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Long-term Visual Acuity Outcomes in Patients with Uveal Melanoma Treated with ¹²⁵I Episcleral OSU-Nag Plaque Brachytherapy

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Abstract

Objective—To report our experience in long-term follow-up of ocular melanoma patients treated with custom OSU-Nag eye plaques utilizing ¹²⁵I sources.

Methods—A retrospective chart review was conducted for 113 consecutive ocular melanoma patients with follow-up visual acuity data who were treated with OSU-Nag plaque episcleral brachytherapy at The Ohio State University Medical Center from 1994 to 2009. Visual acuity, complication data, and recurrence rates were recorded up to 120 months post-brachytherapy.

Results—Median age at presentation was 63.0 years (range 22–93). Median follow-up was 65.5 months (range 2–180). Median radiation dose at the prescription point was 85.8 Gy (range 51.8–103.7). Preservation of useful visual acuity, defined as better than 20/200, was noted in 43/74 (58%) of patients in the current study at 36 months compared with 50.1% of COMS participants. By 120 months, 17/30 (57%, 95% CI: 45–69%) progressed to visual acuity worse than 20/200, while 9/30 (30%) retained visual acuity of 20/40 or better, and 4/30 (13%) were 20/50 to 20/200. The rate of retinopathy after radiation was approximately 40% of all those observed by 60 months. Baseline visual acuity, apical tumor height, AJCC tumor category, and distance between the tumor and the fovea were all significantly associated with loss of visual acuity. The local tumor control rate by 60 months of follow-up was 93% (95% CI: 85–97%).

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Conclusions—The OSU-Nag custom ^{125}I plaque is an effective treatment for uveal melanoma, with preservation of useful visual acuity in 58% of eyes 3 years after treatment and 43% of eyes 10 years after treatment.

Keywords

Brachytherapy; Uveal melanoma; Visual acuity; OSU-Nag plaque; Collaborative ocular melanoma study

INTRODUCTION

Uveal melanoma is the most common primary intraocular cancer in adults.¹ Over the last several decades, brachytherapy has become the standard treatment for primary uveal melanoma at most centers.^{2–4} The effectiveness of ^{125}I brachytherapy for primary treatment was supported by the multicenter, NIH-funded Collaborative Ocular Melanoma Study (COMS), which showed equivalent survival for patients treated with globe-sparing brachytherapy compared with enucleation.^{5–7}

The COMS Group provided initial evidence suggesting the preservation of visual acuity in patients treated with episcleral brachytherapy.⁸ Three years after treatment, 49% of eyes treated demonstrated significant loss of visual acuity, defined as loss of six lines or more from baseline, with 43% demonstrating vision of 20/200 or worse.² Other series utilizing ^{125}I episcleral brachytherapy have shown similar or superior preservation of visual acuity over a longer follow-up period.^{3,9–11} Additionally, studies using alternative radioactive isotopes for brachytherapy (e.g., palladium-103 and ruthenium-106) have demonstrated superior preservation of visual acuity with long-term follow-up.^{3,12,13} Radiation-related complications, including radiation retinopathy, neovascular glaucoma, and cataracts, have also been described by post-COMS studies.^{12,14}

The COMS protocol used five standard circular plaques of varying diameter and required that the tumor be covered with a minimum 2 mm margin.² These plaques are widely used today. At our institution, for patients who did not meet the inclusion criteria for COMS, or who did not want to participate in the study, custom gold ^{125}I OSU-Nag eye plaques were made to encompass the tumor according to its shape, plus a 1–2 mm margin. All patients treated with plaque brachytherapy subsequent to completion of the COMS were treated with these customized plaques. The shape of each plaque was determined by the size and location of the lesion and included circular, oval, notched, and kidney shaped plaques. The customized plaques allowed for more conformal tumor coverage for irregular (i.e., non-circular) lesions, improved the dose conformity and distribution for peripapillary tumors, and irradiated a smaller area of normal retina.¹⁵

A previously published series from our institution suggested that episcleral brachytherapy utilizing ^{125}I OSU-Nag plaques produced survival rates similar to those of the COMS patients after a median follow-up of 49 months. The series also reported local control rates similar to the COMS.¹⁵

The present updated series expands on local recurrence statistics from the previous ¹²⁵I OSU-Nag plaque study, with long-term follow-up of a larger number of patients. The study also details the long-term effects on visual acuity, with comparison to the COMS Group results, and evaluates the impact of AJCC T category and other anatomic factors such as distance to fovea and optic nerve on visual acuity outcome and development of radiation retinopathy, the most common cause of visual acuity loss in this population.¹⁵

