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Scientific Article

Carbon Ion Versus Photon-based Stereotactic Ablative Radiation Therapy for Patients with Choroidal Melanoma

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Purpose: To our knowledge, no study has compared the treatment outcomes of carbon ion radiation therapy (CIRT) and photon-based stereotactic ablative radiation therapy (SABR) in patients with choroidal melanoma. This study aimed to evaluate the treatment outcomes of patients with choroidal melanoma treated with CIRT or photon-based SABR.

Methods and Materials: This study included 346 patients with localized choroidal melanoma who received CIRT or photon-based SABR between April 2001 and November 2021. Patients in the CIRT group received a median of 70 Gy delivered in a median dosage of 14 Gy per fraction, and patients in the SABR group received a median of 60 Gy delivered in a median dosage of 15 Gy per fraction. Propensity score matching (PSM) was performed to account for differences between the 2 groups. The main outcome was progression-free survival (PFS) in the PSM cohort, and secondary endpoints included overall survival, cumulative incidence of local and distant failures, and enucleation.

Results: In all, 282 and 64 patients were included in the CIRT and SABR groups. After PSM, the 5-year PFS was significantly superior in the CIRT group to that in the SABR group (69.0% vs 56.5%, $P = .024$). The CIRT group also showed significantly reduced risks of local failure (5-year local failure rate 5.6% vs 13.4%, $P = .025$) and enucleation (5-year enucleation rate 8.5% vs 24.2%, $P < .001$). Moreover, CIRT was superior in terms of visual acuity preservation: the proportion of patients with visual acuity of ≥20/200 decreased from 64.7% initially to 23.7% at last follow-up in the CIRT group and from 64.1% to 6.3% in the SABR group ($P = .005$).

Conclusions: CIRT was found to be superior to SABR in patients with choroidal melanoma in terms of PFS, local control, and preservation of vision and eye.

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Research data are stored in an institutional repository and will be shared on request to the corresponding author.

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Introduction

Although choroidal melanoma is rare, it is the most prevalent primary malignant tumor of the eye in adults.[1] Incidence rates vary globally, with the relative risk of developing choroidal melanoma being the highest in Caucasians, followed by Hispanics, Asians, and Blacks.[2] Risk factors for choroidal melanoma include light-colored eye or skin, dysplastic nevus syndrome, ocular melanocytosis, and xeroderma pigmentosum.[3-5] Treatment decisions are influenced by several factors, including the visual acuity of both the affected and the contralateral eye, tumor size and location, involvement of surrounding ocular structures, and presence of distant metastasis.[6]

Treatment options for localized choroidal melanoma typically involve either enucleation or eye-conserving approaches, with the more common methods being brachytherapy, stereotactic ablative radiation therapy (SABR), and proton beam therapy (PBT), while less common options include carbon ion radiation therapy (CIRT).[7] In a randomized clinical trial comparing iodine-125 brachytherapy with enucleation, no significant difference in mortality rates was observed, and increasing attention is being given to promoting eye-conserving approaches for choroidal melanoma.[8] SABR is used to deliver high-dose radiation to the target area while minimizing the risk of complications, particularly in cases of large tumors.[9] The 5-year local control rate after SABR varies from 82% to 95.9% in cases of choroidal melanoma.[10,11] The advantages of CIRT include its high linear energy transfer (LET), resulting in a high relative biological effectiveness (RBE), and its sharp penumbra, allowing for precise dose distribution and, thus, showing superior biological effects to SABR in patients with radioresistant tumors including malignant melanoma.[12] A phase 1/2 study from a Japanese group enrolled 59 patients with locally advanced or unfavorably located choroidal melanoma and reported a 3-year local control rate of 97.4% after CIRT.[13] However, CIRT is currently being applied to a limited number of patients because of its restricted accessibility, and no comparative studies with other modalities have been conducted yet.

In this study, we aimed to compare the treatment outcomes of CIRT and photon-based SABR in patients with choroidal melanoma. We performed a comprehensive analysis of treatment outcomes, changes in visual acuity, and treatment-related toxicity of patient cohorts from 2 institutions in South Korea and Japan.

Methods and Materials

Study population

The medical records of patients treated at 2 institutions for choroidal melanoma were reviewed. Patients in the CIRT group were treated at a CIRT center in Japan between April 2001 and September 2021, and patients in the SABR group were treated at a tertiary hospital in South Korea between August 2015 and November 2021.

Patients who had extraocular extension or distant metastasis at diagnosis or those who had not had at least 1 follow-up after treatment were excluded. In total, 346 patients were included in this analysis. This study was approved by the Institutional Review Board of each participating institution (Severance Hospital IRB approval no. 4-2023-0947, QST IRB approval no. N23-021, UMIN registration no. UMIN000053540), and the requirement for informed consent was waived because of the retrospective nature of the study.

