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ORIGINAL ARTICLE

Treatment of Uveal Melanoma With Radioactive Iodine 125 Implant Compared With Proton Beam Radiotherapy

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Abstract

Objective: To review the current state of radiation therapy for uveal melanoma and compare particle radiation and brachytherapy.

Patients and Methods: The medical records of 156 patients treated for uveal melanoma between May 30, 2012, and March 16, 2020, were retrospectively reviewed. Treatments consisted of either radioactive iodine 125 implant (RAI) or fractionated proton radiation (proton beam therapy [PBT]). Baseline characteristics were compared using a Wilcoxon rank sum test or χ^2 test. Outcomes were compared using Cox proportional hazards regression models or logistic regression models.

Results: The median length of follow-up after treatment was 2.7 years (range, 0.5 to 9.0 years). Patients who underwent treatment with RAI were older (median age, 67 vs 59 years; $P<.001$) and had a lower tumor classification (American Joint Commission on Cancer; P=.001) compared with those who underwent PBT. There was no significant difference between RAI and PBT in the outcomes of liver metastases, death, enucleation, tearing, vision loss, retinal detachment, tumor thickness, conjunctivitis, optic neuropathy, iris neovascularization, or neovascular glaucoma (all $P>.05$). Patients who underwent RAI treatment had significantly higher risk of diplopia (P<.001), cataract progression (P<.001), and maculopathy (P=.03) compared with those who received PBT. Patients who underwent RAI were at higher risk of eyelash loss (P=.006) compared with the PBT group.

Conclusion: Treatment with PBT and RAI has similar efficacy; however, there are differences in the adverse outcomes associated with these 2 modalities.

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Uveal melanoma (UM) is the most common form of noncutaneous melanoma, accounting for 5.5% of melanoma cases with a known primary tumor.[1,2] Immunotherapy with checkpoint inhibition is minimally effective in the treatment of metastatic UM,[3] and median survival for metastatic UM is less than 1 year.[4] Survival is better in patients in whom UM is confined to the eye than in patients with metastatic UM.[5-7]

Treatment for primary UM is usually radiation or an enucleation surgical procedure. Laser treatment is reserved for very small tumors and most commonly involves a slow infrared laser to deliver a hyperthermia effect.[8] Internal and external resection of UM has been described.[9-11] External photon radiation has also been described.[12] However, the most common treatment for UM is brachytherapy with an iodine 125, palladium 103, or ruthenium 106 implant.[13-15] Although a multicenter randomized clinical trial of medium-size melanomas[16] found no difference in survival for patients treated with a radioactive iodine 125 implant compared with enucleation, a large multicenter, nonrandomized, size-adjusted study[17] found improved survival with a radioactive iodine 125 implant (RAI) compared with enucleation for UM.

Although RAI is the most common treatment for primary UM,[18] proton beam therapy (PBT) is becoming increasingly common.[19,20]

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The medical literature reveals no difference in survival or incidence of metastasis with RAI vs PBT for treatment of UM.[21,22] The purpose of this study was to review the status of radiation therapy for UM and to compare adverse outcomes associated with RAI vs PBT in the treatment of UM. By comparing these 2 radiation modalities, we hope to provide evidence-based understanding for the role of particle radiation in one cancer.

PATIENTS AND METHODS

Study Population

A total of 156 patients with UM treated at the Mayo Clinic in Florida between May 30, 2012, and March 16, 2020, were included in this retrospective study (92 PBT, 64 RAI). Two patients who were treated during this period were excluded from this analysis because they did not return for follow-up. Patients who received RAI were treated with a dose of 85 Gy radiobiological equivalent to the tumor apex according to the protocol used in the Collaborative Ocular Melanoma Study.[23] This radiation dose was the standard brachytherapy protocol at Mayo Clinic during the study period and is consistent with recommendations of the American Brachytherapy Society. Figure 1 shows intraoperative ultrasonographic verification of RAI placement adjacent to the intraocular tumor. Patients treated with PBT were treated at the University of Florida Health Proton Therapy Institute with a dose of 60 Gy radiobiological equivalent in 4 consecutive fractions according to a previously described protocol.[24] The dedicated eye line uses a high-energy, cyclotron-based proton therapy system. The energy at the entrance of the eye line is 105 MeV. A range modulator wheel generates the spread-out Bragg peak, while a variable range shifter system adjusts the range and spreads the beam laterally. Four tantalum buttons (T-rings; Mira Inc) were implanted to aid in tumor localization. Figure 2 shows surgical placement of tantalum markers[25] with radiologic confirmation of marker locations.

