# Iodine-125 Episcleral Plaque Brachytherapy for AJCC T4 Posterior Uveal Melanoma: Clinical Outcomes in 158 Patients

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**Abstract**

***Background/Aims:*** The aim of this study is to report the burden of ocular morbidity following iodine-125 episcleral plaque brachytherapy (EPBT) in the treatment of American Joint Committee on Cancer (AJCC) T4-staged posterior uveal melanoma (PUM). ***Methods:*** Clinical records of patients with T4-staged PUM treated with $^{125}$I EPBT were analyzed for incidence of treatment failure and radiation-induced complications. ***Results:*** Cumulative incidence of local treatment failure was 9% (95% CI 5–15%) at 5 years and was associated with decreased tumor height (HR = 0.78; $p$ = 0.01). Cumulative incidence of enucleation at 5 years was 21% and was correlated with worsening baseline visual acuity (HR = 1.42; $p$ = 0.05). Increasing patient age was associated with higher rates of vitreous hemorrhage (HR = 1.03; $p$ = 0.02) and cata- ract surgery (HR = 1.05; $p$ < 0.001). Increased tumor height was associated with higher rates of neovascular glaucoma (HR = 1.16; $p$ = 0.03) and vitreous hemorrhage (HR = 1.23; $p$ < 0.001). ***Conclusion:*** $^{125}$I EPBT is an effective treatment for T4-staged PUM and achieves high rates of local control. Treatment failure appears to be more common among minimally elevated tumors. Other causes of ocular morbidity were associated with increasing tumor height, patient age, and baseline visual acuity.

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## Introduction

In 2009, the American Joint Committee on Cancer (AJCC) established the first universally accepted staging classification system for uveal melanoma [1]. Based on initial height, basal diameter measurements, and location, tumors are stratified into 4 separate categories (T1 through T4), each conferring a higher risk of metastatic

disease and mortality. The previous classification scheme established by the Collaborative Ocular Melanoma Study (COMS) existed primarily to identify which tumors could safely undergo globe-sparing treatment with episcleral plaque brachytherapy (EPBT) with no significant decrease in survival based on the results of a prospective randomized controlled trial [2]. The largest category of tumors in the COMS study (height >10.0 mm or basal diameter >16.0 mm) were randomized to either primary enucleation or external beam radiation followed by enucleation. The study was stopped early as there was no observed difference in cohorts [3]. The reported overall mortality at 5 years was 57 and 62% in the enucleation and pre-enucleation radiation treatment arms, respectively [3].

Over the past 2 decades, a growing number of treatment centers have begun to offer conservative therapy for large melanomas which historically would have required enucleation. Multiple case series have demonstrated safety and efficacy for both EPBT and proton beam radiation therapy in treating large tumors [4–6]. Many clinicians may still hesitate to offer plaque brachytherapy to these patients primarily because complications associated with EPBT occur with greater frequency among large melanomas [7–10] and likely result in higher enucleation rates [11]. Current recommendations from the American Brachytherapy Society – Ophthalmic Oncology Task Force (ABS-OOTF) indicate that AJCC T4-staged melanomas can be treated with iodine brachytherapy provided there is no evidence of extraocular extension [12]. However, due to limitations in the dose distribution of iodine-125, patients with tumors greater than 12 mm in height or 20 mm in base should be "counseled regarding alternative therapies" according to the ABS-OOTF guidelines. In our experience, many of these patients are reluctant to proceed with enucleation and may still desire conservative therapy.

To our knowledge, only 3 centers have reported long-term clinical outcomes with iodine brachytherapy for "large melanomas" [13–15], and no publication has specifically addressed conservative therapy for T4-staged posterior uveal melanoma (PUM) exclusively. Our objective for this investigation is to report our single institution experience in treating T4-staged PUM with $^{125}$I brachytherapy by quantifying survival as well as the incidence of ocular morbidity following treatment. We hope that our results will further contribute to the existing body of evidence regarding the efficacy and limitations of globe-sparing treatment for advanced tumors.

## Methods

### Ocular Oncology Database
Following approval by the University of Tennessee Health Science Center's Institutional Review Board, we performed a retrospective chart review of our Health Information Portability and Accountability Act-compliant institutional database for all patients treated between January 1985 and December 2015 for PUM (defined as uveal melanoma involving the choroid or ciliary body). This database contains patient demographic and clinicopathologic data gathered and recorded over the duration of follow-up. All aspects of our investigation were compliant with the Declaration of Helsinki.

### Inclusion/Exclusion Criteria for the Current Study
We included all patients with PUM undergoing $^{125}$I EPBT whose initial tumor dimensions were consistent with the following AJCC staging criteria for the T4 category: (1) tumor height >15 mm, or (2) tumor basal diameter >18 mm, or (3) tumor height >12 mm and tumor diameter >15 mm [1]. Patients with blind and painful eyes, extraocular extension, circumpapillary growth, extensive intraocular hemorrhage, or unclear media were considered poor candidates for EPBT and excluded. Patients undergoing primary treatment with any modality other than $^{125}$I EPBT were excluded.