Treatment

For patients in the CIRT group, 2 titanium markers were sutured to the outer surface of the sclera by a skilled ophthalmologist before treatment planning. Immobilization was achieved using a head frame connected to a bite block, and patients were told to stare at an light-emitting diode light to fix eye movement. A planning computed tomography (CT) with 1-mm slice thickness was obtained, and target delineation was conducted with planning CT/contrast-enhanced orbit magnetic resonance imaging (MRI) fusion. Gross tumor volume (GTV) was defined as the gross tumor seen on planning CT and contrast-enhanced orbit MRI, and planning target volume was generated with a 1- to 2-mm safety margin around the GTV. The radiation therapy (RT) dose was 60 to 70 Gy, delivered in 5 fractions initially, later revised to 64 Gy delivered in 4 fractions and 68 Gy delivered in 4 fractions over the years. The CIRT dose was the relative biological effectiveness-weighted dose, based on the modified microdosimetric kinetic model.[14,15] Beam planning was started with a single vertical fixed beam that later evolved to 1 vertical and 1 horizontal fixed beam and further to 2-port beams by rotating gantry over the years.[16]

Patients in the SABR group were treated with Cyberknife (Accuray), a modality for photon-based stereotactic surgery or SABR. Patients were immobilized using a thermoplastic mask with an acrylic frame to attach a camera. The camera was used for continuous monitoring of the position of the iris through the institutionally developed gaze-tracking program. Planning CT with 1-mm slice thickness was obtained, and the GTV was delineated according to the findings of orbit MRI. The planning target volume was defined as GTV +2-mm margin. A total dose of 60 Gy in 4 fractions was prescribed to the 75% isodose line.[17]

After completion of RT, the patients were followed up every 3 months for the first 2 years, and every 6 months thereafter. Each follow-up session consisted of ophthalmic examinations, including visual acuity assessments, B-scan ultrasonography, or orbit MRI. Systemic assessment with abdominopelvic CT, chest CT, liver MRI or ultrasonography, as appropriate, was performed on signs of tumor progression or at the physicians' discretion. Treatment-related toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analysis

Propensity score matching (PSM) was performed to overcome differences in patient and tumor characteristics between the 2 groups. A 1:3 PSM with the nearest-neighbor method and a caliper width of 0.2 was conducted to account for statistical differences in sex, age, tumor diameter, tumor height, and T stage between the 2 groups. For analyses of overall survival (OS) and progression-free survival (PFS), defined as the duration from the date of RT initiation to the date of event, the Kaplan-Meier method with log-rank test was used. Competing risk analysis was performed to calculate the cumulative incidence of local and distant failures as well as enucleation, and Gray's test was used for statistical comparisons. Cox regression analysis was performed to identify factors associated with treatment failure. P values < .05 were considered statistically significant. Data analysis was performed with SPSS Statistics for Windows software version 28.0.0.0 (IBM Corp.) and RStudio version 2024.09.1 + 394 (Posit). R packages "survminer," "MatchIt," and "networkD3" were used for survival plot, PSM, and Sankey diagram, respectively.

Results

Baseline characteristics

Patient and tumor characteristics of the 2 groups are shown in Table 1. Before PSM, the CIRT group had more females and more patients with smaller tumor height, T1-2 tumors, and good visual acuity than the SABR group. After PSM, 192 and 64 patients remained in the CIRT and SABR groups, respectively, and all factors including sex, age, tumor diameter, tumor height, T stage, and visual acuity were well balanced between the 2 groups. The median tumor diameters were 12 mm (range, 4.0-19.6 mm) and 11.5 mm (range, 6.2-18.4 mm) for the CIRT and SABR groups (P = .602), and median tumor heights were 8.3 mm (range, 2.0-17.0 mm) and 8.4 mm (range, 3.6-18.2 mm) for the CIRT and SABR groups, respectively (P = .716).

Treatment outcomes

The median follow-up periods were 70.2 months and 51.9 months for the CIRT and SABR groups, respectively. OS, PFS, and local and distant failure incidences of the overall patient cohort are shown in Supplementary Fig. E1. In the overall patient cohort, CIRT was superior to SABR in all aspects. Figure 1 shows the survival results of the 2 groups in the PSM cohort. While no statistically significant difference was observed between the 2 groups in terms of the 5-year OS (CIRT: 81.0%, 95% CI, 75.2%-87.2% vs SABR: 70.9%, 95% CI, 60.0%-83.9%, P = .1) (Fig. 1a), a survival benefit in the CIRT group was observed in terms of PFS: the 5-year PFS was 69.0% (95% CI, 62.4%-76.3%) in the CIRT group and 56.5% (95% CI, 45.0%-71.0%) in the SABR group (P = .024) (Fig. 1b). The CIRT group also showed a significantly lower local failure rate than the SABR group: the 5-year local failure rate was 5.6% (95% CI, 2.0%-9.3%) for the CIRT group and 13.4% (95% CI, 4.6%-22.2%) for the SABR group (P = .025) (Fig. 1c). The 5-year distant failure rate showed no significant difference between the 2 groups (CIRT: 27.5%, 95% CI, 20.6%-34.3% vs SABR: 35.0%, 95% CI, 22.1%-47.9%; P = .13) (Fig. 1d). A total of 85 patients developed distant metastases. Among these patients, the liver was the most common site of failure (n = 60, 70.6%), followed by the lungs (n = 12, 14.1%). Sixty-eight patients died, and the majority of deaths were attributed to disease progression (n = 57, 83.8%), most frequently due to extensive hepatic metastases.

