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Original Article

Outcomes of Stereotactic Body Radiation Therapy for Large Uveal Melanoma: A Retrospective Analysis of Asian Population

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Purpose This study aimed to investigate the clinical outcomes of stereotactic body radiation therapy (SBRT) in patients with large uveal melanoma (UM).

Materials and Methods We conducted a retrospective review of 64 consecutive patients with UM treated with CyberKnife at Yonsei Cancer Center from September 2015 to October 2021. The median radiation dose was 60 Gy (range, 48 to 64 Gy) administered in four fractions every alternate day. The local failure-free rate (LFFR), distant metastasis-free rate (DMFR), progression-free survival (PFS), and overall survival (OS) were assessed using the Kaplan-Meier method and log-rank test. Cox regression analysis was performed to analyze the predictive factors affecting survival outcomes and the factors associated with vision loss.

Results The median tumor diameter and height were 11.5 mm and 8.4 mm, respectively. After a median follow-up of 32.1 months (range, 4.9 to 89.9 months), the 3-year LFFR, DMFR, PFS, and OS were 89.5%, 70.5%, 65.5%, and 89.4%, respectively. Enucleation was performed in 13 (20.3%) patients, with three cases attributed to disease progression. A larger tumor diameter was associated with significantly worse DMFR (hazard ratio [HR], 1.35; p=0.015) and OS (HR, 1.49; p=0.026) in the multivariate analysis. Regarding visual prognosis, 41 patients (64.1%) had baseline visual acuity ≥ 20/200, but only four patients (6.3%) maintained visual acuity ≥ 20/200 by the final follow-up. Initial visual acuity ≥ 20/40 (HR, 0.45; p=0.030) was the single favorable significant factor predicting visual retention ≥ 20/200 in multivariate analysis.

Conclusion SBRT using CyberKnife demonstrated a comparable local control rate to that observed in historical studies for patients with large UM. Distant metastasis and treatment-related ocular toxicity remain the limitations of this treatment.

Key words Uveal melanoma, Radiosurgery, Prognosis, Visual acuity

Introduction

Uveal melanoma (UM) is the predominant primary intraocular tumor among adults, with an incidence rate of approximately six cases per million individuals [1]. Approximately 90% of UMs primarily affect the choroid. UM is significantly rarer in Asians, with an incidence rate of approximately 0.25 to 0.64 per million individuals annually, compared to 5 to 6 per million individuals in Western countries [2,3]. Phenotypic traits, such as blue or grey eyes and fair skin in the Caucasian population, predispose individuals to UM. However, the impact of these traits on survival rates and distant metastasis remains unclear [4,5].

Diverse therapeutic interventions are available, encompassing enucleation and approaches aimed at preserving the eye [6,7]. Historically, enucleation has been considered the gold standard treatment for UM. Nevertheless, a shift in perspective has occurred following the findings of the Collaborative Ocular Melanoma Study (COMS), which demonstrated no discernible survival advantage or discrepancy in the rate of distant metastasis between enucleation and radiotherapy (RT) [8,9].

Various RT techniques are available for the preservation of the eye in the management of UM. Plaque brachytherapy is deemed appropriate for small tumors with heights ≤ 6 mm when employing ruthenium-106 [7,10]. This necessitates invasive surgical procedures, frequently resulting in complications arising from the impact of radiation on neighboring tissues. Proton beam therapy (PBT) has been frequently used for both small and large tumors due to its advantages of sharp dose fall-off and little radiation exposure to adjacent tissues. However, surgical intervention is unavoidable, as a radiopaque target must be inserted onto the surface of the eye to achieve precise beam targeting. Moreover, considering

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the limited availability of PBT facilities than that of photon RT, it is imperative to acknowledge that accessibility to PBT is compromised, presenting a potential impediment to its universal availability on demand.

CyberKnife (Accuray), a modality for photon stereotactic surgery (SRS)/stereotactic body radiation therapy (SBRT), requires relatively lower installation and operational costs and can be more easily integrated into existing radiation facilities. It is capable of treating UM without the need for surgical intervention and reduces radiation exposure to adjacent tissues. Given the rarity of UM in Asian populations, which has led to a scarcity of region-specific data on photon SRS/SBRT, this investigation aimed to examine the clinical efficacy of CyberKnife treatment, emphasizing parameters such as survival rates, occurrence of distant metastasis, and local tumor control in Asian populations. Additionally, this study evaluated the rates of ocular complications and visual outcomes, recognizing the preservation of visual acuity without complications as the primary objective of eye-preserving therapy for UM.

Materials and Methods

We conducted a retrospective analysis of 77 consecutive patients with UM who underwent SBRT using CyberKnife at Yonsei Cancer Center from September 2015 to October 2021. Larger UMs with a height > 6 mm are treated using CyberKnife in our institution, whereas small UMs with a height of ≤ 6 mm are treated using plaque brachytherapy [10]. The inclusion criteria comprised individuals meeting the following conditions: (1) patients with UM who had undergone SBRT using CyberKnife and (2) those with an Eastern Cooperative Oncology Group performance status ≤ 2. Patients were excluded if they met any of the following criteria: (1) the presence of distant metastasis at the initiation of RT, (2) a history of prior or concurrent malignancies, (3) a record of radiation to the orbital area, (4) incomplete RT (biologically effective dose < 40 Gy), and (5) absence of any follow-up after RT. Based on these criteria, 13 patients were excluded and 64 patients were included in the study.