### Clinical Evaluation
All patients selected for review were diagnosed with PUM between 1985 and 2015 based on clinical examination and diagnostic imaging. Baseline tumor dimensions were measured with B-scan ultrasonography and dilated fundus examination. All patients underwent metastatic screening prior to treatment with chest X-ray, liver imaging (computed tomography or ultrasound), and liver function tests. Patients were offered enucleation or globe-preserving therapy with EPBT. Informed consent was obtained following a detailed discussion of the potential risks and benefits of EPBT with specific emphasis on radiation-related complications. Patients with poor baseline vision were generally advised against conservative therapy but were not categorically excluded.

### Surgical Treatment with $^{125}$I EPBT
Tumor margins were delineated intraoperatively using transillumination and scleral depression with indirect ophthalmoscopy. Plaque size was selected for a diameter at least 4 mm greater than the maximum basal diameter of the tumor to ensure that the tumor base was fully encompassed by the effective treatment zone. As maximum plaque size is limited to 24 mm, patients with a tumor basal diameter exceeding 20 mm who elected to proceed with EPBT were counseled accordingly regarding potential limitations of therapy. Notched plaques were selected for juxtapapillary melanomas involving less than 180 degrees of the optic nerve head margin. Each plaque was surgically implanted for the duration necessary to achieve a cumulative apex dose of 85 Gy (dosing rate maintained at >50 cGy per hour) in compliance with the American Association of Physics in Medicine TG-43 recommendations. The targeted tumor apex height was calculated based on ultrasound measurements and adding 1 mm for thickness of the sclera. B-scan ultrasonography was performed on postoperative day 1 to verify that each plaque was well-centered around the tumor base, extending at least 2 mm peripheral to the tumor margin.

**Fig. 1.** Kaplan-Meier survival curves for overall survival and metastasis-free survival in patients with T4-staged posterior uveal melanoma treated with iodine-125 episcleral plaque brachytherapy. Dotted lines indicate 95% confidence intervals.
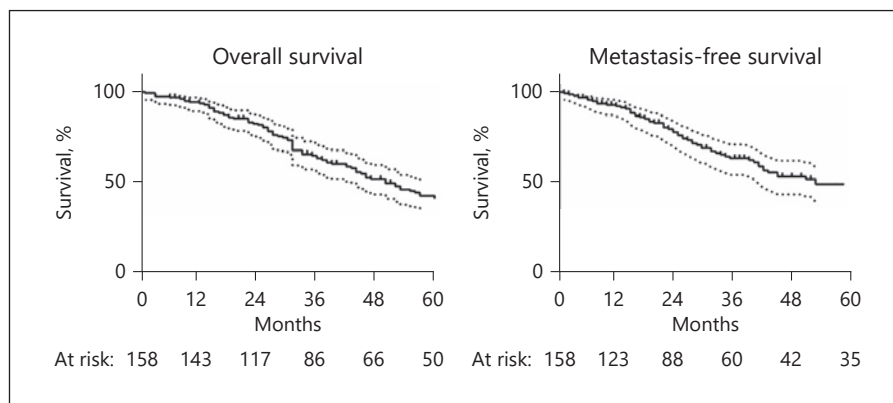
*Patient Follow-up*

Each patient was re-examined every 3–4 months during the first year after treatment and then every 6 months during each subsequent year. The occurrence of the following ocular complications or adverse events was documented prospectively at each appointment:

1 Enucleation: removal of the eye was indicated for patients with local recurrence, scleromalacia, or blind, painful eyes.
2 Local recurrence was diagnosed based on definitive tumor growth on ultrasonography or clinical exam.
3 Cataract removal was indicated for any patient with progressive lens opacification after brachytherapy who was deemed to have significant short-term vision potential. The decision to proceed with surgery was at the discretion of the patient's local ophthalmologist.
4 Vitreous hemorrhage was diagnosed based on the fundus exam.
5 Neovascular glaucoma was diagnosed in patients with neovascularization of the iris with intraocular pressure >21 mm Hg.
6 Scleromalacia was diagnosed for any patient with a full or partial thickness scleral defect occurring within the plaque treatment zone.
7 Radiation retinopathy was diagnosed in eyes with exudative changes occurring within the posterior pole, including macular edema, intraretinal hemorrhage, cotton wool spots, or exudates.
8 Radiation optic neuropathy was diagnosed in eyes with exudative or ischemic changes in the optic nerve.

