Estimates of Ocular and Visual Retention Following Treatment of Extra-Large Uveal Melanomas by Proton Beam Radiotherapy

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Objective: To assess outcomes of proton beam radiotherapy for the treatment of extra-large uveal melanomas in patients specifically referred to the University of California, San Francisco, for ocular conservation therapy. Series patients uniformly refused enucleation both at an outside institution and again as a treatment option after extensive discussion at the University of California, San Francisco.

Design: In a retrospective, nonrandomized cohort study, 21 patients with extra-large choroidal or ciliochoroidal melanomas measuring at least 10 mm in maximum thickness or 20 mm in maximum basal diameter or tumors located within 3 mm of the optic nerve measuring at least 8 mm in maximum thickness or 16 mm in maximum basal diameter met inclusion criteria. Main outcome measures were frequency of (1) anterior segment complications (lash loss, keratopathy, cataract, and neovascular glaucoma), (2) posterior segment complications (vitreous hemorrhage, radiation retinopathy, and radiation papillopathy), (3) treatment failure (tumor growth, enucleation, or metastases), and (4) final visual acuity.

Results: Median follow-up was 28 months. Mean age at treatment was 58.3 years. The frequencies of hypertension and diabetes mellitus were 14.3% and 9.5%, respectively. Mean tumor thickness and mean basal diameter were 8.6 mm and 18.7 mm, respectively. Lash loss occurred in 52.4%; dry eye, in 23.8%; cataract, in 28.6%; neovascular glaucoma, in 38.1% (100% in patients with diabetes mellitus); radiation retinopathy, in 9.5%; and radiation papillopathy, in 9.5%. No patient developed radiation-associated scleral necrosis or vitreous hemorrhage. The 2-year Kaplan-Meier estimate of local tumor growth after treatment was 33%, and the rate of distant metastasis was 10%. Visual acuity of 20/200 or better was preserved in 25% of patients, including 4 patients (19%) who experienced an average of 4 lines of Snellen visual acuity improvement. Development of neovascular glaucoma was associated with tumors in close proximity to the optic nerve (P = .04), while cataract (P = .03) and lash loss (P = .02) occurred with more anteriorly located tumors. Proton beam radiotherapy provided a 67% probability of local control and 90% probability of clinically discernable metastases-free survival at 24 months after treatment.

Conclusion: Proton beam radiotherapy is an ocular-conserving option that may be considered for the treatment of extra-large uveal melanoma in carefully selected patients.


Supported by data from the Collaborative Ocular Melanoma Study, radiotherapy has become a valuable asset in the treatment of uveal melanoma, allowing preservation of the globe. Both plaque brachytherapy and proton beam radiotherapy (PBRT) are well established as treatments for medium-sized tumors. Survival following radiotherapy is comparable with that for enucleation. Eye conservation is often the preferred choice for large uveal melanoma, certain patient factors may favor eye-conserving treatments. Such factors in our series included poor vision in the contralateral eye; contraindications to enucleation surgery, including poor patient health or advanced age; or a strong patient desire for ocular retention. Recent reports have investigated the use of plaque brachytherapy and tumor resection as eye-sparing treatments for large melanoma. Theoretically, while customized plaques of any dimension can be constructed, the size of plaques that can be reasonably applied is limited by the amount of radiation that can be tolerated by the sclera, as well as by the physical constraints of ocular and orbital anatomy. In particular, tumors located close to the optic nerve may be difficult...
to plaque and demonstrate a higher probability for development of radiation maculopathy or optic neuropathy, as well as increased risk for marginal failure.7 Tumors involving a large extent of the ciliary body are associated with complications such as cataract formation and neovascular glaucoma (NVG).5 In most large series, the majority of tumors treated by plaque brachytherapy are less than 18 mm in maximal diameter.4,6,8 The use of tumor resection is another option. This procedure, however, frequently requires hypotensive anesthesia and the possibility of additional vitreoretinal surgery and may be less feasible in patients who are poor surgical candidates.3 In addition, tumor resection involves a high potential for residual tumor cells remaining outside the surgical margins.

