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CyberKnife Robotic-Assisted Stereotactic Radiosurgery for Advanced Stages of Ciliochoroidal Uveal Melanoma. Preliminary Results in Mexico

Gustavo Ortiz-Morales
Hospital Alta Especialidad

Irving Dominguez-Varela
Hospital Alta Especialidad

Daniela E. Gomez-Elizondo
Hospital Alta Especialidad

Erik Perez-Ramos
Hospital Alta Especialidad

Sara González-Godínez
Hospital Alta Especialidad

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ORIGINAL ARTICLE

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Sistema de radiocirugía robótica estereotáctica CyberKnife en estadios avanzados de melanoma uveal ciliocoroideo. Resultados preliminares en México

*Gustavo Ortiz-Morales[1,2], Irving Dominguez-Varela[1,2], Daniela E. Gomez-Elizondo[1,2], Erik Perez-Ramos[1,2], Sara González-Godínez[1,2], Dione Aguilar y Méndez[1,2,] Christian Estrada-Hernández[1], Ramiro Corral[3], Octavio Zamorano-Gómez[3], Carol L. Shields[4], Lauren A. Dalvin[5], Efren Gonzalez-Monroy[6], and David Ancona-Lezama[1,2]**

[1]Ocular Oncology Service, Institute of Oncology; [2]School of Medicine and Health Sciences, Tecnológico de Monterrey; [3]Radiation Oncology Department, Christus Muguerza, Hospital Alta Especialidad. Monterrey, Mexico; [4]Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, United States; [5]Department of Ophthalmology, Mayo Clinic, Rochester, MN, United States; [6]Ocular Oncology Service, Boston Children's Hospital and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

Abstract

Objective: *The objective of this study was to report the early results of CyberKnife® (CK®) stereotactic radiosurgery in advanced stages of ciliochoroidal (CBCh) melanoma in Mexican patients.* **Methods:** *A retrospective review of charts was performed to analyze the outcomes of patients who underwent CK® (Accuray Inc, Sunnyvale, CA, United States).* **Results:** *Four patients with CBCh melanoma were treated under this protocol. The mean age was 53.2 ± 5.3 years (range, 47-60). Median of follow-up was 9.5 ± 3.1 months (range, 5-12). Mean tumor diameter was 13.49 mm, mean thickness, 11.74 mm, and mean gross tumor volume was 1251.97 mm^3. Tumors were dome- (50%) and mushroom-shaped (50%) in medium-to-large sizes. Three patients had T3b tumors, and one had a T4d tumor at the early tumor staging according to the American Joint Committee on Cancer. A mean dose of 2763 ± 181.3 cGy was prescribed to the 90% isodose line. All patients achieved local tumor control after single-session radiosurgery at the latest follow-up. One patient presented with acute toxicity (extensive serous retinal detachment associated with radiation induced tumor vasculopathy) that was promptly managed. None of the patients required secondary enucleation.* **Conclusions:** *CK® appears to be an effective therapy for medium to large-sized CBCh melanoma. A prospective comparative study with longer follow-up is needed to confirm these findings and to evaluate long-term morbidity.*

Keywords: *CyberKnife. Uveal Melanoma. Stereotactic Radiosurgery. Multidisciplinary treatment. Ocular Oncology.*