All patients were concurrently followed by a medical oncologist at 6-month intervals for metastatic disease surveillance, and the occurrence of metastatic relapse was verified by medical record correspondence from the oncologist. Patient mortality was confirmed by family notification or review of public records in the United States Social Security Death Index (SSDI).

*Statistical Analysis*

Time-to-event calculations were measured from the day plaque brachytherapy was initiated. Kaplan-Meier analysis was carried out using Prism 6 software (GraphPad Software Inc., La Jolla, CA, USA) to estimate overall and metastasis-free survival at 1-, 3-, and 5-year intervals. Relative survival calculations were conducted according to the method proposed by Dickman et al. [16] using the US Census Bureau gender- and age-specific population estimates

data with SAS version 9.4 (SAS Inc., Cary, NC, USA). Once age-, gender-, and follow-up-specific relative survival estimates were obtained for the study cohort, the results were summarized as overall and by gender and age ranges as appropriate.

The incidence of ocular complications was then estimated using the cumulative incidence function, which adjusts Kaplan-Meier estimates in the presence of competing events, such as death before the primary event [17]. Due to the high incidence of mortality and enucleation in this cohort, death or loss of the eye were treated as competing events with each complication. This was calculated with SAS version 9.4 (SAS Inc.). Univariate and multivariate Cox proportional hazard regression analysis was performed with SPSS 24 software (IBM Corp., Armonk, NY, USA) to test the association between the time to each ocular complication occurrence and the following patient- or eye-specific covariates: (1) patient age, (2) tumor maximum basal diameter, (3) tumor height, (4) visual acuity at presentation, (5) ciliary body involvement, and (6) posterior tumor margin location. The Pearson correlation coefficient was used to assess for collinearity between different covariates. To reduce the issue of multicollinearity, each covariate was then separated into 1 of 2 multivariate models controlling for the following: (1) patient age, tumor diameter, tumor height, and posterior margin location, or (2) patient age, tumor diameter, visual acuity, and ciliary body involvement. All visual acuity measurements were converted from Snellen units to logarithm of the minimum angle of resolution (logMAR) units for analysis. There were 4 patients who presented with light perception or no light perception vision who were excluded from proportional hazard regression analysis as visual acuity cannot be quantified in logMAR units.

## Results

Of 1,521 patients with PUM treated with EPBT, we identified 158 patients (*n* = 83 males) who met our inclusion criteria with AJCC T4 tumors. Of the 158 tumors, 58 (37.4%) were predominantly ciliary body tumors and 100 arose from the choroid. Median age at diagnosis was 65 years (range 13–88 years). Median logMAR visual acuity

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**Table 1.** Cumulative incidence of treatment complications at 1, 3, and 5 years

| Cumulative incidence | 1 year, % (95% CI) | 3 years, % (95% CI) | 5 years, % (95% CI) |
|---|---|---|---|
| Enucleation | 4.7 (2.1–9.0) | 19.9 (13.5–27.3) | 21.0 (14.4–28.6) |
| Local recurrence | 1.3 (0.2–4.3) | 9.0 (4.9–14.7) | 9.0 (4.9–14.7) |
| Cataract surgery | 14.8 (9.3–21.5) | 32.8 (24.4–41.4) | 45.0 (35.3–54.2) |
| Vitreous hemorrhage | 15.7 (10.4–21.9) | 27.1 (20.0–34.6) | 33.7 (25.6–41.9) |
| Neovascular glaucoma | 4.8 (2.1–9.1) | 21.2 (14.7–28.6) | 24.2 (17.1–32.1) |
| Scleromalacia | 6.6 (3.4–11.3) | 11.2 (6.7–17.1) | 12.1 (7.3–18.2) |
| Radiation retinopathy | 10.1 (5.9–15.6) | 38.8 (30.6–47.0) | 43.7 (34.9–52.0) |
| Radiation optic neuropathy | 5.5 (2.6–10.0) | 23.3 (16.5–30.9) | 31.0 (23.0–39.3) |

at diagnosis was 0.6 (equivalent to approximately 20/80 in Snellen units). Median tumor height at diagnosis was 10.4 mm (range 3.3–19.4 mm) and median maximum basal diameter was 20.0 mm (range 15.1–29.0 mm). Median duration of follow-up for ocular complications was 28 months (range 0–254 months).