Each patient was positioned supine and immobilized using a thermoplastic mask, while maintaining a fixed-straight gaze. An acrylic frame was attached to the mask to secure the camera. During this time, the patient's gaze was directed towards the center of the camera lens, and a gaze-tracking program, which was developed at our institution, was activated. This program tracks the position of the iris in real-time and returns the central coordinates of the iris, which can be continuously monitored through the camera. If the tracking proved stable, the simulation computed tomography (CT) scan was conducted accordingly. The CT images were obtained with a 1-mm slice thickness. Radiation oncology experts performed three-dimensional segmentation of the UM using MIM Software ver. 6.5.8 (MIM Software Inc.). The gross tumor volume (GTV) was defined based on magnetic resonance imaging (MRI) findings, while bilateral organs at risk (OAR)—optic chiasm, lacrimal glands, lenses, optic nerves, and orbits—were delineated on CT images. A 2 mm margin was added to the GTV to determine the planning target volume (PTV), and a total dose of 60 Gy in four fractions was prescribed to the 75% isodose line. Our planning approach focused on ensuring adequate PTV coverage, according to the prescribed dose, rather than on reducing the dose to the OAR. Treatment plans were derived using a non-isocentric inverse algorithm and the treatment was administered every other day. During the actual treatment, the stability of the gaze tracking was reassessed. Once the patient's iris movement was determined to be minimal and stable, a 2 mm margin was created based on the current coordinates as a threshold for deviation of iris movement. Iris movement was tracked real-time and if the patient's gaze deviated outside the predetermined 2 mm margin, the beam was manually interrupted with a delay of approximately 2 seconds due to the manual operation. Ophthalmic examinations were performed at baseline, 3 months after RT, and every 6 months thereafter. Visual acuity assessments, routine ophthalmic examinations, and measurement of tumor base dimensions and height using standardized B-scan ultrasonography or MRI were performed at each follow-up session. The treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors ver. 1.1, and the best response was documented after treatment.

Data analysis was conducted using SPSS ver. 25.0 (IBM Corp.). Survival outcomes, including the local failure-free rate (LFFR), distant metastasis-free rate (DMFR), progression-free survival rate (PFS), and overall survival rate (OS), were assessed using the Kaplan-Meier method and log-rank test. All rates were defined as the duration from the date of diagnosis to event occurrence. The Cox proportional hazards model was used for the univariate and multivariate analyses of independent prognostic clinical factors for each survival type. Variables significantly associated with survival rates in univariate analysis were selected as candidates for multivariate analysis. The Kaplan-Meier method and chi-squared test were used to investigate factors influencing visual outcomes, and Cox regression analysis was performed to identify risk factors associated with vision loss. Radiation-induced toxicities were scored according to the Common Terminology Criteria for Adverse Events ver. 5.0.

Results

1. Clinical characteristics

Patient, tumor, and treatment characteristics of the 64 patients with UM treated with CyberKnife are described in Table 1. The median age of the patients was 60 years (range, 27 to 91) and with 40 males and 24 females. The median diameter and height of tumors were 11.5 mm (range, 6.2 to 18.4 mm) and 8.4 mm (range, 3.6 to 18.2 mm), respectively. Fifty-nine patients had tumors confined to the choroid without ciliary body involvement, five patients had choroidal tumors involving the ciliary body, and none showed iris involvement or extraocular extension. A median total dose of 60.0 Gy (range, 48.0 to 64.0 Gy) was administered in four fractions with median of 15.0 Gy (range, 12.0 to 16.0 Gy) for each fraction. The median GTV was 0.95 cm^3 (range, 0.23 4.72 cm^3), the median PTV value was 2.65 cm^3 (range, 1.15 to 10.48 cm^3), and the maximum PTV dose was median 80.0 Gy (range, 70.6 to 90.1 Gy), respectively. Seventeen (26.6%) patients had an initial visual acuity of ≥ 20/40, 24 patients (37.5%) had an initial visual acuity of ≥ 20/200, < 20/40, and 23 patients had an initial visual acuity of < 20/200.

Table 1. Patients, tumor, and treatment characteristics

Variable	Value (n=64)
Age (yr)	60 (27-91)
Sex	
Male	40 (62.5)
Female	24 (37.5)
ECOG PS	
0	51 (79.7)
1	13 (20.3)
Initial visual acuity	
≥ 20/40	17 (26.6)
≥ 20/200, < 20/40	24 (37.5)
≥ 20/2,000, < 20/200	8 (12.5)
Counting fingers	3 (4.7)
Hand motion	9 (14.1)
Light perception (+)	2 (3.1)
Light perception (–)	1 (1.5)
Tumor diameter (mm)	11.5 (6.2-18.4)
Tumor height (mm)	8.4 (3.6-18.2)
T category	
T2	24 (37.5)
T3	38 (59.4)
T4	2 (3.1)
AJCC stage	
IIA	23 (35.9)
IIB	38 (59.4)
IIIA	3 (4.7)
Total dose (Gy)	60.0 (48.0-64.0)
Fractional dose (Gy)	15.0 (12.0-16.0)
Maximum PTV dose (Gy)	80.0 (70.6-90.1)
PTV mean dose (Gy)	69.7 (38.4-81.0)
PTV minimum dose (Gy)	50.6 (20.8-73.4)
GTV (cm^3)	0.95 (0.23-4.72)
PTV (cm^3)	2.65 (1.15-10.48)

Values are presented as median (range) or number (%). AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance score; GTV, gross tumor volume; PTV, planning target volume.