***Correspondence:**
David Ancona-Lezama
E-mail: davidancona@medicos.tecsalud.mx

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Resumen

Objetivo: *Reportar los resultados iniciales de la cirugía esterotáctica con CyberKnife® (CK) para etapas avanzadas de melanoma ciliocoroideo (CBCh) en pacientes mexicanos.* **Métodos:** *Revisión retrospectiva de expedientes clínicos. Se analizaron los resultados de los pacientes que se realizaron CK® (Accuray Inc, Sunnyvale, CA, USA).* **Resultados:** *Cuatro pacientes con melanoma CBCh fueron tratados bajo este protocolo. La edad promedio fue 53.2 ± 5.3 años (rango 47-60). El seguimiento promedio fue de 9.5 ± 3.1 meses (rango 5-12). El diámetro promedio del tumor fue 13.49 mm, grosor promedio 11.74 mm y volumen tumoral promedio 1251. 97 mm^3. Los tumores tuvieron una configuración de domo (50%) y de hongo (50%) de tamaño mediano a grande. Tres pacientes tuvieron un tumor T3b y uno T4d en su estadiaje inicial, de acuerdo al AJCC. Se prescribió una dosis promedio de radiación de 2763 ± 181.3 cGy al 90% de la línea de isodosis. Todos los pacientes lograron el control local del tumor después de una sesión de radiocirugía en el último control de seguimiento. Un paciente presentó datos de toxicidad aguda (desprendimiento seroso de retina) que fue manejado exitosamente. Ninguno de los pacientes requirió enucleación secundaria.* **Conclusión:** *El abordaje multidisciplinario con CK® es una terapia efectiva para melanoma CBCh mediano-a-grande. Es necesario mayor tiempo de seguimiento para confirmar estos hallazgos y evaluar la morbilidad a largo plazo.*

Palabras clave: *Cyberknife. Melanoma uveal. Radiocirugía esterotáctica. Abordaje multidisciplinar. Oncología Ocular.*

Introduction

Uveal melanoma is a malignant tumor that stems from melanocytic cells most often located in the choroid (90%) followed by the ciliary body (6%) and the iris (4%)[1]. It is most frequently diagnosed in Caucasians (98%) followed by Hispanics (1%)[2]. Other predisposing factors include fair skin complexion, light hair color, less ability to tan, ocular melanocytosis, cutaneous, iris or choroidal nevi, *BAP1* mutation, and exposure to artificial ultraviolet light[1,3,4]. Simultaneous infiltration of melanoma into adjacent uveal structures is sometimes identified: iridociliary (iris and ciliary body), ciliochoroidal (ciliary body and choroid), and iridociliochoroidal melanoma (iris, ciliary body, and choroid) and is often associated with late diagnosis[5]. Therefore, ciliochoroidal (CBCh) melanoma can remain hidden for a long time behind the iris and only become symptomatic when sufficiently large, resulting in higher rates of extraocular extension, metastatic tumors, and mortality[3,6-11].

Available treatments for CBCh melanoma include primary enucleation, brachytherapy, proton beam radiation, and stereotactic radiosurgery including CyberKnife® (CK®) Robotic Radiosurgery System (Accuray Inc, Sunnyvale, CA, United States)[12-15]. Primary enucleation of uveal melanoma has not shown any advantage regarding survival rates compared to radiation therapy[16-18], and survival rates among radiation therapies seem comparable[13,19-22]. The equivalence of survival rates among the alternatives available allows physicians to decide on the proper treatment while considering the patients' preferences and expectations for each therapeutic option. As far as we know, this is the first study to assess the safety and efficacy profile of CK® for the management of CBCh melanoma in the Mexican population.

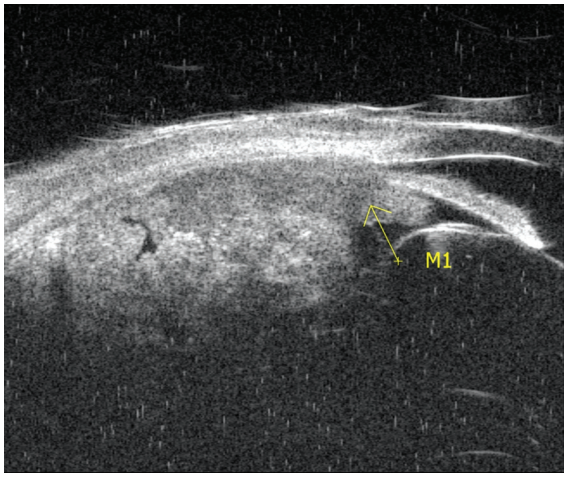

Figure 1. A: the Multiplan® Treatment Planning System (Accuray Inc, Sunnyvale, CA, United States) in patient #1 enabled the creation of radiosurgical maps with excellent conformality and coverage with steep dose gradients. **B:** the fused image was marked for gross tumor volume and organs at risk as defined by both the ocular oncologist and radiation oncologist.