Mortality was confirmed in 103 of 158 patients based on review of public records. Kaplan-Meier estimates for overall survival at 1, 3, and 5 years were 93.6% (95% CI 88.4–96.5), 62.9% (95% CI 54.5–70.2), and 42.0% (95% CI 33.5–50.3), respectively (Fig. 1). Diagnosis of metastatic disease was confirmed in 68 patients with a median time to metastasis of 25 months (0–165 months). Kaplan-Meier estimates for metastasis-free survival at 1, 3, and 5 years were 91.7% (95% CI 85.9–95.2%), 61.6% (95% CI 52.0–69.8%), and 46.8% (95% CI 36.5–56.4%), respectively (Fig. 1). Relative survival analysis was performed to quantify the extent of melanoma-related mortality compared with age- and gender-matched controls. Cumulative relative survival at 1, 3, and 5 years was 97.4, 77.5, and 75.6%, respectively. There was a trend toward increased relative survival among younger patients. Five-year relative survival in patients <65 years old was 81.3% compared with 64.7% in patients ≥65 years old (Wilcoxon-Mann-Whitney test, $p = 0.10$). There was no significant difference in 5-year relative survival between males and females at 76.2 and 75.2%, respectively (Wilcoxon-Mann-Whitney test, $p = 0.39$).

Local recurrence was diagnosed in 12 patients with a median time to recurrence of 15 months (range 5–33 months). Of those 12 patients, 9 were treated with enucleation, 2 refused subsequent treatment, and 1 underwent transpupillary thermotherapy. Adjusting for mortality and enucleation as competing events, cumulative incidence of local recurrence at 1, 3, and 5 years was 1% (95% CI 0–4%), 9% (95% CI 5–15%), and 9% (95% CI 5–15%), respectively (Table 1). Cox proportional hazards analysis revealed that local recurrence rate was significantly associated with decreased tumor apex height (HR = 0.78; 95% CI 0.64–0.95; $p = 0.01$) (Table 2). There was a weak association between local recurrence and increased largest basal diameter (HR = 1.08; 95% CI 0.89–1.32; $p = 0.43$); however, this was not statistically significant. Eight of 12 patients diagnosed with local recurrence eventually died with metastatic disease.

Thirty-two patients ultimately required enucleation following primary treatment with EPBT. Eighteen of these underwent enucleation due to blind, painful eyes, 14 of which had been diagnosed with neovascular glaucoma. Nine required enucleation for local recurrence, and 5 were enucleated for progressive scleromalacia. Adjusting for mortality as a competing event, cumulative incidence of enucleation at 1, 3, and 5 years was 5% (95% CI 2–9%), 20% (95% CI 14–27%), and 21% (95% CI 14–29%), respectively. Cox proportional hazards analysis revealed a significant association between enucleation frequency and poorer baseline logMAR visual acuity in the multivariate model (HR = 1.42; 95% CI 1.00–2.01).

Neovascular glaucoma accounted for the highest number of enucleations and was diagnosed in 33 patients at a median time of 18 months after brachytherapy (range 4–126 months). Cumulative incidence of neovascular glaucoma at 1, 3, and 5 years was 5% (95% CI 2–9%), 21% (95% CI 15–29%), and 24% (95% CI 17–32%), respectively. Development of neovascular glaucoma was significantly associated with increasing tumor height (HR = 1.16; 95% CI 1.02–1.33). Scleromalacia was diagnosed in a total of 17 patients, 5 of whom ultimately required enucleation. Median time from brachytherapy to onset of scleromalacia was 8 months (range 2–38 months). Cumulative incidence was 7% (95% CI 3–11%) at 1 year, 11% (95% CI 7–17%) at 3 years, and 12% (95% CI 7–18%) at 5 years. Scleromalacia frequency was positively associated with ciliary body involvement (HR = 2.76; 95% CI 1.05–7.27).