METHODS

A retrospective chart review of 113 consecutive primary choroidal or ciliary body melanoma patients treated with OSU-Nag episcleral plaque brachytherapy for whom follow-up visual acuity data was available at The Ohio State University Medical Center from 1994 to 2009 was performed. The diagnosis of choroidal melanoma was made using funduscopy, fundus photographs, B-scan ultrasonography, and fluorescein angiography. Patients were treated with episcleral brachytherapy¹⁵ and were followed at approximately 6-month intervals. At each follow-up visit, corrected visual acuity and pinhole visual acuity were measured using a Snellen eye chart. The better measurement was used in the study analysis. Those patients treated with the OSU-Nag plaque brachytherapy during the time the COMS was concurrently being conducted either did not meet the inclusion criteria for, or declined participation in the COMS. Baseline characteristics of each patient, including gender, age at diagnosis, concurrent diabetes at enrollment, presence/absence of macular edema at baseline, visual acuity, and tumor characteristics were obtained from the patient's initial referral visit and from initial tumor workup notes. The distances of the tumor to the fovea and optic nerve were determined using the COMS measurement data sheet, with data from ophthalmoscopy and imaging studies. Radiation dose at the prescription point was recorded. In addition, visual acuity and the presence of any complications or retinopathy were recorded at 6, 12, 18, 24, 36, 60, 84, and 120 months post-brachytherapy.

Radiation retinopathy was evaluated with ophthalmoscopy and fluorescein angiography. Radiation retinopathy was diagnosed if any of the following features were present in the macula: retinal edema, retinal exudation, intraretinal hemorrhages, microaneurysms, cotton wool spots, vascular sheathing, or capillary nonperfusion. In addition, a diagnosis of radiation retinopathy was made if any of the listed features were present in combination with retinal neovascularization, vitreous hemorrhage, or extensive retinal ischemia on fluorescein angiography. Radiation optic neuropathy was diagnosed if there was peripapillary exudation and hemorrhage, optic disc swelling, or neovascularization of the disc. Neovascular glaucoma was defined as elevated intraocular pressure with accompanying neovascularization of the iris and/or angle on slit lamp examination and gonioscopy. Local recurrence was evaluated with color fundus photography, fluorescein angiography, A-scan or B-scan ultrasound and defined using the COMS definition.⁷

Brachytherapy

The OSU-Nag eye plaques (Figure 1) were specially fabricated from 0.6 mm thick 18k gold, with each one having a counterpart “dummy” plaque with a central cut-out (Figure 2) allowing the surgeon to ensure adequate coverage of the base of the tumor prior to placing

the active plaque. Although most plaques are circular or oval, we have made kidney-shaped plaques for tumors close to the optic disc. By turning the concave surface anteriorly, these can also be used to treat tumors adjacent to the cornea. In order to assist the surgeon in placing and securing plaques that are posterior, “rabbit-ear” plaques having 2–3 elongated anterior wings (Figure 2) are specifically designed to reach posterior-located tumors. The inner surface of the plaque is raised 2 mm from the surface of the sclera to reduce the dose to the sclera and increase the depth dose.

Using custom designed plaques achieved better conformity to the shape and location of the individual tumor. OSU-Nag plaques also lack a “lip” or rim, compared with the rimmed COMS plaque. The unrimmed surface allowed for easier sliding motion during placement of the plaque and extension of the dose distribution beyond the physical edge of the plaque, which permitted use of a smaller margin.¹⁵ The radioisotope sources were glued to the inside of the plaque rather than the COMS technique of a silicon carrier, allowing for flexibility in seed arrangement and optimization of dose distribution. Invariably, fewer seeds were utilized than for a COMS plaque. Three-dimensional dose distributions of OSU-Nag versus COMS plaque, were compared, and the doses along the central axis were approximately equivalent, with the OSU-Nag plaque delivering very slightly higher doses at distances less than 6 mm and slightly lower doses at distances greater than 6 mm.¹⁶ In the COMS the prescribed radiation dose (85 Gy) was to a point along the midline equal to 5 mm if height was 5 mm or at the apex if the apical height was > 5 mm. The prescription point for this series had minor variations from this definition for years 1994 to 2005. During this time period, the majority of cases used the following definition for dose prescription: prescribed at the edge of the lesion at a distance equal to the maximum lesion height. For tumors 5 mm or greater in height, this resulted in higher doses to the apex than the COMS series and for a small number of lesions with height less than 5 mm, the dose was lower than COMS series as the COMS used a minimum prescription height of 5 mm. After 2005, due to a change in radiation oncology faculty, and the publication of the American Brachytherapy Society recommendations for brachytherapy of uveal melanomas¹⁷ the prescription point in this series corresponded with the COMS prescription point. For some lesions in the current series with height approaching or greater than 10 mm, a point slightly shallower than the apex was chosen to reduce the risk of scleral melt. Though we did not have a maximum scleral dose limit, modification to the prescription point was considered if the maximum scleral dose exceeded 500 Gy.