The factors associated with PFS are listed in Table 2. Before PSM, CIRT, female sex, younger age, smaller tumor diameter and height, and initial visual acuity of ≥20/200 were significantly associated with improved PFS in the univariate analysis. CIRT remained a significant factor for improved PFS after adjusting other significant factors in the multivariate analysis (hazard ratio (HR), 2.32, 95% CI, 1.32-4.08, P = .004). After PSM, CIRT, younger age, and smaller tumor diameter were significant factors associated with improved PFS in the univariate analysis. Again, CIRT remained as a significant factor for improved PFS in the multivariate analysis (HR, 3.04; 95% CI, 1.59-5.83, P < .001). The results of univariate and multivariate analyses of factors associated with OS, local failure, and distant failure are shown in Supplementary Tables E1 to E3. Younger age and smaller tumor diameter were common significant factors predicting improved OS, local failure, and distant failure.

Supplementary Figure E2 shows the cumulative incidence of enucleation in the overall patient cohort. In the total cohort, 21 (7.4%) and 14 (21.9%) patients underwent enucleation in the CIRT and SABR groups, respectively. In the PSM cohort, 16 (8.3%) and 14 (21.9%) patients underwent enucleation in the CIRT and SABR groups. The 5-year cumulative incidence of enucleation was higher in the SABR group (CIRT: 8.5%, 95% CI, 4.2%-12.9% vs SABR: 24.2%, 95% CI, 12.9%-35.4%, P < .001) (Fig. 2). Regarding the cause of enucleation, cancer progression was the major reason for enucleation in the CIRT group (10 of 16 patients, 62.5%), whereas treatment-related toxicity was the major reason for

Table 1 Baseline characteristics of the CIRT and SABR groups before and after PSM.

	Before PSM					After PSM				
	CIRT (n = 282)		SABR (n = 64)			CIRT (n = 192)		SABR (n = 64)		
	Median/N	Range/%	Median/N	Range/%	*P* value	Median/N	Range/%	Median/N	Range/%	*P* value
Sex										
Male	135	47.9	40	62.5	.038	115	59.9	40	62.5	.712
Female	147	52.1	24	37.5		77	40.1	24	37.5	
Age (y)	56.0	15.0-89.0	60.0	27.2-90.5	.091	60.0	23.0-89.0	60.0	27.2-90.5	.332
Tumor diameter (mm)	11.0	4.0-20.0	11.5	6.2-18.4	.233	12.0	4.0-19.6	11.5	6.2-18.4	.602
Tumor height (mm)	7.5	1.8-17.0	8.4	3.6-18.2	.011	8.3	2.0-17.0	8.4	3.6-18.2	.716
T stage										
T1	52	18.4	0	0	<.001	11	5.7	0	0	.132
T2	109	38.7	24	37.5		68	35.4	24	37.5	
T3	106	37.6	38	59.4		99	51.6	38	59.4	
T4	15	5.3	2	3.1		14	7.3	2	3.1	
Initial visual acuity*										
≥20/40	130	46.9	17	26.6	.005	73	38.4	17	26.6	.132
20/200∼20/40	64	23.1	24	37.5		50	26.3	24	37.5	
20/2000∼20/200	33	11.9	8	12.5		29	15.3	8	12.5	
Counting fingers	20	7.2	3	4.7		14	7.4	3	4.7	
Hand motion	11	4.0	9	14.1		10	5.3	9	14.1	
Light perception (+)	14	5.1	2	3.1		10	5.3	2	3.1	
Light perception (−)	5	1.8	1	1.6		4	2.1	1	1.6	
RT total dose (Gy)	70	60-85	60	48-64	<.001	70	60-85	60	48-64	<.001
RT fraction dose (Gy)	14	12-17	15	12-16	.118	14	12-17	15	12-16	.066

Abbreviations: CIRT = carbon ion radiation therapy; PSM = propensity score matching; RT = radiation therapy; SABR = stereotactic ablative radiation therapy.
*Initial visual acuity was measured in 277 patients before PSM and in 190 patients after PSM in the CIRT cohort.