**Table 2.** Cox proportional hazard regression analysis of treatment complications following iodine-125 brachytherapy

|  | β (SE) | p value | Hazard ratio (95% CI) |
|---|---|---|---|
| *Enucleation* |  |  |  |
| Univariate regression |  |  |  |
|   Age (at diagnosis) | −0.004 (0.01) | 0.76 | 1.00 (0.97–1.02) |
|   Tumor LBD | −0.006 (0.07) | 0.94 | 1.00 (0.87–1.14) |
|   Tumor height | 0.036 (0.07) | 0.60 | 1.04 (0.91–1.18) |
|   LogMAR visual acuity | 0.33 (0.18) | 0.06 | 1.39 (0.99–1.96) |
|   Ciliary body involvement | 0.19 (0.38) | 0.62 | 1.21 (0.57–2.56) |
|   Posterior margin ≤6 DD from fovea | −0.07 (0.41) | 0.86 | 0.93 (0.41–2.09) |
| Multivariate regression model |  |  |  |
|   Age (at diagnosis) | −0.01 (0.01) | 0.55 | 0.99 (0.97–1.02) |
|   Tumor LBD | 0.04 (0.07) | 0.59 | 1.04 (0.91–1.19) |
|   logMAR visual acuity | 0.35 (0.18) | 0.05 | 1.42 (1.00–2.01) |
|   Ciliary body involvement | 0.11 (0.41) | 0.78 | 1.12 (0.50–2.49) |
| *Local recurrence* |  |  |  |
| Univariate regression |  |  |  |
|   Age (at diagnosis) | 0.02 (0.02) | 0.26 | 1.02 (0.98–1.07) |
|   Tumor LBD | 0.08 (0.10) | 0.43 | 1.08 (0.89–1.32) |
|   Tumor height | −0.25 (0.10) | 0.01 | 0.78 (0.64–0.95) |
|   LogMAR visual acuity | −0.13 (0.36) | 0.73 | 0.88 (0.43–1.79) |
|   Ciliary body involvement | −0.48 (0.67) | 0.47 | 0.62 (0.17–2.29) |
|   Posterior margin ≤6 DD from fovea | −0.83 (0.78) | 0.28 | 0.44 (0.10–1.99) |
| Multivariate regression model |  |  |  |
|   Age (at diagnosis) | 0.03 (0.02) | 0.20 | 1.03 (0.99–1.07) |
|   Tumor LBD | 0.04 (0.12) | 0.77 | 1.04 (0.82–1.30) |
|   Tumor height | −0.23 (0.10) | 0.02 | 0.79 (0.66–0.96) |
|   Posterior margin ≤6 DD from fovea | −0.85 (0.79) | 0.28 | 0.43 (0.09–2.01) |
| *Vitreous hemorrhage* |  |  |  |
| Univariate regression |  |  |  |
|   Age (at diagnosis) | 0.03 (0.01) | 0.02 | 1.03 (1.00–1.05) |
|   Tumor LBD | 0.03 (0.06) | 0.55 | 1.03 (0.93–1.15) |
|   Tumor height | 0.21 (0.06) | <0.001 | 1.23 (1.11–1.37) |
|   LogMAR visual acuity | 0.41 (0.13) | 0.002 | 1.51 (1.17–1.97) |
|   Ciliary body involvement | 0.04 (0.30) | 0.89 | 1.04 (0.58–1.89) |
|   Posterior margin ≤6 DD from fovea | 0.002 (0.32) | 0.99 | 1.00 (0.54–1.87) |
| Multivariate regression model |  |  |  |
|   Age (at diagnosis) | 0.03 (0.01) | 0.01 | 1.03 (1.01–1.05) |
|   Tumor LBD | 0.04 (0.05) | 0.39 | 1.04 (0.95–1.15) |
|   Tumor height | 0.21 (0.05) | <0.001 | 1.24 (1.11–1.37) |
|   Posterior margin ≤6 DD from fovea | −0.28 (0.33) | 0.40 | 0.76 (0.40–1.45) |
| *Cataract surgery* |  |  |  |
| Univariate regression |  |  |  |
|   Age (at diagnosis) | 0.05 (0.01) | <0.001 | 1.05 (1.03–1.08) |
|   Tumor LBD | 0.09 (0.05) | 0.10 | 1.09 (0.99–1.21) |
|   Tumor height | 0.03 (0.05) | 0.61 | 1.03 (0.93–1.14) |
|   LogMAR visual acuity | −0.06 (0.16) | 0.70 | 0.94 (0.69–1.28) |
|   Ciliary body involvement | −0.05 (0.30) | 0.87 | 0.95 (0.53–1.71) |
|   Posterior margin ≤6 DD from fovea | 0.40 (0.30) | 0.18 | 1.50 (0.83–2.69) |
| Multivariate regression model |  |  |  |
|   Age (at diagnosis) | 0.05 (0.01) | <0.001 | 1.05 (1.03–1.08) |
|   Tumor LBD | 0.05 (0.05) | 0.27 | 1.06 (0.96–1.16) |
|   logMAR visual acuity | −0.05 (0.15) | 0.74 | 0.95 (0.70–1.28) |
|   Ciliary body involvement | 0.01 (0.30) | 0.98 | 1.01 (0.56–1.83) |