At the University of California, San Francisco (UCSF), we are specifically referred a number of patients with extra-large uveal melanomas who desire eye-sparing therapy with proton beam irradiation and who are unable or unwilling to pursue other treatment options. Many of these patients have tumors that are considered too large for brachytherapy by referring retina specialists, and many of the tumors involve the macula or are located adjacent to the optic nerve. We wished to study this difficult category of patients and review our treatment experience, with small numbers and short follow-up, to be certain that PBRT did not adversely affect clinical outcomes.

**METHODS**

We conducted a retrospective review of the clinical records of patients with choroidal or ciliochoroidal melanoma treated with PBRT at UCSF between March 1997 and May 2002. All patients with tumors, irrespective of location, measuring 10 mm or more in maximum thickness or 20 mm or more in maximum basal diameter or tumors within 3 mm of the optic nerve or foveola (0-3 mm or >3 mm from the optic nerve, respectively). Forty-three percent of the patients initially had uveal melanoma evaluation prior to any discussion of local therapy. All patients were referred for complete metastatic melanoma workup that measured 8 mm or more in maximum thickness or 16 mm or more in maximum basal diameter were included in the study.12 Tumor dimensions were determined by a combination of clinical assessment and A-scan and B-scan ultrasonography. All patients were referred for complete metastatic melanoma evaluation prior to any discussion of local therapy. All patients refused enucleation after extensive counseling regarding the treatment options and risks involved with PBRT, either because they did not wish to undertake removal of an eye or because they had poor vision in the fellow eye. Total dose PBRT for all patients was 5600 cGy delivered in 4 fractions during 4 days.

Minimum follow-up was 13 months. Patient data included age, sex, eye involved, and intercurrent medical problems including hypertension and diabetes mellitus. Tumor data included anatomical location (ciliary body or choroid), proximity to the optic nerve or foveola (<3 vs >3 mm from the optic nerve and foveola), maximum basal diameter, and maximum thickness (by A-scan and B-scan ultrasonography measurement, as well as by ultrasound biomicroscopy for ciliary body tumors). Treatment parameters included total radiation dose, fractionation, and duration of follow-up. Clinical outcomes data were collected for complications involving the anterior segment (lash loss, keratopathy, cataract, scleral necrosis, and NVG), posterior segment (vitreous hemorrhage, radiation papillopathy, radiation retinopathy, and serous retinal detachment), local failures, enucleation, metastases, all-cause mortality, and visual acuity.

Complications were defined as follows: lash loss, absence of contiguous lashes within the field of irradiation; dry eye, development of 5 mm or less of wetting on Shirmer testing after PBRT; keratopathy, development of punctate erosions or epithelial defects after PBRT; cataract, presence of lens opacity not present prior to PBRT; NVG, presence of iris and/or angle new vessels and raised intraocular pressure after PBRT; radiation scleral necrosis, scleral thinning at the site of irradiation allowing visualization of the underlying uvea; vitreous hemorrhage, presence of any vitreous red blood cells detectable on slitlamp biomicroscopy or on indirect ophthalmoscopy post-PBRT; radiation retinopathy, presence of 1 or more of the following post-PBRT (not present prior to treatment): retinal hemorrhages, retinal exudation, retinal edema, vascular sheathing, nerve fiber layer infarctions, capillary changes on fundus fluorescein angiography, or retinal new vessels (proliferative forms); serous retinal detachment (as determined by a combination of clinical examination, fundus fluorescein angiography, and ultrasonography), post-PBRT separation of neurosensory retina from the retinal pigment epithelium by subretinal fluid; or radiation optic neuropathy, partial or complete optic disc pallor following PBRT. Local tumor recurrence was defined as any documented tumor growth (base or thickness) post-PBRT detected by A-scan or B-scan ultrasonography, ultrasound biomicroscopy, or serial comparison of fundus photographs and fluorescein angiograms. Metastatic disease was documented by physical examination, ancillary investigations, and histopathologic examination at the metastatic site. Final best-corrected visual acuity was determined at the last follow-up visit by Snellen visual acuity testing.