Statistical Methods

Patient demographics, tumor characteristics, and treatment characteristics were described through summary statistics and compared to the COMS data using Fisher’s exact test. The risk of local recurrence, radiation retinopathy and visual acuity worse than 20/200 were calculated using life-table methods, and the differences in the risk of each outcome between groups were assessed via the Cox proportional hazards model. Cox proportional hazards models were used to estimate hazard ratios (HR) and associated confidence intervals (CI). Multivariable modeling was restricted to adjustment for patient age at diagnosis due to the limited number of events and patients. Time to local recurrence was the time from brachytherapy to local recurrence; time to radiation retinopathy was defined as the time from

brachytherapy to the time of diagnosis of retinopathy; time to visual acuity worse than 20/200 was defined only for those patients with 20/200 vision or better at baseline and was the time from brachytherapy to time of vision worse than 20/200. In all three endpoints, patients were censored, when no event was observed at the date of last observation. All reported p-values and confidence intervals are two-sided and unadjusted for multiple comparisons. Analyses were performed in STATA (version 13, StataCorp, College Station, TX). This study was conducted after Institutional Review Board (IRB) approval, and is Health Insurance Portability and Accountability Act compliant. It adhered to the tenets of the Declaration of Helsinki.

RESULTS

COMS Comparisons

Baseline characteristics of the OSU-Nag patient cohort alongside the same characteristics in the COMS data⁸ are found in Table 1. Patient demographics were similar, with those in the OSU-Nag cohort of somewhat older age on average. Concurrent presence of diabetes mellitus at time of diagnosis was slightly more prevalent in the current study than the COMS. A higher percentage of patients presenting with 20/200 or worse visual acuity at diagnosis was observed in the OSU-Nag cohort ($p=.048$). It is worthwhile to note that 11% (12/113) of patients in the current study had macular edema at baseline.

Regarding tumor size/T category, the COMS excluded patients who had tumors with apical height of less than 2.5mm or greater than 10.0mm, as well as tumors with largest basal diameter less than 4.5mm or greater than 16.0mm. In the current study, 19% of patients fell outside of these criteria, predominantly for apical height (most were less than 2.5mm); and 3.5% of patients fell outside of the criteria for largest basal diameter.

A larger proportion of patients in the current study had tumors whose closest border was more than 8.0 mm from the foveal avascular zone (37/97=38%, (95% CI: 28%–49%) as compared to 15.2% in the COMS). Similarly, 35/99 (35%, 95% CI: 26%–46%) patients in the current study had tumors whose closest border was more than 8.0 mm from the optic disc, as compared to 14.6% for the COMS. Radiation dose at the prescription point varied more widely in our series than in the COMS, most notably in the percentage of patients receiving more than 90 Gy (36/100=36%, 95% CI: 27%–46%, in our study versus 2.7% in the COMS). Complete radiation dosing data was not available for 13 of the 113 patients.

Table 2 describes visual acuity over the course of follow-up in the OSU-Nag cohort and in the COMS data (taken from COMS report No. 16).⁸ Preservation of useful visual acuity, defined as better than 20/200, was noted in 50.1% of COMS participants, as compared to 58% of patients in our series at 36 months. At 120 months, 13 of 30 (43%) of our patients retained useful visual acuity. At the 60-month visit, 4 patients (7%) had retained visual acuity of 20/20 or better. Of these, 2 were lost to follow-up at 120 months, while 2 experienced a decrease in visual acuity to 20/30. It should be noted that each of these patients developed cataracts between the two time points.

After the 60 months of follow-up, 3 patients (5%) were noted to have no light perception (NLP) visual acuity. All 3 developed neovascular glaucoma prior to presenting with NLP vision. In total for the OSU-Nag study, 38 eyes developed cataracts, 13 developed radiation keratopathy, 6 developed neovascular glaucoma, and 6 developed optic neuropathy.

Actuarial Analysis for OSU-Nag Data

The cumulative risk of each time to event outcome over the course of follow-up is presented in Table 3. Table 3 accounts for those patients who were not able to be followed for the entire follow-up period and provides an appropriate summary of the risk of each outcome over time. As calculated by the life-table method, 30% (95% CI: 22–41%) of patients with 20/200 vision or better at baseline regressed to visual acuity worse than 20/200 by the 36-month time point. By 120 months, 57% (95% CI: 45–69%) progressed to visual acuity worse than 20/200. Local recurrence was relatively rare in this cohort, with 6 total events observed. The rate of retinopathy after radiation was 39% (95% CI: 29%–50%) by 60 months of follow-up.