**Table 2** (continued)

|  | β (SE) | *p* value | Hazard ratio (95% CI) |
|---|---|---|---|
| *Neovascular glaucoma* |  |  |  |
| Univariate regression |  |  |  |
| Age (at diagnosis) | −0.01 (0.01) | 0.45 | 0.99 (0.97–1.01) |
| Tumor LBD | 0.09 (0.06) | 0.14 | 1.10 (0.97–1.23) |
| Tumor height | 0.15 (0.07) | 0.03 | 1.16 (1.02–1.33) |
| LogMAR visual acuity | 0.08 (0.19) | 0.67 | 1.08 (0.75–1.56) |
| Ciliary body involvement | −0.46 (0.41) | 0.26 | 0.63 (0.28–1.41) |
| Posterior margin ≤6 DD from fovea | −0.47 (0.43) | 0.28 | 0.63 (0.27–1.45) |
| Multivariate regression model |  |  |  |
| Age (at diagnosis) | −0.01 (0.01) | 0.51 | 0.99 (0.97–1.02) |
| Tumor LBD | 0.08 (0.06) | 0.14 | 1.09 (0.97–1.22) |
| Tumor height | 0.18 (0.07) | 0.02 | 1.19 (1.03–1.37) |
| Posterior margin ≤6 DD from fovea | −0.49 (0.45) | 0.27 | 0.61 (0.26–1.46) |
| *Scleromalacia* |  |  |  |
| Univariate regression |  |  |  |
| Age (at diagnosis) | 0.03 (0.02) | 0.14 | 1.03 (0.99–1.07) |
| Tumor LBD | 0.06 (0.09) | 0.48 | 1.06 (0.90–1.26) |
| Tumor height | 0.11 (0.09) | 0.21 | 1.12 (0.94–1.34) |
| LogMAR visual acuity | −0.30 (0.30) | 0.33 | 0.74 (0.41–1.35) |
| Ciliary body involvement | 1.02 (0.49) | 0.04 | 2.76 (1.05–7.27) |
| Posterior margin ≤6 DD from fovea | 0.66 (0.49) | 0.18 | 1.93 (0.74–5.00) |
| Multivariate regression model |  |  |  |
| Age (at diagnosis) | 0.03 (0.02) | 0.11 | 1.03 (0.99–1.07) |
| Tumor LBD | 0.04 (0.09) | 0.66 | 1.04 (0.87–1.25) |
| logMAR visual acuity | −0.33 (0.30) | 0.28 | 0.72 (0.40–1.30) |
| Ciliary body involvement | 1.11 (0.50) | 0.03 | 3.03 (1.13–8.10) |
| *Radiation retinopathy* |  |  |  |
| Univariate regression |  |  |  |
| Age (at diagnosis) | −0.02 (0.01) | 0.07 | 0.99 (0.97–1.00) |
| Tumor LBD | 0.002 (0.05) | 0.97 | 1.00 (0.91–1.10) |
| Tumor height | −0.10 (0.05) | 0.03 | 0.91 (0.83–0.99) |
| LogMAR visual acuity | −0.13 (0.15) | 0.37 | 0.88 (0.66–1.17) |
| Ciliary body involvement | −0.59 (0.30) | 0.05 | 0.56 (0.31–0.99) |
| Posterior margin ≤6 DD from fovea | −0.16 (0.29) | 0.57 | 0.85 (0.48–1.49) |
| Multivariate regression model |  |  |  |
| Age (at diagnosis) | −0.02 (0.01) | 0.10 | 0.99 (0.97–1.00) |
| Tumor LBD | −0.001 (0.05) | 0.99 | 0.99 (0.90–1.11) |
| Tumor height | −0.10 (0.05) | 0.04 | 0.91 (0.83–1.00) |
| Posterior margin ≤6 DD from fovea | −0.03 (0.30) | 0.93 | 0.98 (0.55–1.74) |
| *Radiation optic neuropathy* |  |  |  |
| Univariate regression |  |  |  |
| Age (at diagnosis) | −0.01 (0.01) | 0.51 | 0.99 (0.97–1.01) |
| Tumor LBD | 0.04 (0.06) | 0.46 | 1.05 (0.93–1.17) |
| Tumor height | −0.03 (0.06) | 0.66 | 0.98 (0.87–1.10) |
| LogMAR visual acuity | 0.70 (0.16) | 0.67 | 1.07 (0.78–1.48) |
| Ciliary body involvement | −0.73 (0.38) | 0.06 | 0.48 (0.23–1.02) |
| Posterior margin ≤6 DD from optic nerve | 0.87 (0.40) | 0.03 | 2.39 (1.09–5.24) |
| Multivariate regression model |  |  |  |
| Age (at diagnosis) | −0.01 (0.01) | 0.68 | 0.99 (0.97–1.02) |
| Tumor LBD | 0.04 (0.06) | 0.48 | 1.04 (0.93–1.17) |
| Tumor height | −0.001 (0.06) | 0.99 | 0.99 (0.89–1.12) |
| Posterior margin ≤6 DD from optic nerve | 0.85 (0.41) | 0.04 | 2.33 (1.05–5.16) |

SE, standard error; CI, confidence interval; LBD, largest basal diameter; DD, disc diameters; LogMAR, logarithm of the minimum angle of resolution.