2. Treatment response

The best therapeutic responses to SBRT for patients with primary UM were as follows: none achieved a complete response, 20 (31.3%) showed partial response, 39 (60.9%) exhibited stable disease, and five (7.8%) presented with locally progressive disease. Among the five patients with locally progressive disease, two underwent enucleation only, one underwent enucleation and systemic chemotherapy with dacarbazine, and two underwent systemic chemotherapy only because of extensive liver metastases.

3. Treatment outcomes and predictive factors

Over a median follow-up period of 32.1 months (range, 4.9 to 89.9 months), the 3-year OS was 89.4% (Fig. 1A), and the 3-year PFS was 65.5% (Fig. 1B). The rate of 3-year LFFR reached 89.5% (Fig. 1C) while the 3-year DMFR was 70.5% (Fig. 1D). Six cases (9.4%) of local failure were noted, with two (3.1%) involving only local failure and four (6.3%) involving both local failure and distant metastasis. Additionally, 20 cases (31.3%) of distant metastasis were observed, with 16 (25.0%) involving only distant metastasis and four (6.3%) involving distant metastasis with local failure. Patterns of failure are described in S1 Fig.

The predictive factors related to LFFR, DMFR, PFS, and OS were investigated. For LFFR, no significant factor was identified in the univariate analysis (S2 Table); hence, further multivariate analysis was not performed. Larger tumor diameter and GTV volume were significant factors in predicting worse DMFR in the univariate analysis (hazard ratio [HR], 1.35; 95% confidence interval [CI], 1.11 to 1.6; p=0.002 and HR, 1.48; 95% CI, 1.04 to 2.12; p=0.031, respectively) (S3 Table), whereas only tumor diameter was identified as a significant factor in the multivariate analysis (HR, 1.35; 95% CI, 1.06 to 1.71; p=0.015) (S3 Table). In the univariate analysis on PFS, larger tumor diameter (HR, 1.22; 95% CI, 1.03 to 1.45; p=0.025), GTV volume (HR, 1.49; 95% CI, 1.07 to 2.08; p=0.019), and PTV volume (HR, 1.19; 95% CI, 1.01 to 1.41; p=0.036) were significant predictive factors, while there was no significant predictive factor for PFS in the multivariate

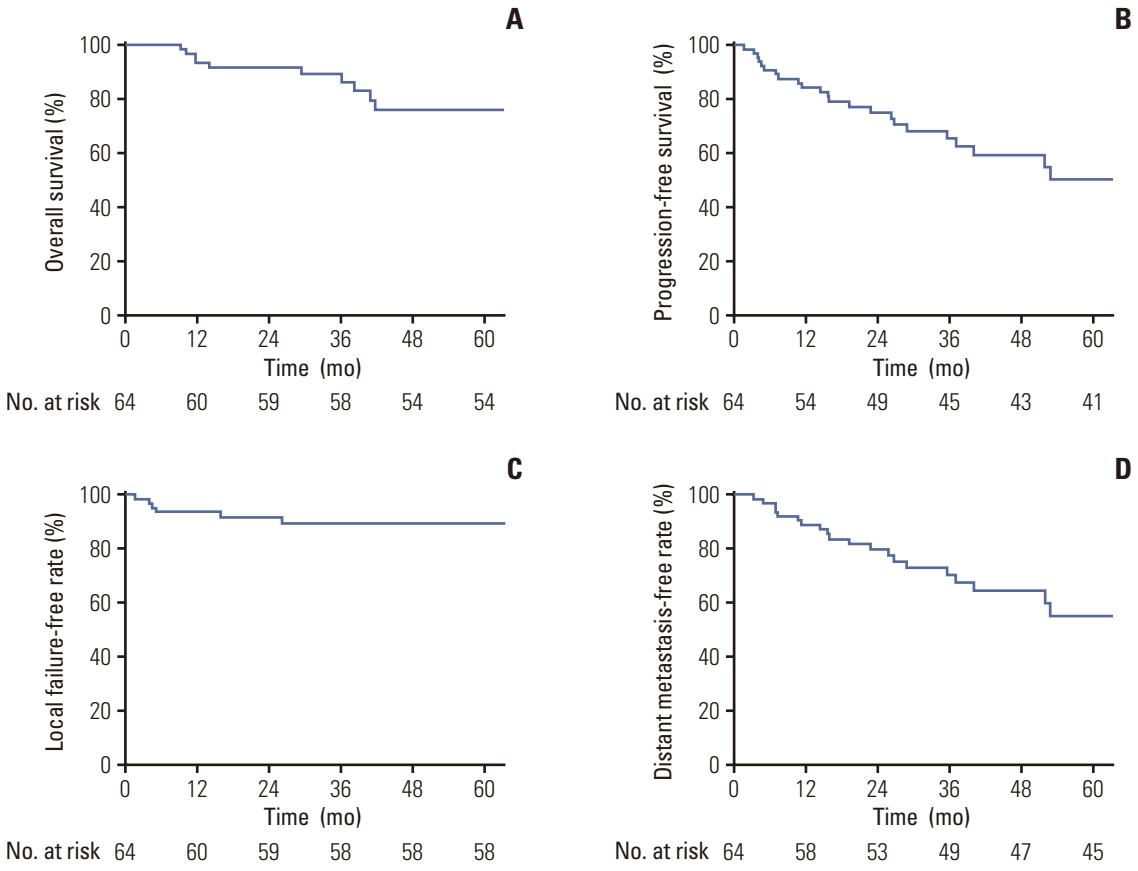

Fig. 1. Kaplan-Meier survival curves of overall survival (A), progression-free survival (B), local failure-free rate (C), and distant metastasis-free rate (D) of uveal melanoma patients after stereotactic body radiotherapy.