Risk Factor Analysis for OSU-Nag Data

Table 4 describes unadjusted associations for each outcome of interest and potential risk factors. These analyses revealed that baseline visual acuity, apical height, AJCC category, and the distance from closest border to the center of the foveal avascular zone were influential predictors in a patients' risk of progression to visual acuity worse than 20/200. The risk was increased over 8 times (HR: 8.67, 95% CI: 2.03–36.93) for patients with baseline visual acuity between 20/25 and 20/40 compared to those with 20/20 or better at baseline and was even higher for patients with baseline visual acuity worse than 20/40. This association was not substantially influenced by adjustment for age. Age-adjusted hazard ratios are not shown for this analysis.

Similarly, larger apical height at baseline was associated with increased risk of visual acuity decline and was not influenced by adjustment for age. Not only was the risk for those with the largest category of apical height, 7.6–11.5 mm, greater than those with the smallest, 0.0–2.4 mm (Age-adjusted Cox model Wald test p-value=0.016), but the risk was also significantly increased for the highest two groups compared to those with 2.5–5.0 mm at baseline (Age-adjusted Cox model: 5.1–7.5 vs. 2.5–5.0, HR: 2.26 (95% CI: 1.27–5.08, p-value=0.009); 7.6–11.5 vs. 2.5–5.0, HR: 4.66 (95% CI: 2.01–10.81, p-value <0.001)). Further, more severe AJCC T-category at baseline was estimated to have increased risk of poor eventual visual acuity in crude and age-adjusted models. Age-adjusted hazard ratios are also not shown for this analysis. In contrast, increased distance from the fovea was protective (for >5 mm from the foveal avascular zone, HR: 0.23, 95% CI: 0.09–0.57).

The most influential predictor of radiation retinopathy was baseline visual acuity. Adjusted for age, the risk of radiation retinopathy was increased over two times (Age-adjusted HR: 2.26, 95% CI: 0.99–5.19) for those with baseline visual acuity 20/50–20/200. However, none of the potential risk factors presented in Table 4 significantly increased the risk of developing radiation retinopathy.

Figure 3 further illustrates the impact of important anatomic and tumor factors on the development of visual acuity worse than 20/200. Importantly, tumors with apical height of 5.1 mm or greater, AJCC category T3, distance to fovea of 0 mm, and distance to optic nerve of 0–4 mm demonstrated the most rapid visual decline.

DISCUSSION

The OSU-Nag custom ^{125}I plaque is an effective treatment for uveal melanoma, with preservation of useful visual acuity (20/200 or better) in 58% and 43% of eyes 3 and 10 years after treatment, respectively.

Baseline patient demographics were similar between the COMS and the current study, with notable differences including the percentage of patients over 70 years of age (23.3% COMS vs. 39% OSU-Nag); percentage of patients with 20/200 or worse vision at baseline (9.8% COMS vs. 19.8% OSU-Nag); and percentage of patients with proximal tumor border more than 8.0 mm from the foveal avascular zone (15% COMS vs. 32% OSU-Nag). While the current series included 15 patients (13% of sample population) with tumors less than 2.5 mm in apical height, it also included 4 patients with large choroidal melanoma. Age, baseline diagnosis of diabetes,² proximity to the foveola, and tumor size are known to be associated with poor visual prognosis.¹⁴

Radiation dose at the prescription point was skewed toward higher doses in the OSU-Nag plaque study, with 32% of OSU-Nag patients receiving more than 90 Gy, compared with 2.7% in the COMS. A recent report comparing smaller tumors treated with this 5 mm prescription point method to tumors treated with doses prescribed strictly to the apical height demonstrated increased visual complications in the 5 mm prescription point group.¹⁸ This indicates that the dosing approach used in the present study and in the COMS may be driving visual complication rates and loss of visual acuity. The importance of radiation dosing in predicting visual loss is supported by a recent review by Perez et al (2014),⁹ which noted that increasing radiation doses correlate with greater visual acuity loss, worse final visual acuity outcomes, and greater rates of radiation complications.⁹ Interestingly, no dose response was noted in terms of local control, distant metastases or overall survival between radiation dose groups of <69 Gy, 69–81 Gy, 81–89 Gy, >89 Gy. Local recurrence rates for the four dose ranges were 6%, 11%, 15%, and 4% respectively ($p=0.26$). These recent data suggest the doses used in the COMS and the present OSU-Nag study may potentially be higher than necessary to achieve tumor control.