Vision declined precipitously following treatment. Among the 117 patients who maintained follow-up for at least 1 year, median visual acuity at the most recent exam had declined to logMAR = 3.0 (hand motion). Vision loss was typically attributed to cataract, vitreous hemorrhage, or radiation retinopathy. 135 patients were phakic at the time of brachytherapy, and 51 patients subsequently required cataract surgery. Median time from brachytherapy to cataract surgery was 20 months (range 2–81 months). Cumulative incidence of cataract surgery was 15% (95% CI 9–22%) at 1 year, 33% (95% CI 24–41%) at 3 years, and 45% (95% CI 35–54%) at 5 years. Cataract surgery rates following brachytherapy were significantly associated with increased patient age at diagnosis (HR = 1.05; 95% CI 1.03–1.08). At the most recent follow-up exam, median visual acuity was equivalent among patients who had undergone cataract surgery and those who remained phakic at logMAR 3.0 (hand motion).

Forty-eight patients developed vitreous hemorrhage at a median time of 13.5 months (range 1–82 months) after brachytherapy. Cumulative incidence of vitreous hemorrhage at 1, 3, and 5 years was 16% (95% CI 10–22%), 27% (95% CI 20–35%), and 34% (95% CI 26–42%), respectively. Vitreous hemorrhage rates were positively associated with increased patient age (HR = 1.03; 95% CI 1.00–1.05), increased tumor height (HR = 1.23; 95% CI 1.11–1.37), and poor baseline logMAR visual acuity (HR = 1.51; 95% CI 1.17–1.97).

Radiation retinopathy and optic neuropathy were diagnosed in 59 and 39 patients, respectively. Median time to radiation retinopathy diagnosis was 17 months (range 2–83 months). Median time to optic neuropathy diagnosis was 19 months (range 5–60 months). Cumulative incidence of radiation retinopathy at 1, 3, and 5 years was 10% (95% CI 6–16%), 39% (95% CI 31–47%), and 44% (95% CI 35–52%), respectively. Cumulative incidence of radiation optic neuropathy at 1, 3, and 5 years was 6% (95% CI 3–10%), 23% (95% CI 17–31%), and 31% (95% CI 23–39%), respectively. Frequency of optic neuropathy was positively associated with tumor proximity (≤6 disc diameters) to the optic nerve (HR = 2.39; 95% CI 1.09–5.24).

## Discussion

In this study, we investigated clinical outcomes following EPBT for the most advanced category of PUM under the AJCC cancer staging criteria [1]. Previous studies have demonstrated that treatment failure rates increase proportionately with tumor size [7, 9]. Nevertheless, ocular oncology centers are still more apt to treat large PUM with globe-sparing therapies based on our current understanding of uveal melanoma biology and the possibility of subclinical micrometastatic disease [18–20]. To our knowledge, this is the first large retrospective study investigating EPBT exclusively for T4-staged PUM, and median tumor dimensions were larger in this cohort than in any other previously published case series. Our results may, therefore, lend further insight into the burden of treatment-related morbidity among the largest and most advanced tumors.

As expected, survival in this cohort was poor, with a 5-year metastasis-free survival of 47.1%. This was comparatively lower than that previously reported for T4 melanomas in the AJCC criteria validation study by the OOTF which observed a 5-year disease-specific survival of 61% (95% CI 49–71%) [21]. However, our estimates are within the confidence interval of a similar validation study performed by the European Ocular Oncology Group (EOOG) who reported a 5-year melanoma-specific survival of 53% (95% CI 46–56%) [22]. As cause of death information was not available for all patients in this cohort, relative survival analysis was performed to better estimate melanoma-associated mortality. This is widely regarded as a more rigorous measure of disease-associated mortality and may also be useful for patient counseling [23, 24]. Population-based studies not limited to large tumors have observed 5-year relative survival rates ranging from 77 to 84% [25]. As expected, estimates for this cohort were comparatively lower, particularly among patients >65 years old where 5-year relative survival was only 65%. This trend between increased age and lower relative survival has been observed at other centers [26] and likely reflects the correlation between increasing age and metastatic disease [27].

Treatment efficacy – as defined by local control of intraocular disease – was remarkably consistent with the findings of previous investigations of $^{125}$I EPBT for large melanoma. Cumulative incidence of local recurrence at 5 years was 9% in this study and 6 and 9% in the reports by Puusaari et al. [13] and Shields et al. [14], respectively. In our investigation, the frequency of local recurrence was associated with decreased tumor thickness (HR = 0.78; 95% CI 0.64–0.95) and increased tumor basal diameter (HR = 1.08; 95% CI 0.93–1.15), although the latter finding was not statistically significant ($p = 0.43$). It has been well established in the literature that increased tumor thickness and basal diameter are significant risk factors for treatment failure after brachytherapy; however, these

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findings have been limited primarily to medium sized melanomas [7, 11]. Caujolle et al. [8] noted that local recurrence was most common amongst wide and thin melanomas, many of which may exhibit a diffuse-type growth pattern where tumor margins are more difficult to delineate prior to treatment. Our results appear to confirm their findings. In this investigation, there were 99 tumors (63%) which exceeded the maximum diameter or height limitations for ^{125}I EPBT as defined by the ABS-OOTF [12]. Of the 12 tumors which developed local recurrence, only 3 were >12 mm in height, and 5 were >20 mm in diameter. Based on our findings, we cannot conclude that there is a significantly increased risk for treatment failure when tumor dimensions exceed the prescribed dose limitations for iodine brachytherapy, despite a weak correlation with increased tumor diameter (HR = 1.08; 95% CI 0.89–1.32). Clinicians should still exercise caution when treating these tumors with conservative therapy.