analysis (Table 2). Larger tumor diameter and GTV volume were significant factors in predicting worse OS in univariate analysis (HR, 1.51; 95% CI, 1.13 to 2.01; p=0.005 and HR, 1.68; 95% CI, 1.05 to 2.70; p=0.032, respectively) (Table 2), while tumor diameter was the only significant factor in multivariate analysis (HR, 1.49; 95% CI, 1.05 to 2.13; p=0.026) (Table 2).

4. Complications and Enucleation

During the follow-up period, 53 patients (82.8%) showed complications after SBRT. Post-RT ocular complications are shown in Table 3. The most common adverse event was dry eyes (n=16, 25%). To treat ophthalmologic disorders such as radiation retinopathy involving ischemia and neovascularization 24 patients (37.5%) received intraocular bevacizumab injections. and 13 patients (20.3%) underwent enucleation of the ipsilateral eye. Among them, only three patients underwent enucleation because of local UM progression, whereas ten underwent enucleation due to ocular complications: neovascular glaucoma or an increase in intraocular pressure in four patients, ocular pain in three patients, hemorrhage in two patients, and retinal detachment in one patient. The median time to enucleation was 11.7 months, and the 3-year enucleation-free rate was 75.6% (S4 Fig.). GTV volume (cm^3) (HR, 1.94; 95% CI, 1.20 to 3.13; p=0.007) and PTV volume (cm^3) (HR, 1.40; 95% CI, 1.11 to 1.76; p=0.004) were significant predictive factors for enucleation in the univariate analysis whereas no significant predictive factor was identified in the multivariate analysis (S5 Table).

5. Visual outcomes and predictive factors

The distribution of visual acuity at the time of initial diagnosis and the last follow-up is shown in Fig. 2. The median visual acuity decreased from 20/50 at baseline to light perception present (LP+) at the last follow-up. Forty-one patients (64.1%) had baseline visual acuity ≥ 20/200, but only four (6.3%) maintained visual acuity ≥ 20/200 by the final follow-up (Fig. 2). Notably, one patient whose baseline visual acuity was worse than 20/200 improved to better than 20/200 after undergoing RT and subsequent trans-pars plana vitrectomy.

We conducted statistical analysis on the subgroup of patients with initial visual acuity ≥ 20/200. The median visual retention time of the visual acuity loss to < 20/200

Table 2. Univariate and multivariate analysis of predictive factors for progression-free survival and overall survival

Variable	Progression-free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)	1.01 (0.98-1.04)	0.613	-	-	1.01 (0.97-1.07)	0.530	-	-
Sex								
Male	1.00 (ref)				1.00 (ref)			
Female	1.00 (0.43-2.31)	0.999	-	-	0.65 (0.17-2.52)	0.536	-	-
ECOG PS								
0	1.00 (ref)				1.00 (ref)			
1	1.00 (0.34-2.96)	0.996	-	-	1.26 (0.26-6.03)	0.770	-	-
Diameter (mm)	1.22 (1.03-1.45)	0.025	1.15 (0.92-1.43)	0.212	1.51 (1.13-2.01)	0.005	1.49 (1.05-2.13)	0.026
Height (mm)	0.97 (0.83-1.14)	0.712	-	-	1.01 (0.80-1.27)	0.933	-	-
AJCC stage								
II	1.00 (ref)				1.00 (ref)			
III	0.66 (0.09-4.93)	0.682	-	-	1.79 (0.22-14.25)	0.583	-	-
GTV (cm^3)	1.49 (1.07-2.08)	0.019	1.48 (0.45-4.88)	0.516	1.68 (1.05-2.70)	0.032	1.03 (0.50-2.12)	0.936
PTV (cm^3)	1.19 (1.01-1.41)	0.036	0.91 (0.53-1.58)	0.742	1.21 (0.95-1.55)	0.116	-	-
PTV max dose (Gy)	1.11 (0.99-1.24)	0.066	-	-	1.11 (0.97-1.28)	0.133	-	-
PTV mean dose (Gy)	0.99 (0.92-1.07)	0.821	-	-	1.08 (0.94-1.24)	0.267	-	-
PTV min dose (Gy)	0.99 (0.96-1.03)	0.755	-	-	1.01 (0.95-1.07)	0.813	-	-
Initial visual acuity ≥ 20/200								
No	1.00 (ref)				1.00 (ref)			
Yes	1.16 (0.47-2.84)	0.746	-	-	1.21 (0.31-4.68)	0.783	-	-

AJCC, American Joint Committee on Cancer; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GTV, gross tumor volume; HR, hazard ratio; PTV, planning target volume.