Information was collected regarding baseline characteristics, including date of birth, Snellen visual acuity in each eye, cataract status in the tumor eye, macular status in the tumor eye, tumor thickness, tumor largest basal diameter, subretinal fluid, American Joint Committee on Cancer classification T score, date and nature of treatment, any associated extraocular muscle disinsertion, needle aspiration cytology results, and tumor gene expression profile (Table 1). Cytology and gene expression profile were not performed on all patients and only done when clinically indicated or requested by the patient. Outcomes were also recorded and included death, liver metastases, persistent diplopia (at least 3 months), epiphora, subsequent enucleation surgical procedure, visual acuity in each eye at each follow-up visit, presence of subretinal fluid at each follow-up visit, tumor thickness at each follow-up visit, presence of iris neovascularization at each follow-up visit, neovascular glaucoma diagnosed at each follow-up visit, cataract status in the treated eye at each follow-up visit, and optical coherence tomography consistent with macular edema at each follow-up visit in the treated eye.

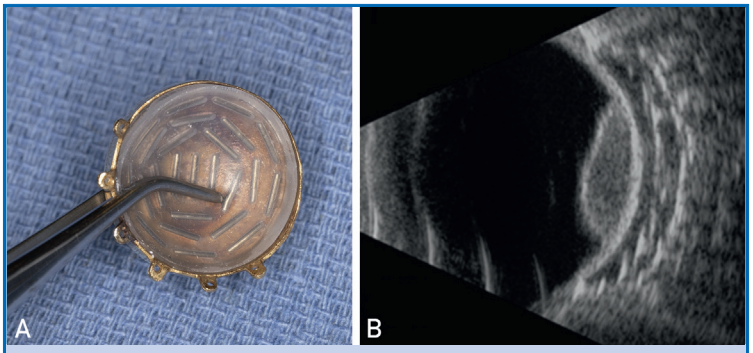

FIGURE 1. A, Radioactive implant with iodine 125 seeds loaded and ready for surgical implantation. B, Intraoperative ultrasonographic image confirms the correct placement of the radioactive implant adjacent to the intraocular tumor.

Statistical Analyses

Continuous variables were summarized with the sample median and range. Categorical variables were summarized with number and percentage of patients. Comparisons of baseline characteristics between the proton beam and radioactive implant groups were made using a Wilcoxon rank sum test (continuous and ordinal variables) or a χ^2 test (categorical variables).

Comparisons of outcomes between the RAI and PBT groups were made using Cox proportional hazards regression models for

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time-to-event outcomes (death, liver metastases, epiphora, enucleation, disappearance of subretinal fluid, occurrence of 20/200 or worse visual acuity in patients with better than 20/200 visual acuity at baseline, occurrence of a 30% decrease in tumor thickness from baseline, progression of cataract, neovascularization of iris, neovascular glaucoma, and macular edema in patients without maculopathy at baseline). Logistic regression models were used for binary outcomes not dependent on follow-up length (persistent double vision, epiphora, and eyelash loss). Hazard ratios and 95% CIs were estimated for Cox regression models, while odds ratios and 95% CIs were estimated for logistic regression models. In Cox regression analysis, censoring occurred at the date of last known follow-up, death, liver metastases, enucleation, disappearance of subretinal fluid, occurrence of 20/200 or worse vision, and occurrence of a 30% decrease in tumor thickness from baseline. Unadjusted models were first assessed, followed by multivariable models that were adjusted for baseline characteristics that had the strongest difference (ie, lowest *P* value) between the RAI and PBT groups, allowing no more than 1 variable in the model for each 10 patients who experienced the given outcome per recommended guidelines.[26]

$P<.05$ was considered statistically significant, and all statistical tests were 2-sided. Statistical analysis was performed using R statistical software (version 3.6.2; R Foundation for Statistical Computing).