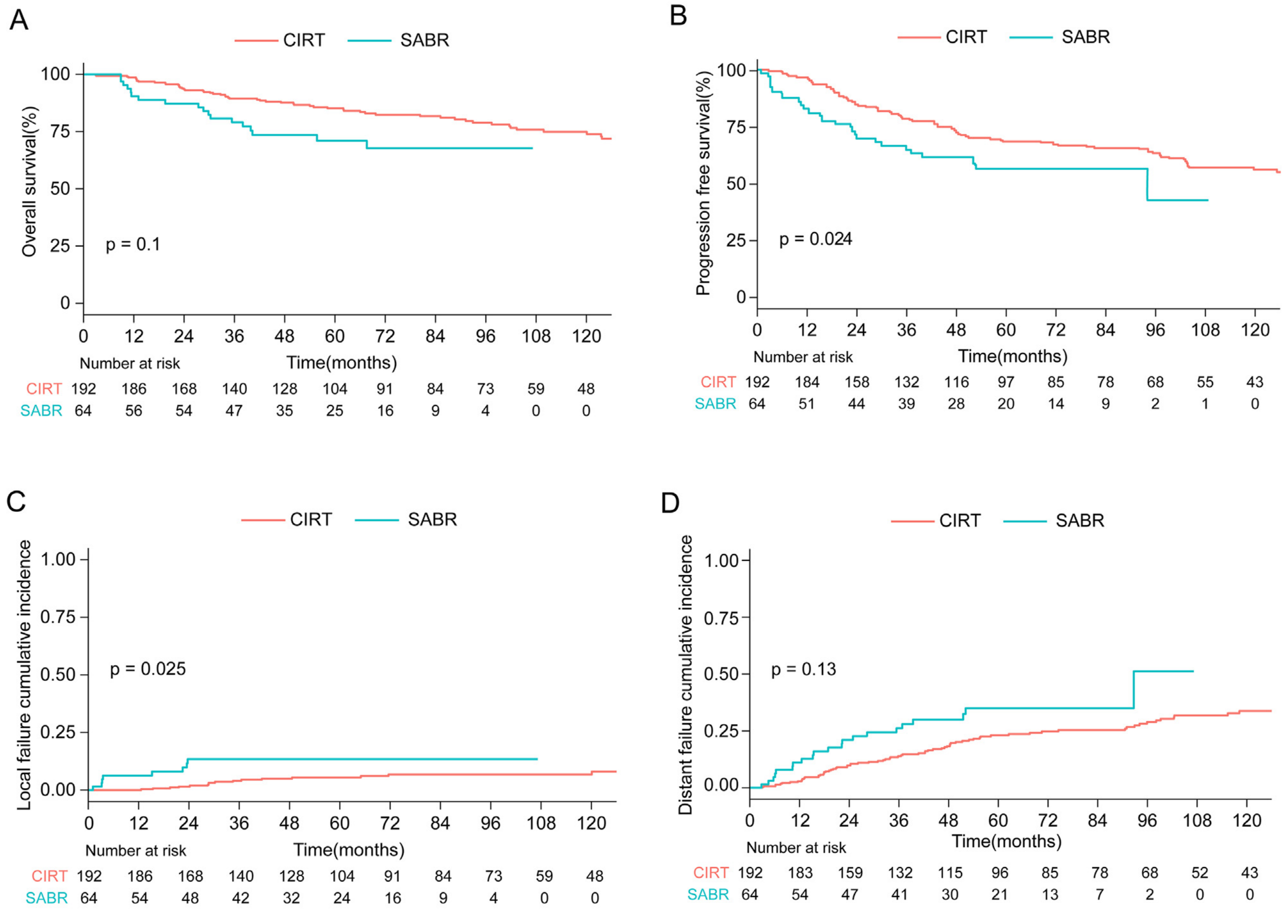

Figure 1 Treatment outcomes of the carbon ion radiation therapy (CIRT) and stereotactic ablative radiation therapy (SABR) groups. Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival, and cumulative incidence of (C) local failure and (D) distant metastasis of the CIRT and SABR groups in the propensity score-matched patient cohort.

enucleation in the SABR group (9 of 14 patients, 64.3%). Risk factors associated with enucleation are listed in Supplementary Table E4. Before PSM, CIRT, female sex, younger age, smaller tumor diameter and height, and initial visual acuity of ≥20/200 were significant factors predicting less enucleation in the univariate analysis. CIRT remained significant after adjusting other significant factors in the multivariate analysis (HR, 2.63; 95% CI, 1.64-4.21, P < .001). After PSM, CIRT, younger age, and smaller tumor diameter were significant factors associated with less enucleation in the univariate analysis, and CIRT remained significant after adjusting for other significant factors in the multivariate analysis (HR, 2.52; 95% CI, 1.55-4.09, P < .001).

Changes in visual acuity

Initial and final visual acuity of patients in the CIRT and SABR groups after PSM are shown in Fig. 3 (data shown as n [%]). In the CIRT group, 123 patients (64.7%) initially had a visual acuity of ≥20/200, but only 45 patients (23.7%) had a visual acuity of ≥20/200 at the last follow-up. In the SABR group, 41 patients (64.1%) initially had a visual acuity of ≥20/200, but only 4 patients (6.3%) had a visual acuity of ≥20/200 at the last follow-up (P = .005).

Regarding factors associated with visual acuity loss to <20/200 in patients with initial visual acuity ≥20/200, CIRT, smaller tumor diameter and tumor height, and initial visual acuity ≥20/40 were significant factors predicting visual acuity preservation in the univariate analysis. CIRT, along with smaller tumor height and initial visual acuity ≥20/40 remained significant factors for visual acuity preservation in the multivariate analysis (SABR: HR, 3.59; 95% CI, 1.18-10.94, P = .024) (Supplementary Table E5). Glaucoma posttreatment was reported in 86 (30.5%) and 11 (17.2%) patients in the CIRT and SABR groups, respectively.

Discussion

In this study, we compared the treatment outcomes of CIRT and photon-based SABR in patients with choroidal melanoma and observed superior outcomes in terms of

Table 2 Factors associated with progression-free survival in the overall and the propensity score-matched cohort.