Table 3. Post-radiotherapy ocular complications (n=64)

Complication	Grade				
	1	2	3	4	Overall
Ocular pain	4 (6.3)	5 (7.8)	2 (3.1)	-	11 (17.2)
Dry eye syndrome	12 (18.8)	4 (6.3)	-	-	16 (25.0)
Cataract	12 (18.8)	3 (4.7)	-	-	15 (23.4)
Serous retinal detachment	-	-	13 (20.3)	1 (1.6)	14 (21.9)
Radiation retinopathy	-	4 (6.3)	18 (28.1)	11 (17.2)	33 (51.6)
Vitreous hemorrhage	5 (7.8)	3 (4.7)	4 (6.3)	-	12 (18.8)
Neovascular glaucoma	3 (4.7)	3 (4.7)	2 (3.1)	-	8 (12.5)
Secondary glaucoma	4 (6.3)	3 (4.7)	2 (3.1)	-	9 (14.1)
Optic neuropathy	1 (1.6)	-	-	-	1 (1.6)
Radiation maculopathy	5 (7.8)	3 (4.7)	1 (1.6)	-	9 (14.1)

Values are presented as number (%).

was 3.91 months in this subgroup (S6 Fig.). In the univariate analysis, significant predictive factors for visual acuity loss to < 20/200 in this subgroup were GTV volume (HR, 1.50; 95% CI, 1.03 to 2.18; p=0.036), PTV volume (HR, 1.21; 95% CI, 1.02 to 1.45; p=0.031), and initial visual acuity ≥ 20/40 (HR, 0.40; 95% CI, 0.20 to 0.79; p=0.009) (Table 4). Initial visual acuity ≥ 20/40 was the only significant factor in the multivariate analysis (HR, 0.45; 95% CI, 0.22 to 0.93; p=0.030) (Table 4), and the median time of visual acuity loss to < 20/200 was 10.2 months and 1.51 months in patients with initial visual acuity ≥ 20/40 and < 20/40, respectively.

Ocular complications also affected visual prognosis and

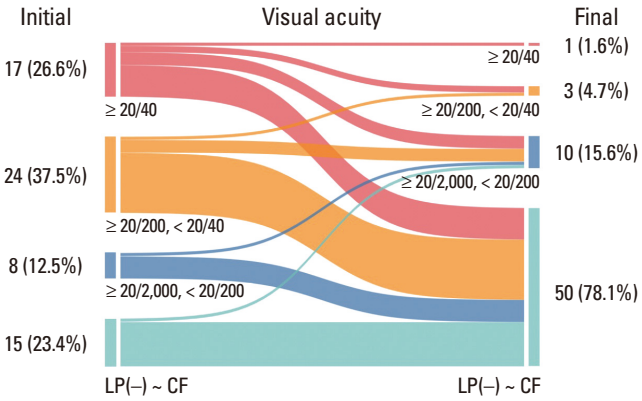

Fig. 2. Distributions of visual acuity at the time of diagnosis and the last follow-up on Sankey diagram. CF, counting finger; LP, light perception.

35 out of 41 patients (85.4%) experienced at least one ocular complication. Of the patients who had complications, only two (4.9%) managed to retain a visual acuity of 20/200 or better. In contrast, two out of six (33.3%) patients without any complications retained visual acuity better than 20/200 (p=0.032).

Discussion

The primary goal for treating UM is local control of the tumor and prevention of recurrence and distant metastasis. The COMS results demonstrated no significant difference in the OS and risk of distant metastasis when comparing the outcomes of enucleation with those of various eye-preserving RT methods [11,12]. In a meta-analysis of 49 articles [13], local treatment failure rates for plaque brachytherapy, photon-based SBRT, and charged particle radiation therapy were 9.5%, 7.9%, and 4.2%, respectively. These findings have promoted a shift towards eye-sparing treatments, resulting in a discernible increase in the number of institutions equipped to provide such therapies, especially particle therapies over time [14,15]. While many patients with UM undergo PBT, geographical disparities in the availability of PBT facilities,—along with variations in insurance coverage for this costly treatment,—highlight the practical necessity for treatment with and research on more accessible options like plaque brachytherapy, photon SRS/SBRT using Gamma Knife, CyberKnife and other photon-based RT. As previously mentioned, UM is significantly rarer in Asia than in Western countries [2,3,16] and reports on photon SRS/SBRT of UM in Asians are scarce. This study is particularly important

Table 4. Univariate and multivariate analysis of risk factors for visual acuity loss to < 20/200 in patients with initial visual acuity ≥ 20/200

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)	0.99 (0.97-1.02)	0.472	-	-
Sex				
Male	1.00 (ref)			
Female	1.78 (0.86-3.67)	0.121	-	-
ECOG PS				
0	1.00 (ref)			
1	0.72 (0.32-1.66)	0.445	-	-
Diameter (mm)	1.08 (0.95-1.23)	0.215	-	-
Height (mm)	1.09 (0.95-1.25)	0.240	-	-
AJCC stage				
II	1.00 (ref)			
III	0.61 (0.14-2.58)	0.499	-	-
GTV (cm^3)	1.50 (1.03-2.18)	0.036	0.87 (0.34-2.22)	0.768
PTV (cm^3)	1.21 (1.02-1.45)	0.031	1.24 (0.79-1.97)	0.352
PTV max dose (Gy)	0.98 (0.91-1.06)	0.655	-	-
PTV mean dose (Gy)	1.01 (0.97-1.05)	0.648	-	-
PTV min dose (Gy)	0.99 (0.96-1.02)	0.680	-	-
Initial visual acuity ≥ 20/40				
No	1.00 (ref)		1.00 (ref)	
Yes	0.40 (0.20-0.79)	0.009	0.45 (0.22-0.93)	0.030

AJCC, American Joint Committee on Cancer; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GTV, gross tumor volume; HR, hazard ratio; PTV, planning target volume.