RESULTS

A comparison of baseline patient characteristics in the RAI and PBT groups is shown in Table 1. Compared with patients who underwent PBT, those who received RAI were older (median age, 67 vs 59 years; $P<.001$), had a lower pretreatment largest basal diameter (median, 11.1 vs 13.5 mm; $P=.01$), had a lower pretreatment tumor thickness (median, 3.8 vs 5.0 mm; $P=.02$), and had a less severe American Joint Committee on Cancer T class at presentation ($P=.001$). Outcomes are compared between the 2 treatment groups in Table 2. The median length of follow-up after treatment was 2.7 years (range, 0.5 to 9.0 years). Follow-up was not significantly different between the PBT group (median, 2.7 years; range, 0.5 to 9.0 years) and the RAI group (median, 2.5 years; range, 0.5 to 7.0 years) ($P=.67$).

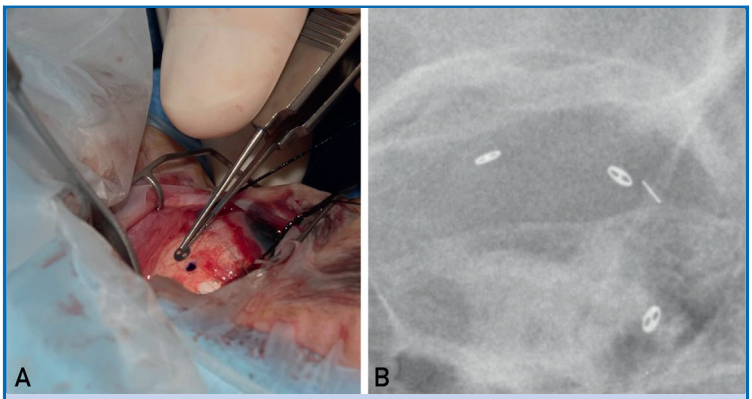

FIGURE 2. A, Tantalum button used as a fiducial marker; 4 of these buttons are sewn to the sclera with nylon suture to aid in locating the tumor on radiography. B, Portion of a skull radiograph taken after the tantalum buttons have been implanted.

In unadjusted analysis, patients who received RAI had a significantly higher risk of double vision (OR, 0.06; $P<.001$) and were significantly more likely to have muscle disinsertion during the surgical procedure (OR, 0.01; $P<.001$) compared with patients who underwent PBT. Patients who received RAI had a significantly lower likelihood of eyelash loss after radiation ($P=.006$; Figure 3) and were significantly more likely to have development of cataract during the follow-up period than patients in the PBT group ($P=.001$). Patients in the RAI group also had a significantly higher likelihood of a 30% decrease in tumor thickness from baseline adjusting for potential confounding variables (Table 2; $P=.XX$). No significant differences between RAI and PBT were observed regarding death, liver metastases, enucleation, disappearance of subretinal fluid, or occurrence of visual acuity of 20/200 or less (Table 2; all $P>.05$).

Several other pieces of information were also of interest. First, 29 patients had a fine-needle aspiration biopsy. Of these 29 patients, 23 (79.3%) were evaluated for genetic expression profile (Castle Biosciences, Inc); 10 (43.5%) were class 1A; 3 (13.0%) were class 1B; and 10 (43.5%) were class 2. Second, of the patients who had

TABLE 1. Comparison of Baseline Patient Characteristics in Proton Beam and Radioactive Implant Groups[a,b]

Variable	Proton beam (N=92)	Radioactive implant (N=64)	*P* value
Age at treatment (y)	59 (25-94)	67 (32-94)	<.001
Male sex	44 (47.8)	30 (46.9%)	.91
Snellen visual acuity in affected eye			.19
20/20	18 (19.6)	6 (9.4)	
20/25	14 (15.2)	10 (15.6)	
20/30	10 (10.9)	7 (10.9)	
20/40	14 (15.2)	11 (17.2)	
20/50	8 (8.7)	10 (15.6)	
20/60	8 (8.7)	2 (3.1)	
20/70	3 (3.3)	3 (4.7)	
20/80	2 (2.2)	1 (1.6)	
20/100	3 (3.3)	2 (3.1)	
20/200	2 (2.2)	5 (7.8)	
20/400	5 (5.4)	3 (4.7)	
CF	1 (1.1)	2 (3.1)	
HM	4 (4.3)	1 (1.6)	
LP	0 (0.0)	1 (1.6)	
NLP	0 (0.0)	0 (0.0)	
Snellen visual acuity in unaffected eye			.006
20/20	52 (56.5)	20 (31.2)	
20/25	16 (17.4)	18 (28.1)	
20/30	12 (13.0)	11 (17.2)	
20/40	3 (3.3)	11 (17.2)	
20/50	1 (1.1)	2 (3.1)	
20/60	0 (0.0)	0 (0.0)	
20/70	2 (2.2)	0 (0.0)	
20/80	0 (0.0)	0 (0.0)	
20/100	1 (1.1)	2 (3.1)	
20/200	1 (1.1)	0 (0.0)	
20/400	0 (0.0)	0 (0.0)	
CF	1 (1.1)	0 (0.0)	
HM	1 (1.1)	0 (0.0)	
LP	1 (1.1)	0 (0.0)	
NLP	1 (1.1)	0 (0.0)	
Pretreatment largest basal diameter (mm)	13.5 (4.7-22.0)	11.1 (5.0-17.1)	.01
Pretreatment thickness (mm)	5.0 (0.7-13.0)	3.8 (1.9-12.0)	.02
Subretinal fluid at presentation	85 (92.4)	52 (81.2)	.04
AJCC presentation			.001
T1	26 (28.3)	25 (39.1)	
T2	21 (22.8)	24 (37.5)	
T3	26 (28.3)	14 (21.9)	
T4	19 (20.7)	1 (1.6)	