Subjects and methods

A retrospective review of medical records was conducted to analyze the safety and efficacy profile of the CK® (Accuray Inc, Sunnyvale, CA, United States) for the management of CBCh melanoma in our ocular oncology unit. After having obtained the previous written informed consent and following the principles established at the Declaration of Helsinki, four patients were treated with CK® to treat their CBCh melanoma at the ocular oncology unit of Tecnológico de Monterrey, Mexico back in 2020.

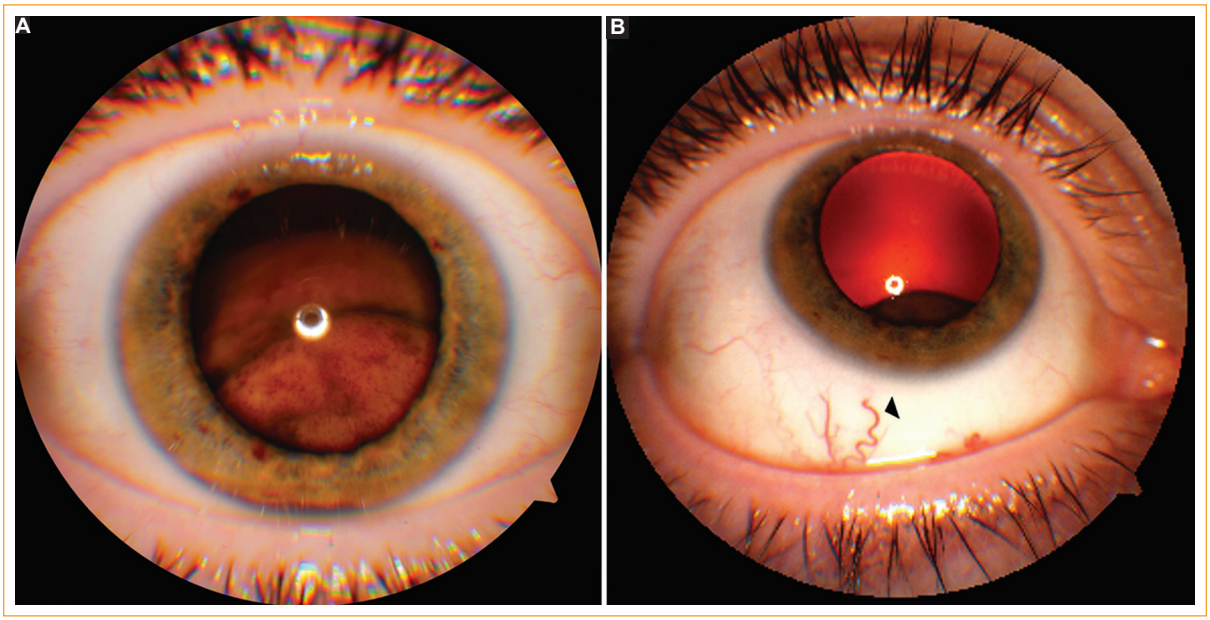

Figure 2. The ultrasound biomicroscopy performed on patient #4 confirmed a vascularized mass (yellow arrow marked M1) simultaneously involving the ciliary body and the choroid.

Before treatment, all patients underwent extensive ophthalmological evaluation including the assessment of visual acuity, tonometry, anterior segment biomicroscopy, fundus examination, gonioscopy, and a transscleral biopsy followed by cytopathologic analysis (when available) within the same week of treatment (Fig. 1). Standardized A- and B-scan ultrasounds were used to assess tumor dimensions in all the patients (Fig. 2). CK® was offered as a therapeutic option due to tumor dimensions that exceeded brachytherapy with ruthenium-106 and iodine-125 along with the patients' preferences to avoid primary enucleation. Despite iodine-125 not being currently available at our center, all patients were informed on the alternative of iodine-125 plaque in a treatment center in Mexico City, Mexico. However, the treatment with iodine-125 plaque was not advisable in any case due to tumor size, and radiosurgery was chosen to attempt globe salvage. The CK® system consists of a compact linear accelerator mounted on a multi-axis robotic manipulator. This system delivers of X-ray-guided, non-isocentric, and non-coplanar treatment beams with high precision[23]. Complete systemic evaluation and additional imaging studies were performed to exclude metastatic disease in all the cases.