At baseline evaluation, a greater percentage of COMS patients (89.2%) had visual acuity better than 20/200, as compared to 83% for our study. At 36 months, the last published time point for visual acuity distribution in the COMS, 50.1% of COMS patients retained visual acuity of better than 20/200, as compared to 58% of OSU-Nag plaque patients. Long-term data for our study are also promising, with 25/60 (42%) and 13/30 (43%) maintaining visual acuity better than 20/200 at five years and 10 years respectively. While some aspects of our study population, including initial visual acuity, inconsistent recording of best-corrected visual acuity, and radiation dosage could predispose OSU-Nag patients to poorer visual acuity outcomes when compared to the COMS, other aspects, such as the inclusion of small

tumors and the larger proportion of patients with tumors more than 8.0 mm from the foveal avascular zone could predispose OSU-Nag patients to better visual acuity outcomes in comparison to the COMS. Thus, formal comparisons of the OSU-Nag and COMS outcomes are fundamentally flawed.

While this discussion centers around visual acuity results after ^{125}I brachytherapy, it is worth noting that other long-term studies with different radioisotopes have demonstrated effective preservation of visual acuity.^{3,12,13} A study by Finger et al. (2002) using ^{103}Pd demonstrated visual acuity of 20/200 or better in 73% of patients (n=100) after a mean follow-up period of 55 months.¹² Studies^{3,13} describing visual acuity results in patients treated with ^{106}Ru have also demonstrated good preservation of visual acuity, with one study³ reporting only 29% of patients developing visual loss greater than two Snellen lines after six years of follow-up.

Table 3 displays life-table summaries for the time to outcome for loss of visual acuity, local recurrence, and radiation retinopathy. The accumulated risk of visual loss < 20/200 was greatest prior to 60 months (40%), while only 17% of the cumulative risk was observed between 60–120 months. In addition, the life-table analyses of local recurrences and radiation retinopathy frequency demonstrate decreased rate of decline after the 60-month time point. These data correlate logically with the visual acuity data. However, 6.7% (2/30) of patients examined at the 10-year time point did develop radiation retinopathy between their 7-year and 10-year follow-ups. This suggests that surveillance for radiation retinopathy should continue for at least 10 years, although definitive conclusions about appropriate surveillance periods would require a larger sample size at these 7-year and 10-year follow-up visits.

Table 4 provides results of analyses of unadjusted associations between various demographic, tumor, and treatment characteristics and two key visual outcomes: loss of useful visual acuity and development of radiation retinopathy. These analyses demonstrate that baseline visual acuity, apical tumor height, AJCC tumor category, and distance between the tumor and the fovea are significant predictors of eventual loss of visual acuity. Distance to the closest border of the optic disc demonstrated a trend toward significance ($p=.100$). Apical tumor height and distance to the fovea had been previously demonstrated to be correlated with preservation of visual acuity.^{6,9,14} Higher AJCC tumor categories are correlated with lower overall survival,¹⁹ and were also correlated with loss of visual acuity in our study. Figure 3 demonstrates the strikingly rapid decline in visual acuity in patients with tumors of apical height 5.1 mm or greater, tumors involving the fovea, or tumors that were AJCC category T3.

Interestingly, radiation dose at the prescription point was not significantly associated with a loss of visual acuity as it was in a recent study by Perez et al. (2014)⁹, although the variation in dosing in our study may not have been adequate to compare different doses. None of the demographic, tumor, or treatment characteristics investigated in our study demonstrated a significant correlation with development of radiation retinopathy after treatment.

The unique design of the OSU-Nag plaques (unrimmed, individualized custom-made size and shape of plaque, smaller margins) as detailed in our earlier report¹⁵ allows accurate

placement by the ophthalmologist and, as each plaque is designed to treat the lesion with margins of 1–2 mm in all directions, the volume of normal tissue (especially retina) irradiated is less and in some cases much less than circular plaques. This may account for the long term visual acuity preservation despite higher prescribed doses and a larger proportion of patients with decreased vision at time of diagnosis in the current series compared to COMS.

This study was limited primarily by its retrospective nature. Corrected visual acuity was documented, but best corrected visual acuity data was not always available. We utilized pinhole visual acuity as an imperfect measure of visual potential. All patients reviewed had choroidal melanoma and were treated with OSU-Nag plaque brachytherapy, but patients were not excluded for coexisting ocular or systemic conditions. In addition, a number of patients treated with the OSU-Nag plaque at our institution were treated during the COMS enrollment period. These patients had either failed to qualify for the COMS, or had refused participation. As 15 of the OSU-Nag patients had tumors with apical height too small to qualify for the COMS, this could have skewed the results toward better outcomes for OSU-Nag plaque patients. On the other hand, OSU-Nag plaque series also included patients that did not qualify for COMS as the tumor was too large either in height (>10 mm) or greatest basal diameter (>16 mm) or were too close to the optic nerve. These are poor prognostic criteria and could have skewed the results toward worse outcomes for OSU-Nag plaque patients. Finally, our long-term visual acuity data is limited by attrition in participation, with 30 patients maintaining follow-up at the 10-year visit.