	Before PSM						After PSM					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Modality												
CIRT	1.00			1.00			1.00			1.00		
SABR	2.01	1.30-3.12	.002	2.32	1.32-4.08	.004	1.68	1.07-2.65	.025	3.04	1.59-5.83	<.001
Sex												
Male	1.00			1.00			1.00			1.00		
Female	0.62	0.44-0.87	.007	0.74	0.52-1.07	.108	0.72	0.48-1.08	.108	0.70	0.47-1.06	.094
Age (y)	1.02	1.01-1.03	<.001	1.02	1.01-1.04	<.001	1.02	1.01-1.04	.004	1.02	1.01-1.04	.002
Tumor diameter (mm)	1.23	1.15-1.31	<.001	1.26	1.17-1.36	<.001	1.18	1.10-1.27	<.001	1.25	1.15-1.35	<.001
Tumor height (mm)	1.10	1.03-1.17	.003	0.98	0.90-1.05	.506	1.02	0.94-1.09	.674	0.94	0.86-1.02	.140
Initial visual acuity ≥20/200												
Yes	1.00			1.00			1.00			1.00		
No	1.48	1.03-2.11	.032	1.32	0.91-1.92	.146	1.39	0.94-2.06	.101	1.36	0.90-2.06	.141
RT total dose (Gy)	1.01	0.97-1.04	.672	1.03	0.99-1.07	.186	1.02	0.98-1.06	.454	1.04	0.99-1.08	.082
RT fraction dose (Gy)	1.06	0.94-1.20	.319				1.08	0.93-1.26	.316			

Abbreviations: CIRT = carbon ion radiation therapy; HR, hazard ratio; PSM = propensity score matching; RT = radiation therapy; SABR = stereotactic ablative radiation therapy.

tumor control and eye preservation, as well as visual acuity preservation in the CIRT group. While PBT or plaque brachytherapy are considered the established treatments for choroidal melanoma, PBT has limited accessibility, and plaque brachytherapy is suitable primarily for patients with tumors of appropriate size and location. Brachytherapy can be applied to tumors up to approximately 12 mm in height and with a basal diameter of ≤16 mm at centers of excellence, achieving excellent local control and eye preservation rates; however, tumors located near critical structures such as the macula or optic disc require careful planning. As a result, patients with larger or unfavorably located tumors are often treated with photon-based SABR.[18] Additionally, although individual studies have reported the outcomes with the CIRT, it has not yet been proven to be superior to photon-based SABR. To our knowledge, this study is the first to directly compare the treatment outcomes of CIRT versus photon-based SABR in patients with choroidal melanoma. Given that no prospective phase 3 trial is currently underway and no immediate results are expected, our study provides valuable clinical data on this matter.

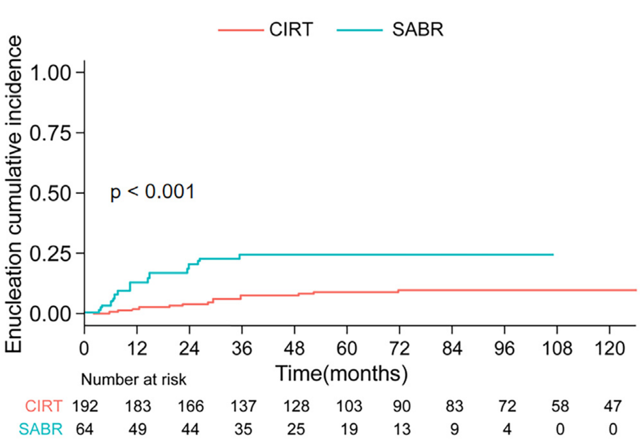

Figure 2 Cumulative incidence of enucleation. Cumulative incidence of enucleation of the carbon ion radiation therapy (CIRT) and stereotactic ablative radiation therapy (SABR) groups in the propensity score-matched patient cohort.

We found that CIRT was superior to photon-based SABR in terms of PFS and local control. The 5-year local failure rates reported in this study were 5.6% and 13.4% for the CIRT and SABR groups, respectively. Because of the relatively short history of CIRT and the limited number of institutions offering this treatment worldwide, clinical data regarding CIRT compared to data regarding photon-based RT or PBT are scarce. However, the physical and biological properties of CIRT, including its precise dose localization and high LET, have been extensively studied and are well established.[19] The high LET of CIRT is associated with a higher RBE and a lower oxygen enhancement ratio, which may contribute to its potential advantages in treating radioresistant tumors, such as