[a]AJCC, American Joint Committee on Cancer Classification; CF, count fingers; HM, hand motion; LP, light perception; NLP, no light perception.
[b]Data are presented as median (range) or No. (percentage) of patients.

development of liver metastases, survival at 1 year was 28.0% (95% CI, 14.3% to 55.0%) (6 of 21 patients). Third, there was a strong association between double vision and muscle disinserted ($P<.001$); of the 40 patients who had an extraocular muscle temporarily detached from the globe, 13 (32.5%) had double vision compared with 7 of 116 patients (6.0%) without muscle disinserted.

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TABLE 2. Comparisons of Outcomes Between Proton Beam and Radioactive Implant Groups[a,b]

Outcome	No. of patients	No. (%) of patients who experienced the outcome	Association measure	Unadjusted analysis		Multivariable analysis	
				Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Double vision			Odds ratio				
Radioactive implant	64	18 (28.1)		1.00 (Reference)		1.00 (Reference)	
Proton beam	92	2 (2.2)		0.06 (0.009-0.21)	<.001	0.07 (0.01-0.25)	<.001
Death			Hazard ratio				
Radioactive implant	64	15 (23.4)		1.00 (Reference)		1.00 (Reference)	
Proton beam	92	26 (28.3)		1.16 (0.61-2.20)	.66	1.39 (0.65-3.0)	.40
Liver metastases			Hazard ratio				
Radioactive implant	64	9 (14.1)		1.00 (Reference)		1.00 (Reference)	
Proton beam	91	21 (23.1)		1.46 (0.66-3.20)	.35	2.26 (0.96-5.31)	.06
Epiphora			Hazard Ratio				
Radioactive implant	64	1 (1.6)		1.00 (Reference)		1.00 (Reference)	
Proton beam	91	12 (13.2)		5.67 (0.71-45.06)	.10	NA	.13
Muscle disinserted			Odds ratio				
Radioactive implant	64	39 (60.9)		1.00 (Reference)		1.00 (Reference)	
Proton beam	92	1 (1.1)		0.01 (<0.01-0.04)	<.001	<0.01 (<0.01-0.02)	<.001
Enucleation			Hazard ratio				
Radioactive implant	64	5 (7.8)		1.00 (Reference)		1.00 (Reference)	
Proton beam	91	8 (8.8)		1.50 (0.45-5.02)	.51	NA[c]	NA[c]
Disappearance of subretinal fluid in patients with subretinal fluid at baseline			Hazard ratio				
Radioactive implant	52	23 (44.2)		1.00 (Reference)		1.00 (Reference)	
Proton beam	84	41 (48.8)		1.19 (0.71-1.98)	.51	0.80 (0.46-1.41)	.44
Occurrence of 20/200 or worse visual acuity in patients with better than 20/200 visual acuity at baseline			Hazard ratio				
Radioactive implant	52	16 (30.8)		1.00 (Reference)		1.00 (Reference)	
Proton beam	79	36 (45.6)		1.67 (0.92-3.01)	.09	1.50 (0.79-2.84)	.21
Occurrence of a 30% decrease in tumor thickness from baseline			Hazard ratio				
Radioactive implant	64	55 (85.9)		1.00 (Reference)		1.00 (Reference)	
Proton beam	91	66 (72.5)		0.63 (0.43-0.91)	.01	0.69 (0.45-1.05)	.09
Eyelash loss			Hazard ratio				
Radioactive implant	64	2 (3.1)		1.00 (Reference)		1.00 (Reference)	
Proton beam	91	18 (19.8)		7.11 (1.65-30.97)	.008	7.97 (1.79-35.42)	.006
Keratoconjunctivitis			Hazard ratio				
Radioactive implant	64	14 (21.9)		1.00 (Reference)		1.00 (Reference)	
Proton beam	91	21 (23.1)		1.09 (0.55-2.15)	.80	1.06 (0.51-2.20)	.88
Iris neovascularization			Hazard ratio				
Radioactive implant	64	8 (12.5)		1.00 (Reference)		1.00 (Reference)	
Proton beam	91	16 (17.6)		1.48 (0.63-3.47)	.36	2.00 (0.82-4.90)	.13