Descriptive statistics (eg, mean, proportion) were calculated to characterize the patient, tumor, and treatment features. The Kaplan-Meier product limit was used to estimate the probability for remaining free of local or metastatic failure, for ocular retention, and for survival measured from the start of PBRT. Outcomes were further analyzed according to patient age (< 56 years or ≥ 56 years), sex, presence of diabetes mellitus or systemic hypertension, tumor size, and tumor location. Tumors were divided into 2 groups according to maximum thickness (<8 mm vs ≥8 mm in thickness as measured ultrasonographically). Tumors were similarly grouped based on maximum basal diameter (<20 mm vs ≥ 20 mm in diameter). Tumors were also grouped according to anatomical location (>50% ciliary body or > 50% choroid) and distance from the fovea or optic nerve (0-3 mm or >3 mm from the foveola or optic nerve). Subsets were too small to compare distributions of time-related events; such outcomes (eg, time to cataract) were evaluated at risk for the event at 24 months using a Fisher exact test.

Twenty-one patients met inclusion criteria. Mean age at treatment was 58.3 years (median, 56 years [range, 24-92 years]). Thirteen patients (61.9%) were male. The right eye was involved in 67%. Hypertension and diabetes mellitus were present in 14.3% and 9.5% of the cohort, respectively. Forty-three percent of the patients initially had between 20/20 and 20/40 visual acuity. Another 38% had initial acuity between 20/50 and 20/200, and 19% demonstrated worse than 20/200 initial visual acuity. Mean follow-up time was 28 months (range, 13-85 months).

Mean tumor thickness was 8.6 mm (median, 8.0 mm [range, 2.9-17.9 mm]). Mean tumor basal diameter was 18.7 mm (median, 19.2 mm [range, 10-24.4 mm]). Forty-three percent of tumors were located within 3 mm of the
optic nerve or foveola, and 4 tumors (19%) involved the ciliary body.

Table 1 summarizes the ocular complications encountered following PBRT for patients with extra-large melanoma. The most common anterior segment complication was lash loss, occurring in 52.4%, followed by NVG (38.1%), cataract (28.6%), and dry eye or keratopathy (23.8%). Three of the 6 patients who developed cataracts did so at least 24 months after treatment, whereas almost all occurrences of lash loss, NVG, keratopathy, and dry eye were observed within the first 24 months after treatment. Keratopathy was limited in all cases to punctate erosions that responded to tear supplementation without permanent scarring or sequelae. Two patients developed exudative retinal detachment after treatment, which resolved completely in both cases. Two patients developed serous retinal detachments (9.5%) each developed radiation retinopathy and radiation papillopathy. Radiation retinopathy was confined to the nonproliferative form. No patient developed scleral necrosis or vitreous hemorrhage. Patients who developed NVG had larger mean maximum basal diameter (22.06 mm) and mean maximum thickness (10.3 mm). Additionally, all patients with diabetes mellitus and 2 of 3 patients with systemic hypertension developed NVG after PBRT.

Table 2 summarizes treatment failures and the range of intervals to failure in months. The Kaplan-Meier probabilities of local control and eye retention at 24 months after PBRT were 67% and 54%, respectively. Enucleation was performed in 10 patients. Six patients underwent enucleation for complications related to NVG. The remaining 4 patients were enucleated subsequent to demonstrated tumor growth confirmed by histopathologic examination. Three patients developed metastases. All were older (mean age, 80.7 years [range, 72–87 years]) and had tumors with a maximum basal diameter between 21 and 24.4 mm. One patient died of metastases 15 months after treatment. A second patient died of metastatic disease 28 months after PBRT. A third patient died at 14 months during the study period of causes unrelated to melanoma.

Prior to the start of treatment, 81% of patients had visual acuity of at least 20/200. At 24 months of follow-up posttreatment, 25% of patients maintained visual acuity of 20/200 or better. Two of the 5 patients with less than 24 months of follow-up also achieved visual acuity better than 20/200, with 1 patient improving from 20/400 to 20/20 without experiencing any associated complications. Among the 7 patients who did not undergo enucleation and who had at least 24 months of follow-up, final visual acuity of 20/200 or better was preserved in 57%, including 2 patients demonstrating mild to moderate NVG. At 24 months’ follow-up, patients not enucleated on average had lost 4 lines of visual acuity on the Snellen scale. Four patients (19%) gained an average of 4 lines of Snellen visual acuity. These latter patients were younger (mean age, 47 years [range, 26–63 years]), and none had tumors in close proximity to the optic nerve or the fovea.

