96% (Table 3) (15). Changes in our treatment technique from prior decades include more advanced photography and image coregistration with our eye model, improved treatment planning software, and an entirely new physical location and beam source with the relocation of our treatment facility from the Harvard Cyclotron Laboratory to the Francis H. Burr Proton Therapy Center in 2002.

External beam radiation therapy is commonly used to treat intraocular metastases (Table 3). Local control rates as high as 80% have been achieved with photon schedules of 25 Gy in 5 or 10 fractions and in 100% of patients who received 30 Gy in 10 fractions (20). Many more contemporary photon experiences have achieved response and local control rates of 81% to 96%, similar to our study's result (4, 10, 14, 17, 18). Of note, Rosset et al (17) achieved stable or improved visual acuity in 81% of 80 eyes treated with EBRT, and this result was substantially better in patients who received 35.5 Gy or more at calculated dose equivalents of 2 Gy per fraction. Original schedules of radiation treatment are not provided, and because the study was retrospective, it is unclear whether perhaps greater fractionated schedules with overall higher doses might have been directed to specific tumor types that were inherently less likely to incur visual deficit (17). Visual acuity stability or improvement in other series was 47% to 89% (4, 8, 14, 17, 20). The rates of adverse events in other EBRT studies ranged from 0 to 12% (4, 8, 14, 17, 18, 20). Our incidence of mild adverse effects is likely higher because we include all reported symptoms that may have been related to treatment or disease such as subjective reports of flashes, floaters, or any report of pain, which may not have been captured in other studies yet are important when the impact of therapies on quality of life is assessed. Of note, most studies report crude rates of adverse events, whereas we report actuarial rates, thereby examining the cumulative incidence of adverse events over time.

Another option for treating uveal metastases is plaque radiation therapy. This technique has the advantage of requiring only 3 to 4 days of treatment, compared with 3 to 4 weeks of EBRT. This technique is an effective method for treating uveal metastases, similar to current plaque brachytherapy practice used extensively in the definitive and successful management of primary uveal melanomas. Shields et al (11) have reported their experience with 36 patients with uveal metastases, 27 of whom received plaque treatment as primary therapy and 9 of whom received plaque treatment as a secondary therapy after failure of the tumor to respond to alternative therapies, including EBRT. Regression of tumor occurred in 94% of patients, and plaque radiation therapy was able to salvage 5 of 6 eyes in which EBRT had previously failed. Serious adverse events were minimal (8%) (Table 3). The limitations of plaque radiation therapy include dependency on size and location, because plaques often cannot adequately treat tumors

Table 3 Eye metastases studies

Study	Modality	Patients (eyes)	Dose scheme: median total dose (range)/no. of fractions (range)	Median follow-up, mo	Median survival, mo*	Rate of adverse events	LC/tumor response	Visual acuity†
Maor et al, 1977 (20)	EBRT	42 patients	25 Gy/5 or 10 30 Gy/10	-	10	0 0	LC 80% LC 100%	89%
Brady et al, 1982 (18)	EBRT	93 eyes	30 Gy/15 or 56 Gy/28‡	-	8.5	0	Objective response 88.9%	-
Minatel et al, 1993 (14)	EBRT	28 (33)	40 Gy (28-50)/20 (14-25)	-	13	7%	Complete response 59%, partial response 22%	81%
Rudoler et al, 1997 (10)	EBRT	188 (233)	36 Gy (4-63)/1-42	5.8	9	12%	LC 93%	57%
Shields et al, 1997 (11)	Plaques§	36 patients	Mean 86 hours, mean therapeutic dose 68.8 Gy to apex, 235.64 Gy to base	11	8	8%	LC 94%	72%
Rosset et al, 1998 (17)	EBRT	58 (80)	35.5 Gy (20-53)/10-30	-	1-year overall survival 47%	9%	Overall response 96%, complete response 61%	81%
Wiegel et al, 2002 (4)	EBRT	50 (65)	40 Gy/20	5.8	7	5%	Complete response 39%, partial response 44%	86%
Tsina et al, 2005 (15)	Protons	63 (76)	28 Gy/2	10	16	56%	LC 96% response 98%	47%
This study	Protons	77 (99)	20 Gy (16-56)/2	7.7	12.3	7%‖ 31%¶	LC 94%	38%

Abbreviations: EBRT = external beam radiation therapy; LC = local control.
* Time from ocular disease diagnosis.
† Stable or improved vision.
‡ Higher dose levels were pursued in patients who demonstrated disseminated disease.
§ Radioisotopes as follows: iodine 125 in 29 patients, cobalt 60 in 5 patients, ruthenium 106 in 2 patients.
‖ Radiation vasculopathy, per eye.
¶ Posttreatment mild adverse effects, per patient.

overlying the optic disc, and larger lesions may be more likely to recur when this treatment modality is used.

Considering the average poor prognosis of most patients with uveal metastases, it is worth recognizing that not all uveal metastases require treatment. A small metastatic lesion in a patient who is asymptomatic can be followed up, often with systemic disease leading to expiration of the patient before the ocular disease creates symptoms (21). In addition, small lesions that are minimally symptomatic may respond to systemic chemotherapy. For large symptomatic lesions, radiation therapy is the most appropriate modality. Enucleation is largely avoided for the treatment of uveal metastases (18) and is typically reserved for cases of uncontrolled glaucoma with severe discomfort.