Continued on next page

TABLE 2. Continued

Outcome	No. of patients	No. (%) of patients who experienced the outcome	Association measure	Unadjusted analysis		Multivariable analysis	
				Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Neovascular glaucoma			Hazard ratio				
Radioactive implant	64	7 (10.9)		1.00 (Reference)		1.00 (Reference)	
Proton beam	91	16 (17.6)		1.67 (0.69-4.07)	.26	2.11 (0.83-5.40)	.12
Cataract progression in patients without cataract operation at baseline			Hazard ratio				
Radioactive implant	45	30 (66.7)		1.00 (Reference)	NA	1.00 (Reference)	
Proton beam	78	22 (28.2)		0.29 (0.16-0.51)	<.001	0.20 (0.10-0.39)	<.001
Maculopathy in patients without preexisting maculopathy at baseline			Hazard ratio				
Radioactive implant	56	34 (60.7)		1.00 (Reference)	NA	1.00 (Reference)	
Proton beam	52	23 (44.2)		0.56 (0.33-0.97)	.04	0.52 (0.28-0.94)	.03
Optic neuropathy in patients without preexisting optic neuropathy at baseline			Hazard ratio				
Radioactive implant	63	11 (17.5)		1.00 (Reference)	NA	1.00 (Reference)	
Proton beam	74	10 (13.5)		0.71 (0.30-1.69)	.45	0.77 (0.31-1.89)	.56

[a]AJCC, American Joint Committee on Cancer; NA, not applicable.

[b]Odds ratios and 95% CIs result from logistic regression models. Hazard ratios and 95% CIs result from Cox proportional hazards regression models. Multivariable models were adjusted for baseline characteristics that showed the strongest difference between the radioactive implant and proton beam groups, allowing no more than 1 variable in the model for each 10 patients who experienced the given outcome. Specifically, models were adjusted for age at treatment (double vision, liver metastases, eyelash loss, iris neovascularization, neovascular glaucoma, optic neuropathy), age at treatment and AJCC class at presentation (death and keratoconjunctivitis), age at treatment, AJCC class at presentation, and Snellen visual acuity in unaffected eye (muscle disinserted), age at treatment, AJCC class at presentation, Snellen visual acuity in unaffected eye, pretreatment largest basal diameter, and pretreatment tumor thickness (disappearance of subretinal fluid), age at treatment, AJCC class at presentation, Snellen visual acuity in unaffected eye, and pretreatment largest basal diameter (occurrence of 20/200 or worse visual acuity, cataract progression, and maculopathy), and age at treatment, AJCC class at presentation, Snellen visual acuity in unaffected eye, pretreatment largest basal diameter, pretreatment tumor thickness, and subretinal fluid at presentation (occurrence of a 30% decrease in tumor thickness).

[c]No multivariable analysis was performed for enucleation owing to the rare nature of this outcome.

DISCUSSION

This study confirmed that UM can be lethal: 41 of 156 patients died from metastatic UM during the follow-up period, with median follow up of 2.7 years. This study was also designed to identify adverse outcomes associated with RAI and PBT.