Development of NVG was associated with tumors closer to the optic nerve (P = .04). Patients with tumors with a greater maximum thickness (P = .06) also had a tendency to develop NVG. Lash loss (P = .02) and cataract (P = .03) were more commonly observed in patients demonstrating tumors farther away from the fovea or optic nerve. Local recurrence, enucleation, metastasis, and better visual acuity outcome (>20/200) were not significantly associated with any of the factors analyzed.

At UCSF, patients with very large uveal melanomas are referred specifically for treatment with PBRT. The current study represents a group of patients who, after extensive metastatic workup and counseling regarding likely treatment complications, declined enucleation and were referred to us by retina specialists because their tumors were considered too large for any other conservative treatments available in the community. These extra-large tumors were referred for PBRT because of very large tumor dimensions irrespective of location or because of large tumor dimensions in a peripapillary location.1,2 Tumors in the present cohort all had dimensions well in excess of the Collaborative Ocular Melanoma Study criteria for large tumors.1,2 The cohort, therefore, may be regarded as a subgroup of patients with extra-large melanomas with tumor volumes requiring radiation doses approaching the upper limit of that which may be reasonably tolerated by the eye.9 Additionally, many were elderly patients with chronic intercurrent conditions who were at high anesthetic risk. For these reasons, the cohort studied herein, before treatment, represented a group of patients expected to have substantially increased risk for local recurrence, metastatic disease, and adverse outcomes because of ocular complications.9,11 All patients were counseled extensively regarding these likely complications prior to undertaking PBRT.
To our knowledge, no other published studies have specifically evaluated PBRT for extra-large uveal melanoma treatment. Previous studies demonstrate a correlation between tumor size and proximity to the optic nerve or foveola and complication rates. Gragoudas and colleagues\textsuperscript{9,12} indicate that tumor height and lens dose are significant factors in the development of cataract following PBRT. Large tumor size is a significant risk factor for the development of NVG.\textsuperscript{11} and we also found a tendency for NVG development in patients with thicker tumors, although this finding did not reach statistical significance in our study. Patients demonstrating larger tumors, particularly tumors with a maximum thickness greater than 8 mm and maximum basal diameter greater than 16 mm, and tumors closer to the fovea are at greater risk for enucleation.\textsuperscript{7,13,14} Eye-retention rates for patients with large uveal melanomas treated with PBRT have been documented as ranging from 46\% to 89.5\% at 5 to 10 years.\textsuperscript{15,16} As demonstrated in our own cohort, Egan and colleagues\textsuperscript{17} found NVG and tumor growth to be the leading causes of enucleation following PBRT.

We found no published studies examining the role of other conservative therapies (eg, plaque brachytherapy or local resection) specifically for the management of extra-large melanomas.\textsuperscript{1,2} Three recent studies have reported on conservative treatment of large uveal melanomas, which included some patients with extra-large tumors.\textsuperscript{18,19} Bechrakis and colleagues\textsuperscript{18} recently reviewed patients with large melanomas treated with transscleral resection (TSR) or iodine 125 (\textsuperscript{125}I) plaque brachytherapy. Shields et al\textsuperscript{20} and Puusaari et al\textsuperscript{21} have described their experiences with large uveal melanomas treated with plaque radiotherapy. Compared with our study, the study by Bechrakis and colleagues\textsuperscript{18} included patients who were younger (mean age, 40.5 years) with a smaller mean (SD) maximum basal diameter (14.5 [2.8] mm). Additionally, intercurrent conditions (such as hypertension and diabetes mellitus) were not reported. Mean (SD) maximum thickness was slightly greater at 9.4 (1.8) mm. Tumors tended to be further from the optic disc and foveola, with a mean distance of 9.9 mm and 9.4 mm, respectively.\textsuperscript{1} Shields and colleagues\textsuperscript{1} studied patients who were slightly older (mean age, 62 years), reporting hypertension and diabetes in 13\% and 5\%, respectively. Tumor mean maximum thickness in the Shields et al study was slightly greater (9 mm), although mean maximum basal diameter was substantially smaller (14 mm). Compared with the present series, a smaller proportion of patients had tumors close to the optic nerve (35\%).\textsuperscript{6} Finally, the study by Puusaari and colleagues\textsuperscript{6} included patients with a median age of 64 years. Hypertension and diabetes were not reported. Tumor median maximum thickness was greater (10.7 mm), and median maximum basal diameter was smaller at 16.1 mm. In contrast, tumors in the latter series were more anterior (63\% involved the ciliary body, while 10\% were peripapillary in location). In the Puusaari et al study,\textsuperscript{6} the median follow-up of 3.6 years was longer than in either the Bechrakis et al\textsuperscript{18} or Shields et al study.\textsuperscript{1} These differences among the studies cited make objective comparison of the treatment alternatives difficult.