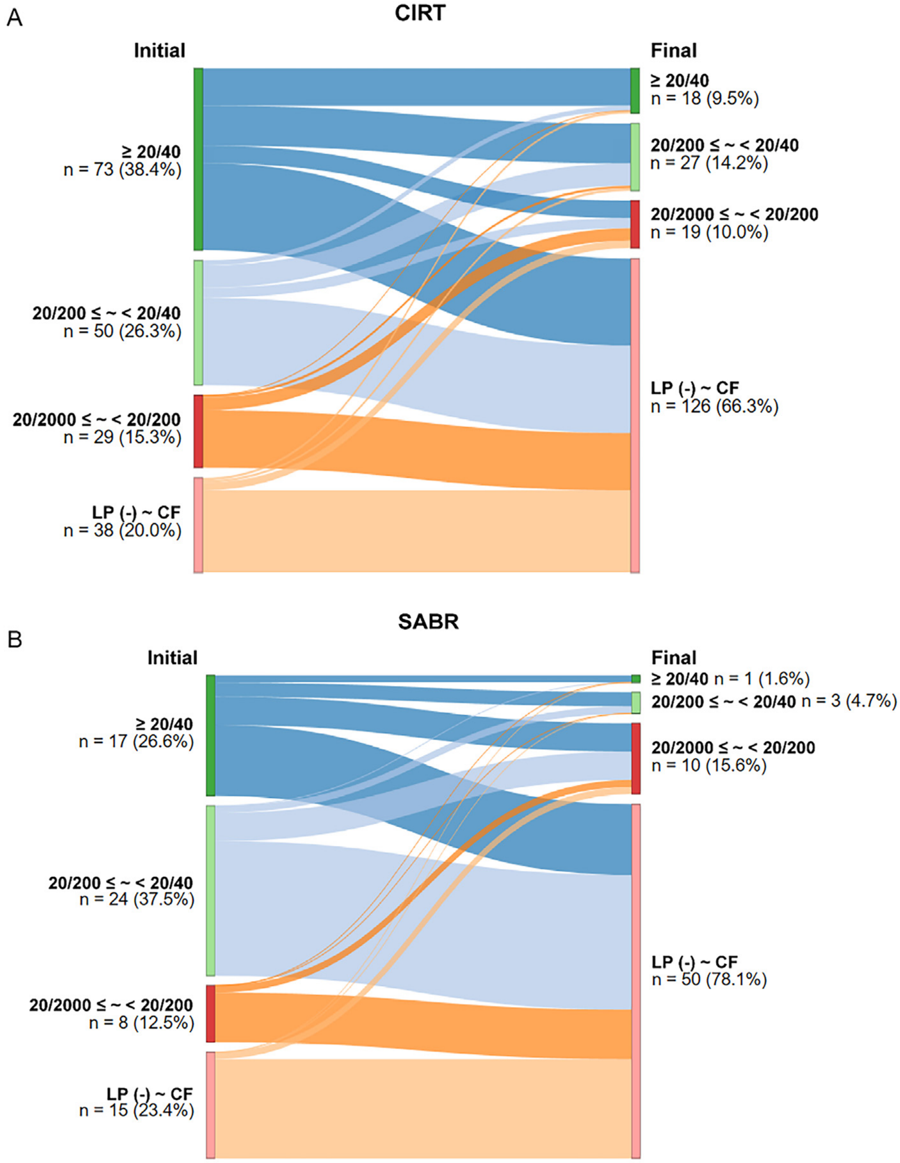

Figure 3 Changes in visual acuity. Sankey diagram showing changes in visual acuity of the (A) carbon ion radiation therapy (CIRT) and (B) stereotactic ablative radiation therapy (SABR) groups. *Abbreviations*: LP, light perception; CF, counting fingers.

adenocarcinomas, sarcomas, and malignant melanomas.[20] Despite the fact that SABR is known to cause more sublethal damage than conventionally fractionated RT, carbon ion beams can induce increased lethal damage to tumor cells because of their superior inherent properties.[21,22] While PBT also offers a superior dose distribution profile compared to photon-based RT, it has a relatively lower RBE and a less steep lateral dose fall-off than CIRT.[23] Although no direct comparative studies between CIRT and PBT have been conducted specifically for choroidal melanoma, the review of existing literature suggests that CIRT offers similar or slightly superior tumor control rates, with PBT showing a 5-year local failure-free rates of 87% to 96%.[24-26] Such findings underscore the need for further direct comparisons between the different RT modalities to fully evaluate the relative effectiveness of CIRT.

Factors associated with PFS included treatment modality, age, and tumor diameter. Age and tumor size have been identified as prognostic factors in choroidal melanoma in many studies.[27-30] Shammas et al[27] hypothesized that younger patients may be diagnosed at an earlier stage of the disease. Larger tumors are thought to spread more easily, likely because of the longer duration of metastasis and shorter doubling times.[31] Nevertheless, despite superior local tumor control with CIRT compared to that with SABR, no significant benefit in terms of distant metastasis or OS was observed in our study. With more effective systemic control, the local control benefit of CIRT may be translated into an OS benefit.

Another finding of this study was that CIRT was superior in terms of eye preservation compared to SABR. Moreover, while more patients received enucleation for cancer progression in the CIRT group, more patients received enucleation for other reasons than cancer progression in the SABR group, including treatment-related toxicities. Previous studies have reported a globe preservation rate of approximately 80% after photon-based RT, which is lower than the 90% observed with PBT.[11,32-36] The reduction in enucleation because of ocular toxicity with CIRT or PBT is likely because of the decreased impact on the surrounding normal eye tissues because of the sharp penumbra and Bragg peak of charged particle beams.[37,38] While no study has directly compared the ocular toxicity rates of CIRT and PBT, carbon ion beams are known to have sharper penumbras than proton beams.[39] Therefore, CIRT may have benefits not only in terms of better tumor control but also for its reduced treatment-related toxicity and increased potential for eye conservation. Regarding specific adverse events, the incidence of glaucoma was higher in the CIRT group. This finding is likely attributable to the beam arrangement used during the early treatment period. Over the years, the CIRT technique evolved from the use of a single vertical beam to a 2-beam configuration (vertical and horizontal), and later to the adoption of rotating gantries and scanning delivery.[40] These technical improvements are expected to have contributed to a lower incidence of glaucoma in more recent years.