By identifying adverse outcomes associated with a treatment, we may be able to avoid some complications by prescribing an alternative modality. For example, patients who received RAI were significantly more likely to have persistent diplopia. Furthermore, there was a strong association between muscle disinsertion and persistent double vision ($P<.001$). Since we can predict which patients will need to have a muscle removed, we can reduce the incidence of double vision by treating those patients with PBT, which does not require muscle disinsertion when using previously described techniques.[24] When performing an RAI operation, the extraocular muscles are temporarily disinserted when doing so is necessary to position the implant properly. A muscle must be temporarily detached from the outside of the globe if the tumor is located

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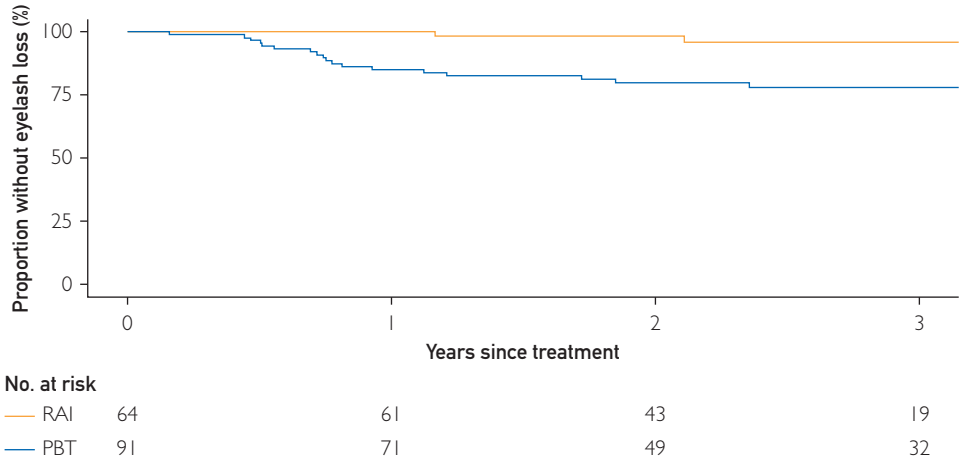

FIGURE 3. Graph shows the increasing incidence of eyelash loss during the 3-year period after treatment in patients without eyelash loss at baseline who were treated with radioactive iodine 125 implant (RAI) and proton radiation (proton beam therapy [PBT]).

immediately adjacent to the muscle insertion on the inside of the globe. It may also be necessary to detach a muscle if a tumor is located adjacent to the optic nerve in order to gain access to the part of the eyeball where the tumor is located.

In our patients, eyelash loss was significantly more likely in patients treated with PBT than RAI, as displayed in Figure 3. The likely reason for eyelash loss in these patients is due to the radiation of the eyelashes in patients with tumors that were located anterior to the equator of the eye. When anteriorly located tumors are treated with PBT, the eyelid typically receives 50% to 100% of the radiation dose. The eyelid gets less than 10% of the radiation dose when anterior tumors are treated with RAI. The reason that the eyelid receives less radiation with RAI in selected patients is because the implant used in this study (and shown in Figure 1) is shielded with a gold carrier that shields the eyelid from radiation in an anteriorly located tumor. The eyelid also gets less radiation with PBT when the tumor is located posterior to the equator due to the sharp falloff of particle radiation. Perhaps PBT should be avoided in patients with anterior tumors if eyelid deformity or ocular surface disease is a concern.

Since this study is not randomized, we know that the treatment groups are dissimilar in some respects. For example, the RAI group was older than the PBT group and for that reason likely had more age-related eye diseases such as cataract or maculopathy. In fact, that is exactly the case. Figure 4 shows that patients who received RAI were more likely to have development of cataract than patients who underwent PBT, and Figure 5 shows that patients in the RAI group were also more likely to have development of maculopathy.

The 2 treatment groups also differ in initial tumor size. Patients who underwent PBT in this study had larger tumors than those who received RAI. This finding may explain why RAI patients were more likely to have a 30% reduction in tumor thickness. A small tumor is more likely to flatten completely, while a large tumor often has a residual thickness.

The size of our study may not have enough power to detect some differences between the PBT and RAI groups. Therefore, the possibility of a type II error is important to consider (ie, a false-negative association). We therefore cannot draw conclusions about survival or the incidence of metastatic melanoma between patients treated with RAI and PBT. The literature, however, does not