Before radiosurgery, a custom-fitted thermoplastic mask (Orfit Industries, Belgium) immobilized the patient during radiotherapy. On the day of the surgery, globe akinesia was achieved using a retrobulbar block with 2 mL of bupivacaine at 0.75% and 2 mL of lidocaine at 2% on 2 separate occasions on the day of treatment. The first retrobulbar block was immediately administered before a gadolinium contrast-enhanced brain magnetic resource imaging (MRI) (T1 and T2 sequence) followed by a high-definition computed tomography (CT) scan (1 mm thickness). The images from the MRI and CT scan were fused by the physicist together with the radiation oncologist (EPR) and ocular oncologist (DAL). The final image was marked for gross tumor volume (GTV) and organs at risk (OAR) as defined by both the ocular oncologist and the radiation oncologist for optimization purposes. Adding a 1 mm margin (PTV), the treatment plan was generated using the integrated inverse treatment planning system (MultiPlan, Accuray Inc, Sunnyvale, CA, United States) (Fig. 3). As part of the multidisciplinary treatment, the patient received companionship therapy to work through the treatment experience, reduce anxiety symptoms, and improve therapeutic compliance. The ocular oncologist applied the second retrobulbar block before starting treatment. Radiation was delivered in a single fraction with a mean dose of 27 Gy to the 90% prescription isodose line. At the end of radiosurgery session, all patients were discharged from the hospital.

Clinical and imaging follow-up consultations were performed 1 day, 1 week, and 1, 3, 6, and 12 months after radiosurgery. Local tumor control (LTC) was defined as either tumor shrinkage or absent progression on the ultrasound. All patients received multidisciplinary

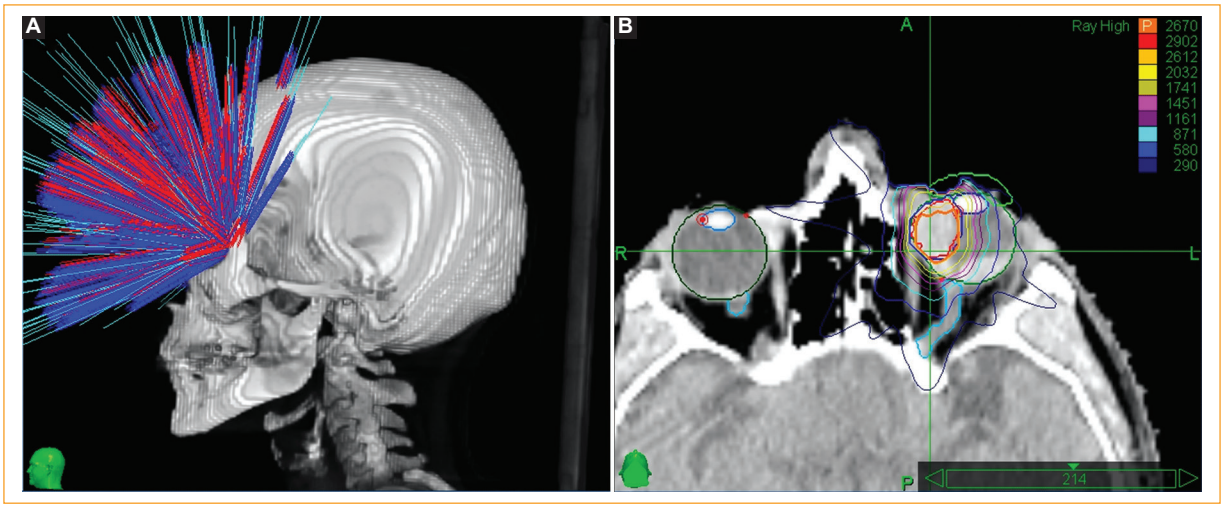

Figure 3. **A:** anterior segment photographs of patient #4 show a large ciliochoroidal melanoma as seen through a dilated pupil. **B:** the sentinel vessel (arrow head) was visible in the upgaze position hidden beneath the lower eyelid.

care from physicians, clinical psychologists, geneticists, medical oncologists, radiation oncologists, and ocular oncology specialists.