Table 5. Outcomes and complications of proton and photon therapy in the literature

Study	Particle	No. of patients, median age	Median tumor size diameter/ height	Median radiation dose	Median follow-up (yr)	Oncologic outcomes		Enucleation rate (%)	Percentage visual acuity ≥ 20/200 at the end of follow-up	Complication (%)
						LFFR (%)	Other outcomes (%)			
Fuss (2001) [29]	Proton	n=78, 61 yr	10.0 mm/ 6.0 mm	70 GyE/ 5 fx	2.8	5-Year 90.5	5-Year CSS/DMFS 75.6/76.2	5-Year 24.7	49.1	Glaucoma 17.9 Pain 16.7 Retinal detachment 38.5 Rubeosis 12.8 Vitreous hemorrhage 9.0
Gragoudas (2002) [30]	Proton	n=1,922, 60 yr	13.0 mm/ 5.3 mm	70 GyE/ 5 fx	5.2	5-Year 96.8	n/a	4.1	n/a	n/a
Egger (2003) [31]	Proton	n=2,645, 56 yr	16.0 mm/ 5.8 mm	60 GyE/ 4 fx	3.7	5-Year 95.8	OS 85.1	Tumor size: large 17.3, medium 6.0	n/a	n/a
Aziz (2009) [32]	Proton	n=76, 64 yr	11.7 mm/ 6.2 mm	58 GyE/ 4 fx	3.2	87	DMFS 90.8	24	n/a	Cataract 20 Maculopathy 4 Optic neuropathy 16 Retinopathy 39 Rubeosis iridis 21 Uveitis 17
Caujolle (2010) [33]	Proton	n=886, 63 yr	15.7 mm/ 5.0 mm	60 GyE/ 4 fx	5.3	5-Year 93.9	5-Year OS/DMFS 79.4/88.3	5-Year 8.9	51.2	Cataract 31.7 Glaucoma 17 (neovascular glaucoma 11) Radiation neuropathy 7.8 Radiation retinopathy 27.5
Seibel (2015) [34]	Proton	n=982	12.0 mm/ 4.4 mm	60 GyE/ 4 fx	5.1	5-Year 96.0	5-Year OS/DMFS 89.0/85.0 (local control group), 80.0/ 76.0 (local recur group)	5	n/a	Neovascular glaucoma 12.1
Papakostas (2017) [35]	Proton	n=336, 60 yr	18.0 mm/ 8.7 mm	70 GyE/ 5 fx	7.0	5-Year 92.2	1-Year CSS 97.6 10-Year CSS 51.5	Large tumor 5-Year 22.6	1-Year 48.6 3-Year 22.6 5-Year 15.9	Neovascular glaucoma 25.3
Mosci (2012) [36]	Proton	n=70, 63 yr	14.8 mm/ 10.8 mm	60 GyE/ 4 fx	4.5	2-Year 86	5-Year CSS/DMFS 62/72	Large tumor 5-Year 26	5-year 32.0	n/a

(Continued to the next page)

Table 5. Continued

Study	Particle	No. of patients, median age	Median tumor size diameter/ height	Median radiation dose	Median follow-up (yr)	Oncologic outcomes		Enucleation rate (%)	Percentage visual acuity ≥ 20/200 at the end of follow-up	Complication (%)
						LFFR (%)	Other outcomes (%)			
Kim (2018) [20]	Proton	n=24, 62 yr	11.0 mm / 8.0 mm	60-70 GyE / 4 fx	3.0	3-Year 95.8	3-Year OS/DMFS 100/95.8	3-Year 4.2	33.4	Blurred vision 4.2 Cataract 4.2 (≥ G3) Erythroderma 37.5 Glaucoma 29.2 (≥ G3 8.4) Retinopathy 4.2 Retinal detachment 8.4 Synechia 12.6 (≥ G3 4.2) Vitreous hemorrhage 4.2 (≥ G3)
Jung (2020) [21]	Proton	n=40, 57 yr	17.4 mm / 7.0 mm	60-70 GyE / 5 fx	2.7	3-Year 97.5	3-Year DMFS 93.3	3-Year 11.8	70	Neovascular glaucoma 21.1 Vitreous hemorrhage 16.9
Dunavoelgyi (2011) [24]	Photon	n=212, 60 yr	11.2 mm / 9.9 mm	50-70 Gy / 5 fx	5.4	5-Year 95.9	5-Year OS/DMFS 82.4/84.6	5-Year 21.4	5-Year 8.8	n/a
Muller (2012) [23]	Photon	n=102, 63 yr	11.9 mm / 6.0 mm	50 Gy/5 fx	2.7	96	5-Year DMFS 75	14.7	Best corrected visual acuity (mean value): initial 20/77, 3 months, 20/125, 4 years 20/667	Cataract 22.5 Dry eye 17.6 Glaucoma 12.7 Keratitis 9.8 Optic disc edema 17.6 Radiation retinopathy 39.2 Uveitis 2.0 Vitreous hemorrhage 9.8
Kang (2012) [37]	Photon	n=22, 53 yr	Height 9.5 mm	20-67.5 Gy / 1 fx	5.6	90.9	5-Year OS 90.9	2-Year 13.6 5-Year 22.7	63.6 visual acuity ≥ hand movement	Cataract 40.9 Glaucoma 9.1 Radiation retinopathy 23 Retinal detachment 9.1 Vitreous hemorrhage 9.1