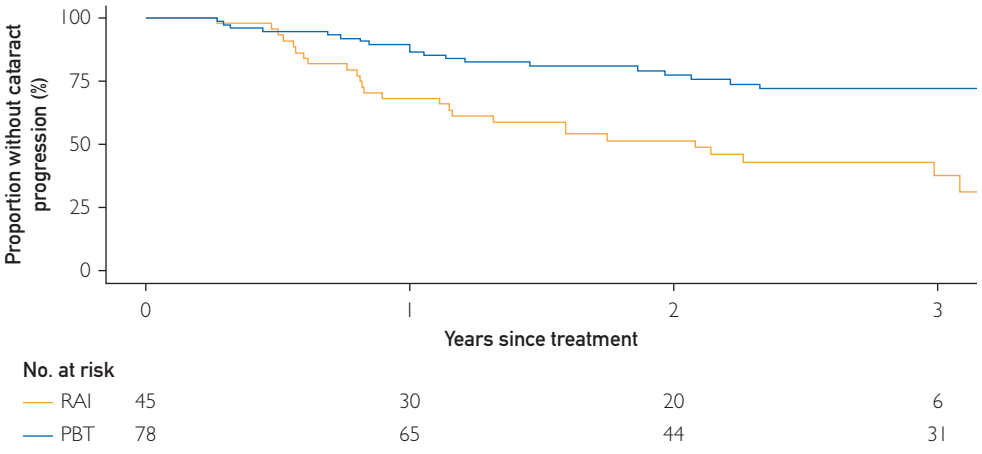

FIGURE 4. Progression of cataract during the 3-year period after treatment in patients without cataract progression at baseline who were treated with radioactive iodine 125 implant (RAI) and proton radiation (proton beam therapy [PBT]). This analysis included only patients who did not have cataract or previous cataract operation at presentation.

document a difference in survival or the likelihood of liver metastases from UM in patients treated with RAI[27-29] or PBT.[30-33] Also, one randomized clinical trial compared helium ion radiation to radioactive iodine implant[22] and found no significant difference in survival. The pertinent literature comparing RAI and PBT is summarized in a 2013 systematic review.[21]

The financial cost of PBT has been scrutinized.[34-36] The cost of RAI, however, can also be significant since RAI includes 2 operations as opposed to 1. Enucleation is less costly than either RAI or PBT.[37]

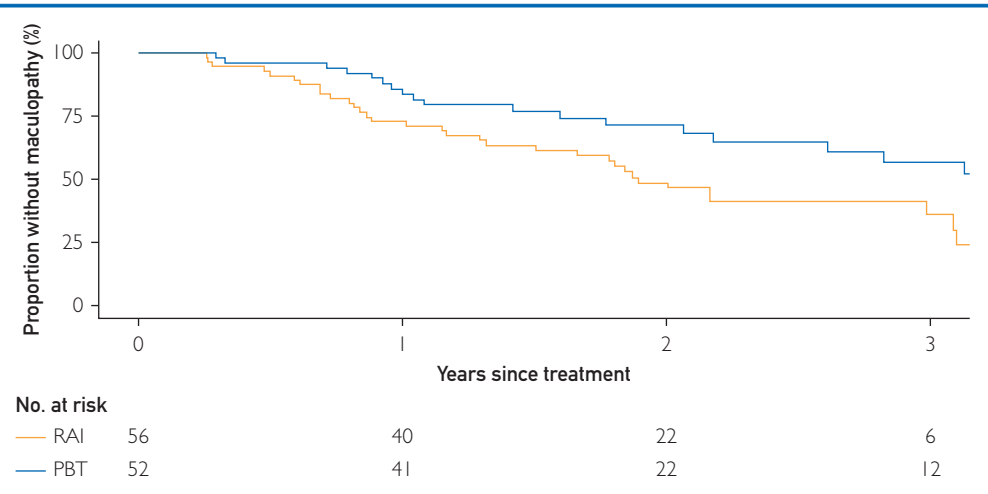

FIGURE 5. Progression of maculopathy during the 3-year period after treatment in patients without maculopathy at basline who were treated with radioactive iodine 125 implant (RAI) and proton radiation (proton beam therapy [PBT]). This analysis included only patients who did not have maculopathy at presentation.

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Prognostic genetic testing can be performed on tumor tissue obtained by fine-needle aspiration biopsy. In our experience, needle biopsy for genetic testing can be included at the time of RAI placement or at the time of placement of fiducial markers for PBT.[38-40]

CONCLUSION

Patients with UM are at significant risk of dying from their disease. Radiation for treatment of primary UM may be delivered by RAI and PBT. In this study, RAI was associated with double vision and PBT was associated with eyelash loss. The utility of proton radiation for treatment of UM may be to reduce morbidity through careful patient selection.

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Abbreviations and Acronyms: **PBT,** proton beam therapy; **RAI,** radioactive iodine 125 implant; **UM,** uveal melanoma

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