The primary limitation of this study is that we could not compare treatment outcomes of CIRT or photon-based SABR with PBT, a well-established treatment method for ocular tumors.[36] Other limitations lie in its retrospective nature. The CIRT group included patients treated over 18 years, a treatment duration that is almost 3 times longer than that of the SABR group. The median follow-up duration was also longer for the CIRT group. The SABR group had more aggressive tumor features, such as larger tumor height and a higher proportion of patients with ≥T3 tumors. At the institution where SABR was conducted, brachytherapy with Ruthenium-106 eye plaque is preferred for small tumors of ≤6 mm, and this may have caused selection bias.[41] In addition, the 2 cohorts were derived from different institutions located in different countries, which may have introduced further unknown biases. Nevertheless, PSM was performed to account for such differences. Despite the rarity of the disease in the Asian population, we have included a relatively large patient cohort and observed meaningful findings in both the overall and PSM cohorts.

In conclusion, the findings of this study suggest that CIRT may be associated with improved tumor control, eye preservation, and visual acuity preservation compared with SABR in patients with choroidal melanoma. However, given the retrospective design of this study, these observations should be interpreted with caution, and further prospective randomized trials are warranted to confirm the potential benefits of CIRT and to guide optimal treatment selection for patients with choroidal melanoma. Although CIRT is not accessible to all patients, this treatment option may be considered in settings where the facilities are available to achieve the best possible outcomes in tumor control and vision preservation.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2025.101915.

References

1. Branisteanu DC, Bogdanici CM, Branisteanu DE, et al. Uveal melanoma diagnosis and current treatment options. *Exp Ther Med*. 2021;22:1-8.
2. Kaliki S, Shields CL. Uveal melanoma: relatively rare but deadly cancer. *Eye*. 2017;31:241-257.
3. Hammer H, Oláh J, Tóth-Molnár E. Dysplastic nevi are a risk factor for uveal melanoma. *Eur J Ophthalmol*. 1996;6:472-474.
4. Shields CL, Kaliki S, Livesey M, et al. Association of ocular and oculodermal melanocytosis with the rate of uveal melanoma metastasis: analysis of 7872 consecutive eyes. *JAMA Ophthalmol*. 2013;131:993-1003.
5. Weis E, Shah CP, Lajous M, Shields JA, Shields CL. The association between host susceptibility factors and uveal melanoma: A meta-analysis. *Arch Ophthalmol*. 2006;124:54-60.
6. Singh P, Singh A. Choroidal melanoma. *Oman J Ophthalmol*. 2012;5:3-9.
7. Groenewald C, Konstantinidis L, Damato B. Effects of radiotherapy on uveal melanomas and adjacent tissues. *Eye*. 2013;27:163-171.
8. Chang MY, McCannel TA. Local treatment failure after globe-conserving therapy for choroidal melanoma. *Br J Ophthalmol*. 2013;97:804-811.
9. Kosydar S, Robertson JC, Woodfin M, et al. Systematic review and meta-analysis on the use of photon-based stereotactic radiosurgery versus fractionated stereotactic radiotherapy for the treatment of uveal melanoma. *Am J Clin Oncol*. 2021;44:32-42.
10. Akbaba S, Foerster R, Nicolay NH, et al. Linear accelerator-based stereotactic fractionated photon radiotherapy as an eye-conserving treatment for uveal melanoma. *Radiat Oncol*. 2018;13:1-9.
11. Dunavoelgyi R, Dieckmann K, Gleiss A, et al. Local tumor control, visual acuity, and survival after hypofractionated stereotactic photon