Bearing these differences in mind, we found that PBRT demonstrated broadly similar rates of anterior segment complications compared with plaque radiotherapy and TSR. Lash loss and dry eye may be higher following PBRT than other treatment modalities because the proton beam must sometimes penetrate the region of the lashes and anterior segment to reach a ciliary body or choroidal tumor. These complications did not result in permanent corneal scarring, however, in any patient in our series. Cataract formation, 28.6\% in this study, is similar to or less than that reported for patients treated with brachytherapy and TSR for large tumors. Our patients with more anteriorly located tumors experienced higher rates of both lash loss and cataract compared with patients with tumors in close proximity to the optic nerve. The rate of NVG (38.1\%) is broadly similar to that seen for 1125 brachytherapy but greater than that seen with TSR (5.6\%). At 24 months’ follow-up, none of our cohort developed vitreous hemorrhage, and only 9.3\% developed radiation retinopathy or papillopathy. In comparison, in patients treated with \textsuperscript{125}I brachytherapy, radiation retinopathy developed in 25\% and papillopathy in 22\% within 24 months of treatment.\textsuperscript{1} Bechrakis and colleagues\textsuperscript{18} reported that 66.6\% of patients developed radiation retinopathy at a mean follow-up of 27 months. Low rates of radiation retinopathy and papillopathy in our study may reflect the use of PBRT, improved radiation planning, small series size, or short follow-up. Additionally, 44.4\% of patients treated by TSR required additional vitreoretinal procedures within the follow-up period because of vitreous hemorrhage and/or retinal detachment. Also, in contrast to the other studies, radiation scleral necrosis was never observed in our cohort.

Previous studies have reported that large tumor volume, posterior tumor location, and male sex are associated with an increased risk for local failure with conservative therapies.\textsuperscript{17-21} The cohort in the present study therefore represents a group of patients at high risk for local failure, and all were extensively counseled regarding this possibility prior to undertaking treatment with PBRT. Our study group also carried a higher risk for distant metastases. Reported risk factors for uveal melanoma metastases include age older than 60 years, male sex, tumor maximum basal diameter greater than 10 mm, and local recurrence.\textsuperscript{22} Of the pretreatment parameters, tumor size appears to be the strongest clinical indicator of high risk for mortality due to metastases.\textsuperscript{10} Demonstration of clinical metastases in our series had occurred in 10\% at 24 months of follow-up. Likelihood of micrometastases having formed prior to treatment in this population of patients is high. Because no clinically relevant test for the presence of micrometastases in uveal melanoma is available, however, the percentage of patients with micrometastases that may develop clinical manifestation cannot be determined empirically. These patients all received extensive metastatic workups overseen by oncologists, including liver function tests; chest radiography; computed tomography of the chest, abdomen, and pelvis; and positron emission tomography. In several patients referred for ocular conservation, metastases were discovered, and local therapy was declined by these patients.
The probability of eye retention following radiation treatment of extra-large uveal melanoma is likely influenced by a complex interaction of patient, tumor, and treatment factors.\textsuperscript{13} Large tumor dimensions have previously been reported to increase the risk, not only for local recurrence, but also for NVG, the major complication requiring enucleation in our series. Other reported risk factors for NVG include tumors closer to the optic nerve; we also observed a significant association between development of NVG and close proximity to the optic nerve in our series.\textsuperscript{7,13-15} Diabetes mellitus has also been associated with an increased incidence and severity of neovascular complications following radiotherapy.\textsuperscript{23-25} Our cohort had a relatively high proportion of patients with vascular risk factors including hypertension and diabetes, both of which occurred more often in patients with NVG, although small numbers preclude meaningful statistical analysis.