CONCLUSION

Overall, our results suggest that the OSU-Nag custom ^{125}I plaque is an effective treatment for uveal melanoma, with preservation of useful visual acuity in 58% of eyes 3 years after treatment and 43% of eyes 10 years after treatment. The OSU-Nag plaque produces similar visual acuity results to those of the COMS plaque. Poor baseline visual acuity, large apical tumor height, high AJCC tumor category, and distance between the tumor and the fovea are significant predictors of eventual loss of useful visual acuity and are important for preoperative patient counseling.

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Abbreviations

AJCC	American Joint Committee on Cancer
UM	Uveal Melanoma
COMS	Collaborative Ocular Melanoma Study

VA	Visual Acuity
CI	Confidence Interval
HR	Hazard Ratio
NLP	No Light Perception
Gy	Gray

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Figure 1.
OSU-Nag plaques with radioactive seeds

Figure 2. OSU-Nag notched plaque dimensions, gold plaque without seeds (upper) and matched “dummy” plaque (lower)

Figure 3. Kaplan-Meier plots for time (months) to visual acuity worse than 20/200.

Table 1

Baseline demographics of patients studied: study eye *

	OSU-Nag (%) N=113	COMS (%) [§] N=623	P-Value **
Baseline Demographics			
Gender			0.760
Male	54 (47.8)	308 (49.4)	
Female	59 (52.2)	315 (50.6)	
Age			0.004
<50	20 (17.7)	160 (25.7)	
50–69	50 (44.3)	318 (51.0)	
70	43 (38.1)	145 (23.3)	
Median (min – max)	63.0 (22–93)		
Diabetes			0.132
Yes	16 (14.2)	59 (9.5)	
No	97 (85.8)	562 (90.2)	
Visual Acuity			0.048
20/20 or better	26 (23.0)	208 (33.4)	
20/25 to 20/40	46 (40.7)	230 (36.9)	
20/50 to 20/150	22 (19.5)	118 (18.9)	
20/200 or worse	19 (16.8)	61 (9.8)	
Median (min–max)	20/30 (20/20–20/500)	20/32	
IOP ^{^^}			< 0.001
10	6 (5.3)	128 (20.5)	
10.1 to 15	54 (47.8)	233 (37.4)	
15.1 to 20	46 (40.7)	188 (30.2)	
>20	6 (5.3)	71 (11.4)	
Not available	1 (0.9)		
Median (min–max)	15 (8–30)		
Tumor & Treatment Characteristics			
Apical height (mm) [^]			0.554
0.0–2.4	15 (13.3)	n/a	
2.5–5.0	60 (53.1)	403 (64.7)	
5.1–7.5	24 (21.2)	157 (25.2)	
7.6–10.0	10 (8.9)	63 (10.1)	
>10.0	4 (3.5)	n/a	
Median (min–max)	4.0 (1–11.5)	4.2	
Largest basal dimension (mm) [^]			0.115
0.0–4.4	1 (0.9)	n/a	

	OSU-Nag (%) N=113	COMS (%) ⁸ N=623	P-Value ^{**}
4.5–8.0	23 (20.4)	84 (13.5)	
8.1–11.0	41 (36.3)	214 (34.3)	
11.1–14.0	36 (31.9)	229 (36.8)	
14.1–16.0	9 (8.0)	96 (15.4)	
>16.0	3 (2.7)	n/a	
<i>Median (min–max)</i>	10.5 (3–18)	11.5	
AJCC Classification			
T1	44 (38.9)		
T2	49 (43.4)		
T3	20 (17.7)		
Tumor size			
Small	15 (13.3)		
Medium	91 (80.5)		
Large	7 (6.2)		
Ciliary body involvement			0.999
Yes	9 (8.0)	53 (8.5)	
No	104 (92.0)	565 (90.7)	
Extrasccleral extension			
Yes	0 (0)		
No	113 (100.0)		
Distance from closest border to center of foveal avascular zone (mm) ^{^^}			< 0.001
0	11 (9.7)	82 (13.2)	
0.1–2.0	18 (15.9)	155 (24.9)	
2.1–5.0	16 (14.2)	183 (29.4)	
5.1–8.0	15 (13.3)	102 (16.4)	
>8.0	37 (32.7)	95 (15.2)	
Not available	16 (14.2)	6 (1)	
<i>Median (min–max)</i>	6 (0–24.5)	3.0	
Distance from closest border to edge of optic disc (mm) ^{^^}			< 0.001
0.0–2.0	12 (10.6)	93 (14.9)	
2.1–4.0	14 (12.4)	194 (31.1)	
4.1–6.0	24 (21.2)	151 (24.2)	
6.1–8.0	14 (12.4)	92 (14.8)	
>8.0	35 (31.0)	91 (14.6)	
Not available	14 (12.4)	2 (0.3)	
<i>Median (min–max)</i>	6 (0–20)	4.5	
Dose at prescription point (Gy) ^{^^}			< 0.001
80	17 (15.0)	19 (3)	