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Table 5. Continued

Study	Particle	No. of patients, median age	Median tumor size diameter/ height	Median radiation dose	Median follow-up (yr)	Oncologic outcomes		Enucleation rate (%)	Percentage visual acuity ≥ 20/200 at the end of follow-up	Complication (%)
						LFFR (%)	Other outcomes (%)			
Wackernagel (2013) [38]	Photon	n=189, 62 yr	11.7 mm/ 6.1 mm	25-80 Gy/ 1 fx	3.3	5-Year 94.4	n/a	14.1	5-Year 13	Cataract 34.5 Glaucoma 17.5 Maculopathy 63.3 Radiation retinopathy 65.5 Retinal detachment 41.2 Rubeosis iridis 19.8 Optic nerve neuropathy 43.5 Tumor vasculopathy 54.8 Vitreous hemorrhage 19.8
Sarici (2013) [39]	Photon	n=50, 53 yr	10.3 mm/ 8.7 mm	30 Gy/1 fx	3.3	90	5-Year OS/DMFS 86/65	5-Year 18	40	n/a
Yazici (2017) [40]	Photon	n=181, 54 yr	10.0 mm/ 8.0 mm	54 Gy/3 fx	2.0	5-Year 73	5-Year OS/PFS/DMFS 98/57/69	5-Year 27	VA stable or increased 66	Cataract 15 Neovascular glaucoma 3 Optic atrophy 4 Radiation papillopathy 11 Radiation retinopathy 42 Retinal detachment 11 Vitreous hemorrhage 4
Modorati (2020) [41]	Photon	n=194, 65 yr	Median volume 475 mm^3	35.8 Gy/ 1 fx	4.8	93.3	n/a	9.3	-	Cataract 41.2 Maculopathy 11.4 Neovascular glaucoma 27.3 Optic neuropathy 18.6 Phthisis bulbi 7.7 Radiation retinopathy 34.5 Vitreous hemorrhage 14.4

(Continued to the next page)

Table 5. Continued

Study	Particle	No. of patients, median age	Median tumor size diameter/ height	Median radiation dose	Median follow-up (yr)	Oncologic outcomes		Enucleation rate (%)	Percentage visual acuity ≥ 20/200 at the end of follow-up	Complication (%)
						LFFR (%)	Other outcomes (%)			
This study	Photon	n=64, 60 yr	11.5 mm / 8.4 mm	60 Gy/4 fx	2.7	3-Year 89.5, 5-Year 89.5	3-Year OS/ PFS/DMFS 89.4/65.5/70.5 5-Year OS/ PFS/DMFS 76.1/50.2/55.2	20.3	6.3	Cataract 23.4 Dry eye syndrome 25.0 Glaucoma 26.6 (neovascular glaucoma 12.5) Maculopathy 14.1 Ocular pain 17.2 Optic neuropathy 1.6 Radiation retinopathy 51.6 Retinal detachment 21.9 Vitreous hemorrhage 18.8

CSS, cancer-specific survival; DMFS, distant metastasis–free survival; LFFR, local failure-free rate; n/a, not available; OS, overall survival; PFS, progression-free survival.

because it focuses on large UMs where brachytherapy cannot be performed, enhancing its importance due to the rarity of such cases. Therefore, our research fills a critical gap by providing valuable data on photon SRS/SBRT for large UMs in Asian populations.

Plaque brachytherapy is generally suitable for treating small tumors, but it tends to be less effective for large tumors. As the tumor size increases, the technical difficulties of plaque insertion escalate, leading to an increased risk of inadequate radiation coverage of the tumor periphery [7,17-19]. PBT, recognized for its efficacy across varying tumor sizes, provides several therapeutic advantages over photon therapy. Beyond their higher relative biological effectiveness compared with that of photons, the Bragg peak effect allows proton beams to exhibit a narrower penumbra, enabling the delivery of higher energy with greater precision and fewer complications [7,20-22]. Defining the penumbra for photon beams can be challenging, as it varies with field size, depth, and photon energy while generally tending to be broader compared to that of proton beams. The photon treatment planning system focuses on optimizing and generating SBRT plans with a steep dose fall-off gradient outside PTV. To achieve this goal, the maximum dose inside the PTV was defined to be greater than 120% as usual, so that the dose fall-off gradient can be steep. The CyberKnife system utilizes a robotic arm that offers a high degree of flexibility in beam delivery, allowing for non-coplanar and highly conformal treatment plans. These non-coplanar and non-isocentric beam configurations can further promote steepness of the dose gradient, contributing to the successful treatment of UM.

The outcomes and complications of UM treated with PBT and photon SRS/SBRT, as documented in the literature, are summarized in Table 5. Local control rates for PBT range from 86% at 2 years to 96.8% at 5 years, whereas photon SRS/SBRT demonstrates a broader range, with 5-year local control rates varying between 73% and 96%. Our data showed a 3-year LFFR of 89.5%, which falls within the range when compared to those reported in the studies summarized in Table 5. This could be attributed to the larger tumor dimensions in our dataset compared to previous data. In the study by Muller et al. [23], the median tumor height was 6.0 mm, compared to 8.4 mm in our study, with LFFR of 96% and 89.5%, respectively. Furthermore, Dunavoelgyi et al. [24] documented a median tumor volume of 0.27 cm^3, compared to 0.95 cm^3 reported in the current study, with an LFFR of 95.9% and 89.5%, respectively. Tumor size is recognized as a critical determinant of local tumor control across various investigations. Nonetheless, we only applied SBRT to large tumors, thus no significant results pertaining to tumor size were observed.