Cumulative incidence for enucleation was 21% – almost double the rate observed with medium-sized melanomas [11] but comparable to that reported in other studies of large melanoma [4, 14]. Unlike Shields et al. [14], we did not find a significant association between enucleation rates and tumor thickness or location. In our multivariate model, poor baseline logMAR visual acuity was the only significant predictor of enucleation (HR = 1.42; 95% CI 1.00–2.01). Poor visual acuity at baseline is generally associated with pre-existing ocular morbidity, and these eyes may be more likely to become blind and painful after treatment. Of the 32 patients who underwent enucleation during the study period, 16 (50%) presented with logMAR visual acuity ≥1.0 (Snellen 20/200). Patients who desire conservative therapy despite poor baseline vision should be counseled regarding the more guarded prognosis for long-term ocular survival.

Cataract removal was the most common surgical procedure performed after brachytherapy with a cumulative incidence of 45% at 5 years. Cataract surgery rates were significantly associated with increased age at diagnosis, likely reflecting more advanced nuclear sclerosis at baseline resulting in a shorter time to cataract progression. Other studies have reported that cataract is more commonly associated with pre-equatorial tumors given their closer proximity to the lens [28, 29]. We did not observe this association, suggesting that radiation dose distribution for most T4-staged tumors may be too extensive to spare the anterior segment, regardless of tumor location.

Five-year cumulative incidence of neovascular glaucoma was 24%, which was nearly identical to the 21% reported by Shields et al. [14]. Puusaari et al. [13] reported an incidence as high as 60%, but this included all forms of secondary glaucoma. Like Puusaari et al. [13], we observed a strong association between increased tumor height and neovascular complications (HR = 1.16; 95% CI 1.02–1.33). Overall, increased tumor height and increased patient age were the most consistent predictors of ocular morbidity following treatment. This corroborates the findings of Shields et al. [14], who observed that increased tumor height and increased patient age were the most significant risk factors for vision loss following brachytherapy.

There was an unexpected negative association between tumor height and development of radiation retinopathy. We speculate that this may reflect a greater incidence of vitreous hemorrhage associated with thicker lesions, which typically precludes fundus examination for retinopathy. Eyes with unclear media were not censored in this investigation, as this would falsely elevate the observed incidence of some complications without accounting for competing events.

Alternatives to iodine brachytherapy have been reported for large melanomas with successful outcomes. Semenova and Finger [6] observed reduced complication and vision loss rates using [103]Pd brachytherapy, which generally results in a lower cumulative radiation dose. This study included only 9 T4-staged melanomas, and direct comparison with our data is difficult. Proton beam teletherapy has been used as an alternative to brachytherapy at some centers. This modality has been associated with higher rates of anterior segment complications with large melanomas, particularly neovascular glaucoma where 5-year estimates range from 35% [30] to over 50% [31]. Our results agree with previous reports demonstrating comparatively lower risk for neovascular glaucoma with brachytherapy [14].

This study is limited by the relatively short duration of patient surveillance, with a median follow-up time of 28 months. This was primarily constrained by the high incidence of mortality in this cohort, as the majority of patients had expired by 5 years. Additionally, because our institutional database does not record visual acuity continuously, we were unable to report visual outcomes in actuarial measures. It is generally accepted that eyes with large melanomas have very poor visual prognosis following conservative therapy [4, 14, 30], and our limited analysis of visual outcomes in this cohort corroborates this.

In this retrospective case series, we have reported our single-institution experience with ^{125}I EPBT in a large co-

hort with T4-staged PUM. Iodine brachytherapy achieved high rates of local control despite that the majority of tumors exceeded the maximum height and diameter thresholds for $^{125}$I EPBT. Decreased tumor thickness was associated with a higher risk of local treatment failure. Ocular morbidity – as defined by the burden of treatment complications and adverse events – appears to be greater with increasing tumor thickness, patient age, and poor visual acuity at presentation. These findings may assist clinicians to better identify those patients with advanced disease who are the most appropriate candidates for conservative therapy.

## Statement of Ethics

Informed consent was obtained following a detailed discussion of the potential risks and benefits of EPBT with specific emphasis on radiation-related complications. All aspects of our investigation were compliant with the Declaration of Helsinki.

## Disclosure Statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial or proprietary support for this work that could have influenced its outcome.

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