	OSU-Nag (%) N=113	COMS (%) ⁸ N=623	P-Value ^{**}
80.1–85	23 (20.4)	344 (55.2)	
85.1–90	24 (21.2)	243 (39)	
>90	36 (31.9)	17 (2.7)	
Not available	13 (11.5)	(n/a)	
<i>Median (min–max)</i>	85.8 (51.8–103.7)	70.5	

^{*} This table was created using data from COMS Report 16.⁸

^{**} Fisher's exact test p-value (two-sided) for comparison of characteristics between OSU-Nag and COMS cohorts.

[^] Comparison combines groups. Groups used in this comparison include: Apical height (0.0 – 5.0 mm, 5.1–7.5 mm, and 7.6 mm) and Largest basal dimension (0.0–8.0 mm, 8.1–11.0 mm, 11.1–14.0mm, and 14.1 mm).

^{^^} Comparison does not include missing/not available subjects for these variables.

Table 2

Visual acuity distribution by months since radiation therapy*

	Months Since Radiation Therapy									
	0		12		36		60		120	
Visual Acuity	OSU-Nag n (%)	COMS ⁸ n (%)	OSU-Nag n (%)	COMS ⁸ n (%)	OSU-Nag n (%)	COMS ⁸ n (%)	OSU-Nag n (%)	COMS ⁸ n (%)	OSU-Nag n (%)	COMS ⁸ n (%)
20/20	26 (23)	208 (33.4)	21 (21)	152 (24.4)	6 (8)	62 (12.4)	4 (7)	n/a	0 (0)	n/a
20/25–20/40	46 (41)	230 (36.9)	32 (32)	203 (32.6)	26 (35)	93 (18.6)	12 (20)	n/a	9 (30)	n/a
20/50–20/80	20 (18)	80 (12.8)	18 (18)	70 (11.2)	10 (14)	53 (10.6)	7 (12)	n/a	2 (7)	n/a
20/100–20/160	2 (2)	38 (6.1)	6 (6)	35 (5.6)	1 (1)	43 (8.6)	2 (3)	n/a	2 (7)	n/a
20/200–20/320	8 (7)	25 (4.0)	8 (8)	37 (5.9)	6 (8)	32 (6.4)	7 (12)	n/a	4 (13)	n/a
20/400–20/640	7 (6)	13 (2.1)	4 (4)	27 (4.3)	5 (7)	24 (4.8)	5 (8)	n/a	1 (3)	n/a
20/800	4 (4)	23 (3.7)	11 (11)	73 (11.7)	16 (22)	116 (23.2)	20 (33)	n/a	12 (40)	n/a
NLP (Nag only)	0 (0)	n/a	1 (1)	n/a	4 (5)	n/a	3 (5)	n/a	0 (0)	n/a
Enucleated	0 (0)	0 (0)	0 (0)	9 (1.4)	5 (7)	31 (6.2)	0 (0)	n/a	0 (0)	n/a
Useful VA (better than 20/200)	94 (83)	556 (89.2)	76 (76)	460 (73.8)	43 (58)	251 (50.1)	25 (42)	n/a	13 (43)	n/a
Total Patients	113	623	101	623	74	501	60	n/a	30	n/a

* This table was created using data from COMS Report 16.⁸

Table 3
Life-table estimates of time to worse visual acuity, local recurrence or radiation retinopathy for OSU-Nag patients