In this study, the 3-year DMFR was 70.5%. This result is

slightly lower than the findings of PBT or other photon-based studies (Table 5), regardless of the success of local control [25-27]. Of the predictive factors affecting treatment outcomes, a larger tumor diameter was associated with a significantly worse prognosis for DMFR and OS in the multivariate analysis.

Visual outcomes in patients with UM are generally poor. In our study, only 6.3% (n=4) of patients maintained visual acuity ≥ 20/200 after treatment among the 41 patients with visual acuity ≥ 20/200 at baseline. Previous studies reported final visual acuity ≥ 20/200 in 15.9%-70.0% of patients treated with PBT and 8.8%-40.0% with photon-based SRS/SBRT (Table 5). The relatively inferior visual outcomes may have been due to the selected population of large tumors in our study. In our analysis, better initial visual acuity (≥ 20/40) was an independent significant factor associated with retaining visual acuity ≥ 20/200. This suggests that patients with better baseline vision have better visual outcomes after treatment. These findings highlight the importance of early UM detection to maximize the chance of preserving visual function, a key goal of eye-preserving treatments.

Our analyses of the complications associated with RT for UM were consistent with those reported by previous literature [28], with enucleation rate ranging from 4.1%-26.0% with PBT, and 9.3%-27.0% with photon SRS/SBRT, respectively (Table 5). Notably, although the enucleation rate in this study was 20.3% (n=13), the majority of enucleations were performed due to complications (15.6%, n=10), with only 4.7% (n=3) attributed to tumor progression. This implies that if access to PBT or carbon ion therapy were to improve, it could potentially reduce complications and thereby significantly decrease the enucleation rate. In addition, in the univariate analysis of the enucleation-free rate in S5 Table, GTV and PTV were significant predictive factors of enucleation. This suggests that the enucleation rate may be influenced by the tumor size at the time of diagnosis, underlining the importance of early detection of UM.

This study has several limitations. One notable limitation pertains to the treatment planning process. During the planning process, only the optic chiasm, lacrimal gland, and optic nerve were contoured, while structures such as the ciliary body, macula, optic disc, and retina were not delineated. This was because our approach focused on ensuring adequate PTV coverage in accordance with the prescribed dose, rather than reducing the dose to these OARs. Table 5 describes the incidence of normal tissue toxicities among modalities. As the table shows, the incidence of neovascular glaucoma in this study was slightly higher than that of other studies. We may achieve better toxicity outcomes in the future if we delineate the ciliary body, macula, disc, and retina. Among the treated patients, two received a relatively low dose radiation because the tumor was located anteriorly; one received 56 Gy in 4 fx, and the other received 48 Gy in 4 fx. These patients were at a substantial risk of developing neovascular glaucoma; however, the occurrence of neovascular glaucoma was averted by administering a dose lower than the prescribed amount. The patient who received 56 Gy in 4 fx developed serous retinal detachment, vitreous hemorrhage, and cataract, whereas the patient who received 48 Gy in 4 fx developed only vitreous hemorrhage. Another major limitation attributable to this study's retrospective design is the possible effect of selection bias. For instance, excluding patients who lack post-RT follow-up data could artificially increase the survival rates observed in the cohorts. Additionally, toxicity evaluations were possibly conducted less rigorously in this study than in prospective studies. This discrepancy could have led to the underestimation or inconsistent reporting of adverse effects associated with treatment, further complicating the interpretation of the study's outcomes. Nevertheless, despite its retrospective nature, the study was meticulously conducted with thorough ophthalmic examinations, and the patients were treated and monitored following a uniform protocol at a single center. Another limitation is the rarity of the disease and the confinement of data collection to a single center, which resulted in a restricted patient sample, thereby imposing constraints on the study. This may have reduced the statistical robustness of the analysis. To strengthen the robustness of our findings, it would be beneficial to conduct future research with a larger sample size and longer follow-up, potentially through multicenter studies. This would allow for more comprehensive clinical data and enhance the validity of our conclusions.

This study demonstrates the potential of SBRT to achieve excellent local control rates in patients with large UMs. However, limitations, such as distant metastasis and adverse effects leading to enucleation, have been identified. Future research should focus on investigating novel treatment approaches aimed at reducing distant metastases and minimizing side effects.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines defined by the International Conference on Harmonization and approved by the Institutional Review Board of Severance Hospital (4-2023-1178, date of approval November 2, 2023). Patient records and information were anonymized and de-identified prior to the analysis. Informed consent was not obtained from participants because of the retrospective nature of the study.

Author Contributions

Conceived and designed the analysis: Park JW, Jun S, Kim KH.
Collected the data: Park JW, Jun S.
Contributed data or analysis tools: Park JW, Jun S, Kim KH.
Performed the analysis: Park JW, Jun S.
Wrote the paper: Park JW, Jun S, Kim KH.
Done the most of the primary work including revision: Park JW.
Discussed: Keum KC, Lee CS.
From introduction to conclusion, directing the research focus and guiding the analysis: Kim KH.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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