Visual acuity of 20/200 or better was preserved at 24 months in 25% of patients, and the estimated probability of retaining visual acuity of 20/200 or better in those patients not enucleated at 24 months was 57%. These results are within the range of reported visual outcomes for other series describing outcomes following conservative treatment for large uveal melanoma, including some patients with extra-large tumors.\textsuperscript{4,6} With plaque brachytherapy, Bechrakis et al\textsuperscript{4} reported 5.5% with visual acuity 20/200 or better, while Shields et al\textsuperscript{5} reported visual acuity of 20/200 or better in 2 years in 87% of patients with large uveal melanomas. One factor possibly influencing this wide variation in acuity outcomes at 24 months of follow-up is the greater incidence of NVG at this point in the Bechrakis et al study (50%) in comparison with posttreatment NVG in the Shields et al\textsuperscript{5} series (8%). Additionally, Bechrakis et al\textsuperscript{3} reported 66.6% of plaque-treated patients required panretinal photocoagulation for treatment of radiation retinopathy. In contrast, Shields et al\textsuperscript{4} reported nonproliferative and proliferative radiation retinopathy at 29% and 11%, respectively, at 24 months. Percentage differences may also be partially a function of the difference in size of the 2 plaque series (Bechrakis et al, n=152; Shields et al, n=354). Tumor location undoubtedly also plays a large role in final visual acuity. Puusaari and colleagues\textsuperscript{6} reported a 42% probability of 20/200 or greater visual acuity at 1 year after diagnosis. Following TSR, 61.1% of patients retained visual acuity of 20/200 or better.\textsuperscript{7} Visual outcomes in patients with extra-large melanomas treated by PBRT are difficult to predict from the present data. We found that neither patients with thicker tumors (P=.31) nor those with tumors closer to the optic nerve and fovea (P=.28) had a significant difference in visual outcome, possibly reflecting the greater importance of age and intercurrent medical conditions, such as diabetes or hypertension, in determining final visual outcome. Factors reported to be predictive of visual loss include tumor size, location close to the optic nerve or the fovea, and poor initial visual acuity.\textsuperscript{26,27} Consistent with these observations, we found that patients who lost visual acuity beyond 20/200 had tumors demonstrating a mean maximum thickness of 11.8 mm and mean maximum basal diameter of 19.8 mm. Interestingly, only 1 of 4 patients who developed significant visual loss had a tumor adjacent to the optic nerve or fovea. The 4 patients who gained an average of 4 lines of visual acuity in our study were younger. All except 1 had pretreatment visual acuity better than 20/200, and none had tumors in close proximity to the optic nerve or foveola.

Several limitations of this study should be recognized. Our experience with PBRT for extra-large tumors is recent. No patient with extra-large melanoma in this series was offered PBRT as an initial treatment modality. All patients had been referred to us when they had refused enucleation at outside institutions. We emphasized enucleation as the standard treatment option in our discussions and also emphasized the possibility of the need for eventual enucleation because of complications from PBRT. Indeed, the local tumor failure rate was 33%, and the 24-month probability of ocular retention was only 54%. In contrast to other treatment modalities, such as plaque radiotherapy, TSR, or enucleation, PBRT is used less frequently as the primary therapy for large choroidal melanomas. We performed the present study and evaluated our 2-year outcomes (mean follow-up, 28 months) to be certain that some benefit was provided to patients in this category, referred to us with expectations for ocular conservation. We have mainly treated extra-large tumors near the optic nerve or fovea in patients not well suited to other therapeutic options. As a result, the present study is limited by sample size and by duration of follow-up. Nevertheless, the present study suggests that in carefully selected patients, acceptable outcomes in terms of ocular and visual retention may be expected following PBRT for extra-large melanoma. Long-term follow-up with larger numbers is needed to confirm our findings. Such studies will also more clearly define subgroups of patients who may experience better or worse outcomes and will clarify the role of PBRT for treatment of extra-large uveal melanoma. Although primary enucleation remains an appropriate option for extra-large uveal melanoma, the present study indicates that in certain patients unwilling to undergo primary eye removal, PBRT may offer an alternative with the possibility of retaining the eye and some vision.

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