Outcome	Interval (mos)	Number at risk	Number of events	Number censored	Cumulative rate of event	95% confidence interval
<i>Visual acuity worse than 20/200</i> *	0 – <6	100	0	2	0.00	-
	6 – <12	98	14	2	0.14	0.08–0.23
	12 – <18	82	3	3	0.18	0.11–0.27
	18 – <24	76	4	3	0.22	0.15–0.32
	24 – <36	69	7	7	0.30	0.22–0.41
	36 – <60	55	7	9	0.40	0.30–0.51
	60 – <84	39	8	11	0.54	0.43–0.66
	84 – <120	20	1	6	0.57	0.45–0.69
<i>Local Recurrence</i> **	0 – <6	111	0	4	0.00	-
	6 – <12	107	0	6	0.00	-
	12 – <18	101	1	4	0.01	0.001–0.07
	18 – <24	96	1	7	0.02	0.01–0.08
	24 – <36	88	3	12	0.06	0.02–0.13
	36 – <60	73	1	11	0.07	0.03–0.15
	60 – <84	61	0	20	0.07	0.03–0.15
	84 – <120	41	0	17	0.07	0.03–0.15
<i>Radiation Retinopathy</i>	0 – <6	113	0	0	0.00	-
	6 – <12 [^]	113	5	12	0.05	0.02–0.11
	18 – <24	96	9	6	0.14	0.08–0.22
	24 – <36	81	10	10	0.25	0.17–0.35
	36 – <60	61	10	11	0.39	0.29–0.50
	60 – <84	40	10	9	0.56	0.45–0.68
	84 – <120	21	2	7	0.61	0.49–0.73

* First recorded time to VA worse than 20/200 in patients who had at least 20/200 vision at baseline (n=100).

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Of 111 patients with recorded dates of local recurrence and follow up.
There were no events between 12 and 18 months, so this interval is not included in the table.
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Table 4

Univariable associations between baseline characteristics with time to vision endpoints for OSU-Nag patients

Outcome	Variable	Hazard Ratio	95% CI	P-value
<i>Time (months) to Visual acuity worse than 20/200 *</i>	Age at diagnosis (for a 1 unit increase)	1.01	0.99–1.04	0.251
	Gender			0.083
	Male	1.70	0.93–3.11	
	Female	1.0		
	Diabetes			0.113
	Yes	1.82	0.87–3.80	
	No	1.0		
	Baseline Visual Acuity			<0.001
	20/20 or better	1.0		
	20/25 to 20/40	8.67	2.03–36.93	
	20/50 to 20/200	17.45	4.05–75.08	
	Apical height (mm)			0.003
	0.0–2.4	1.0		
	2.5–5.0	0.85	0.32–2.27	
	5.1–7.5	2.23	0.78–6.37	
	7.6–11.5	4.02	1.30–12.39	
	AJCC Category			<0.001
	T1	1.0		
	T2	1.64	0.79–3.39	
	T3	6.85	3.10–15.11	
	Distance from closest border to center of foveal avascular zone (mm)			0.014
	0	1.0		
	0.1–5.0	0.37	0.15–0.92	
	> 5.0	0.23	0.09–0.57	
	Distance from closest border to edge of optic disc (mm)			0.100

Outcome	Variable	Hazard Ratio	95% CI	P-value
<i>Time to Radiation Retinopathy</i>	0.0–4.0	1.0		
	4.1–8.0	0.58	0.28–1.22	
	>8.0	0.41	0.18–0.93	
	Dose at prescription point (Gy)			0.454
	80	1.0		
	80.1–85	0.61	0.22–1.69	
	85.1–90	0.43	0.15–1.19	
	>90	0.59	0.25–1.39	
	Age at diagnosis (for a 1 unit increase)	1.00	0.98–1.02	0.964
	Gender			0.857
	Male	1.05	0.60–1.86	
	Female	1.0		
	Diabetes			0.946
	Yes	1.03	0.41–2.62	
	No	1.0		
	Baseline Visual Acuity			0.169
	20/20 or better	1.0		
	20/25 to 20/40	1.47	0.66–3.25	
	20/50 to 20/200	2.08	0.94–4.62	
	Apical height (mm)			0.236
	0.0–2.4	1.0		
	2.5–5.0	1.28	0.49–3.33	
	5.1–7.5	2.36	0.84–6.65	
	7.6–11.5	0.97	0.23–4.08	
	AJCC Category			0.266
	T1	1.0		
	T2	1.50	0.80–2.83	
	T3	1.89	0.80–4.47	

Outcome	Variable	Hazard Ratio	95% CI	P-value
	Distance from closest border to center of foveal avascular zone (mm)			0.639
	0	1.0		
	0.1–5.0	0.68	0.28–1.69	
	> 5.0	0.65	0.28–1.54	
	Distance from closest border to edge of optic disc (mm)			0.807
	0.0–4.0	1.0		
	4.1–8.0	0.81	0.39–1.67	
	>8.0	0.80	0.38–1.68	
	Dose at prescription point (Gy)			0.448
	80	1.0		
	80.1–85	0.43	0.13–1.40	
	85.1–90	0.59	0.21–1.72	
	>90	0.79	0.31–2.00	

* First recorded time to VA worse than 20/200 in patients who had at least 20/200 vision at baseline (n=100).