radiotherapy of choroidal melanoma in 212 patients treated between 1997 and 2007. *Int J Radiat Oncol Biol Phys*. 2011;81:199-205.
12. Li C, Zhang Q, Li Z, et al. Efficacy and safety of carbon-ion radiotherapy for the malignant melanoma: A systematic review. *Cancer Med*. 2020;9:5293-5305.
13. Tsuji H, Ishikawa H, Yanagi T, et al. Carbon-ion radiotherapy for locally advanced or unfavorably located choroidal melanoma: A phase I/II dose-escalation study. *Int J Radiat Oncol Biol Phys*. 2007;67:857-862.
14. Inaniwa T, Furukawa T, Kase Y, et al. Treatment planning for a scanned carbon beam with a modified microdosimetric kinetic model. *Phys Med Biol*. 2010;55(22):6721.
15. Kase Y, Kanai T, Matsufuji N, Furusawa Y, Elässer T, Scholz M. Biophysical calculation of cell survival probabilities using amorphous track structure models for heavy-ion irradiation. *Phys Med Biol*. 2008;53(1):37.
16. Aoki S, Wakatsuki M, Tsuji H, et al. Long-term outcomes of ocular and visual preservation after carbon ion radiation therapy for choroidal malignant melanoma. *Int J Radiat Oncol Biol Phys*. 2025;121(4):991-999.
17. Park JW, Jun S, Keum KC, Lee CS, Kim KH. Outcomes of stereotactic body radiation therapy for large uveal melanoma: A retrospective analysis of Asian population. *Cancer Res Treat*. 2025;57(4):1218-1230.
18. Liegl R, Schmelter V, Fuerweger C, et al. Robotic CyberKnife radiosurgery for the treatment of choroidal and ciliary body melanoma. *Am J Ophthalmol*. 2023;250:177-185.
19. Ohno T. Particle radiotherapy with carbon ion beams. *EPMA J*. 2013;4:1-7.
20. Suit H, DeLaney T, Goldberg S, et al. Proton vs carbon ion beams in the definitive radiation treatment of cancer patients. *Radiother Oncol*. 2010;95:3-22.
21. Kamada T, Tsujii H, Blakely EA, et al. Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience. *Lancet Oncol*. 2015;16:e93-e100.
22. Espenel S, Vallard A, Rancoule C, et al. Melanoma: Last call for radiotherapy. *Crit Rev Oncol Hematol*. 2017;110:13-19.
23. Tinganelli W, Durante M. Carbon ion radiobiology. *Cancers*. 2020;12:3022.
24. Fuss M, Loredo LN, Blacharski PA, Grove RI, Slater JD. Proton radiation therapy for medium and large choroidal melanoma: preservation of the eye and its functionality. *Int J Radiat Oncol Biol Phys*. 2001;49:1053-1059.
25. Egger E, Zografos L, Schalenbourg A, et al. Eye retention after proton beam radiotherapy for uveal melanoma. *Int J Radiat Oncol Biol Phys*. 2003;55:867-880.
26. Aziz S, Taylor A, McConnachie A, Kacperek A, Kemp E. Proton beam radiotherapy in the management of uveal melanoma: Clinical experience in Scotland. *Clin Ophthalmol*. 2009;3:49-55.
27. Shammas HF, Blodi FC. Prognostic factors in choroidal and ciliary body melanomas. *Arch Ophthalmol*. 1977;95:63-69.
28. Damato BE, Heimann H, Kalirai H, Coupland SE. Age, survival predictors, and metastatic death in patients with choroidal melanoma: Tentative evidence of a therapeutic effect on survival. *JAMA Ophthalmol*. 2014;132:605-613.
29. Schmittel A, Bechrakis NE, Martus P, et al. Independent prognostic factors for distant metastases and survival in patients with primary uveal melanoma. *Eur J Cancer*. 2004;40:2389-2395.
30. Diener-West M, Hawkins BS, Markowitz JA, Schachat AP. A review of mortality from choroidal melanoma: II. A meta-analysis of 5-year mortality rates following enucleation, 1966 through 1988. *Arch Ophthalmol*. 1992;110:245-250.
31. Damato B, Coupland S. A reappraisal of the significance of largest basal diameter of posterior uveal melanoma. *Eye*. 2009;23:2152-2162.
32. Muller K, Naus N, Nowak PJ, et al. Fractionated stereotactic radiotherapy for uveal melanoma, late clinical results. *Radiother Oncol*. 2012;102:219-224.
33. Wackernagel W, Holl E, Tarmann L, et al. Visual acuity after Gamma-Knife radiosurgery of choroidal melanomas. *Br J Ophthalmol*. 2013;97:153-158.
34. Sarici AM, Pazarli H. Gamma-knife-based stereotactic radiosurgery for medium-and large-sized posterior uveal melanoma. *Graefes Arch Clin Exp Ophthalmol*. 2013;251:285-294.
35. Yazici G, Kiratli H, Ozyigit G, et al. Stereotactic radiosurgery and fractionated stereotactic radiation therapy for the treatment of uveal melanoma. *Int J Radiat Oncol Biol Phys*. 2017;98:152-158.
36. Hrbacek J, Kacperek A, Beenaker J-WM, et al. PTCOG ocular statement: expert summary of current practices and future developments in ocular proton therapy. *Int J Radiat Oncol Biol Phys*. 2024;120:1307-1325.
37. Durante M, Debus J. Heavy charged particles: does improved precision and higher biological effectiveness translate to better outcome in patients? *Semin Radiat Oncol*. 2018;28:160-167.
38. Fleury E, Pignol J-P, Kiliç E, et al. Comparison of stereotactic radiotherapy and protons for uveal melanoma patients. *Phys Imaging Radiat Oncol*. 2024;31:100605.
39. Beltran C, Amos RA, Rong Y. We are ready for clinical implementation of carbon ion radiotherapy in the United States. *J Appl Clin Med Phys*. 2020;21:6.
40. Toyama S, Tsuji H, Mizoguchi N, et al. Long-term results of carbon ion radiation therapy for locally advanced or unfavorably located choroidal melanoma: usefulness of CT-based 2-port orthogonal therapy for reducing the incidence of neovascular glaucoma. *Int J Radiat Oncol Biol Phys*. 2013;86(2):270-276.
41. Cho Y, Chang JS, Yoon JS, et al. Ruthenium-106 brachytherapy with or without additional local therapy shows favorable outcome for variable-sized choroidal melanomas in Korean patients. *Cancer Res Treat*. 2018;50(1):138-147.