Adverse events from ocular radiation therapy are not trivial and are the reason for careful evaluation for appropriate indication of treatment. Toxicities include chronic dry eye, cataracts, keratitis, iris neovascularization, rubeosis, radiation maculopathy, and papillopathy (6, 15). The most common symptom is worsening of visual acuity (despite tumor regression documented on examination) which increased significantly over 12 months after treatment. We did not find a significant association between dose, tumor size, dose to various eye structures, or beam settings and toxicity. Prior whole brain irradiation was not associated with increased adverse events or worse ocular outcomes such as local recurrence.

Important limitations to this study should be recognized. First, despite many years of practice, our sample size was small. Because of this patient population's limited survival resulting from typically advanced, end-stage malignancy, the follow-up period was relatively short, preventing investigation of potential late effects (15). Ideally, these patients should be studied in a prospective study design with comprehensive evaluation of potential toxicities. The retrospective nature of our study inherently produces unintended biases and underreporting or overreporting of specific outcomes or toxicities. One caveat to assessing toxicities, especially including mild adverse effects such as flashes and floaters, is that these effects could be the result of the disease itself. Every effort was made to distinguish pretreatment effects from posttreatment effects, but this is an important limitation. Treatment of uveal metastases is typically palliative, but as length of survival for patients with metastatic cancer become increasingly prolonged it is important to quantify

both the local control rates in treating these tumors and the potential adverse effects of therapies.

In summary, our results indicate that proton beam therapy is an effective treatment modality for intraocular uveal metastases, with excellent local control rates and minimal active symptoms experienced by patients but a nontrivial rate of progressive vision loss. The easily tolerated and straightforward 2-fraction treatment provides a cost-effective intervention with a net reasonable maintenance of quality of life in the setting of palliative care of metastatic disease.

References

1. Bloch RS, Gartner S. The incidence of ocular metastatic carcinoma. *Arch Ophthalmol* 1971;85:673-675.
2. Ferry AP, Font RL. Carcinoma metastatic to the eye and orbit. I. A clinicopathologic study of 227 cases. *Arch Ophthalmol* 1974;92:276-286.
3. Stephens RF, Shields JA. Diagnosis and management of cancer metastatic to the uvea: A study of 70 cases. *Ophthalmology* 1979;86:1336-1349.
4. Wiegel T, Bottke D, Kreusel KM, et al. External beam radiotherapy of choroidal metastases: Final results of a prospective study of the German cancer society (ARO 95-08). *Radiother Oncol* 2002;64:13-18.
5. Shields CL, Shields JA, Gross NE, et al. Survey of 520 eyes with uveal metastases. *Ophthalmology* 1997;104:1265-1276.
6. Gragoudas ES, Lane AM, Collier M. Charged particle irradiation of uveal melanomas. In: Principles and Practice of Ophthalmology. 3rd ed. Philadelphia: Elsevier; 2008.
7. Park WL, Jenison-Williams T, Pasqua-Darnell T. Uveal melanoma and poor treatment compliance: An atypical outcome with literature review. *Optom Vis Sci* 2003;80:344-355.
8. Goitein M, Miller T. Planning proton therapy of the eye. *Med Phys* 1983;10:275-283.
9. Dobrowsky W. Treatment of choroid metastases. *Br J Radiol* 1988;61:140-142.
10. Rudoler SB, Shields CL, Corn BW, et al. Functional vision is improved in the majority of patients treated with external-beam radiotherapy for choroid metastases: A multivariate analysis of 188 patients. *J Clin Oncol* 1997;15:1244-1251.
11. Shields CL, Shields JA, De Potter P, et al. Plaque radiotherapy for the management of uveal metastasis. *Arch Ophthalmol* 1997;115:203-209.
12. Mewis L, Young SE. Breast carcinoma metastatic to the choroid: Analysis of 67 patients. *Ophthalmology* 1982;89:147-151.
13. Reddy S, Saxena VS, Hendrickson F, et al. Malignant metastatic disease of the eye: Management of an uncommon complication. *Cancer* 1981;47:810-812.
14. Minatel E, Trovo MG, Forner L, et al. The efficacy of radiotherapy in the treatment of intraocular metastases. *Br J Radiol* 1993;66:699-702.
15. Tsina EK, Lane AM, Zacks DN, et al. Treatment of metastatic tumors of the choroid with proton beam irradiation. *Ophthalmology* 2005;112:337-343.
16. Gragoudas ES, Lane AM, Regan S, et al. A randomized control trial of varying radiation doses in the treatment of choroidal melanomas. *Arch Ophthalmol* 2000;118:773-778.
17. Rosset A, Zografos L, Coucke P, et al. Radiotherapy of choroidal metastases. *Radiother Oncol* 1998;46:263-268.
18. Brady LW, Shields JA, Augsburger JJ, et al. Malignant intraocular tumors. *Cancer* 1982;49:578-585.
19. Egger E, Schalenbourg A, Zografos L, et al. Maximizing local tumor control and survival after proton beam radiotherapy of uveal melanoma. *Int J Radiat Oncol Biol Phys* 2001;51:138-147.
20. Maor M, Chan RC, Young SE. Radiotherapy of choroidal metastases: Breast cancer as primary site. *Cancer* 1977;40:2081-2086.
21. Shields JA. Metastatic tumors to the uvea. *Int Ophthalmol Clin* 1993;33:155-161.