Results

The records of four patients (three males, one female) with a mean age of 53.2 ± 5.3 years (range, 47-60) with unilateral CBCh melanoma were reviewed (Table 1). The median of follow-up was 9.5 ± 3.1 months (range, 4-12). Early visual acuity was worse than 20/400 (1.3 LogMAR) in all patients. At presentation, mean diameter was 13.49 ± 2.74 mm and mean thickness was 11.74 ± 2.13 mm. Mean GTV was 1251.97 mm^3. CBCh tumors were dome-shaped in two patients (50%) and mushroom-shaped in another 2 (50%). Three patients had T3b tumors and one had a T4d tumor at the early staging according to the American Joint Committee on Cancer. At the early diagnosis, one patient was found to have extrascleral extension. Initial presentation confirmed the presence of dense vitreous hemorrhages in three patients (75%). Furthemore, two patients (50%) had extensive exudative retinal detachment. Cytopathology analysis confirmed all diagnoses. Mixed cell (50%), spindle cell (25%), and epithelioid cell (25%) types are shown (Fig. 4). Cytogenetic analysis for the risk stratification of metastasis was offered to all patients. However, only patients #2 and #4 accepted. The results were classified according to the Cancer Genome Atlas[24] as Class B and Class D tumors, respectively. Germline mutation analysis was performed in patients #2, #3, and #4. Patient #2 had chromosome 3 disomy, 6p amplification and duplication, 6q monosomy, and 8q amplification. Patient #4 had 1p deletion, chromosome 3 monosomy, 8q amplification, and chromosome X deletion. A mean dose of 2763.27 ± 181.3 cGy (range 26.3-30.3 Gy) was administered to the 90% isodose line. On average, a 23.6% reduction (range, 10-31.2%) in tumor height was observed 1 month after radiosurgery. One patient (25%) developed exudative retinal detachment at follow-up associated with radiation induced tumor vasculopathy 3 months into radiosurgery that resolved with antiangiogenic treatment. At follow-up, all patients achieved local tumor control and remained alive with no evidence of metastatic disease. No patient required secondary enucleation at follow-up.

Discussion

The use of CK® for uveal melanoma was first proposed by Muacevic et al.[26] back in 2008. Advantages of this procedure include excellent LTC[13,19,20,26-30], avoidance of primary enucleation, and the possibility of preserving functional vision. It also allows outpatient treatment, lowers the burden of care, and improves quality of life[31].

In their pioneer study, Muacevic et al.[26] reported on 20 patients with a LTC rate of 100%, and no complications or secondary enucleation with a median of

Table 1. Summary of patients with CBCh melanoma treated with CyberKnife Robot-Assisted Radiosurgery

Patient	Age (year)	Gender	Tumor staging[25]	Tumor cell type	Initial tumor height (mm)	Height reduction at 1 month (%)*	Follow-up (months)	PTV (mm^3)	Mean dose (cGy)**
1	47	Male	T3bN0M0	Spindle	9.51	31.2	12	1920.46	2713.94
2	54	Male	T3bN0M0	Mixed	9.3	10	5	1275.25	3030.89
3	60	Male	T4dN0M0	Mixed	12.21	26.7	11	2279.28	2673.81
4	52	Female	T3bN0M0	Epithelioid	13.29	26.7	10	1364.73	2634.46

*Size reduction estimated as tumor height immediately before treatment minus tumor height 1 month after treatment. **Mean dose to the planning target volume.
AJCC: American Joint Committee on cancer; CBCh: ciliochoroidal melanoma; PTV: planning target volume.

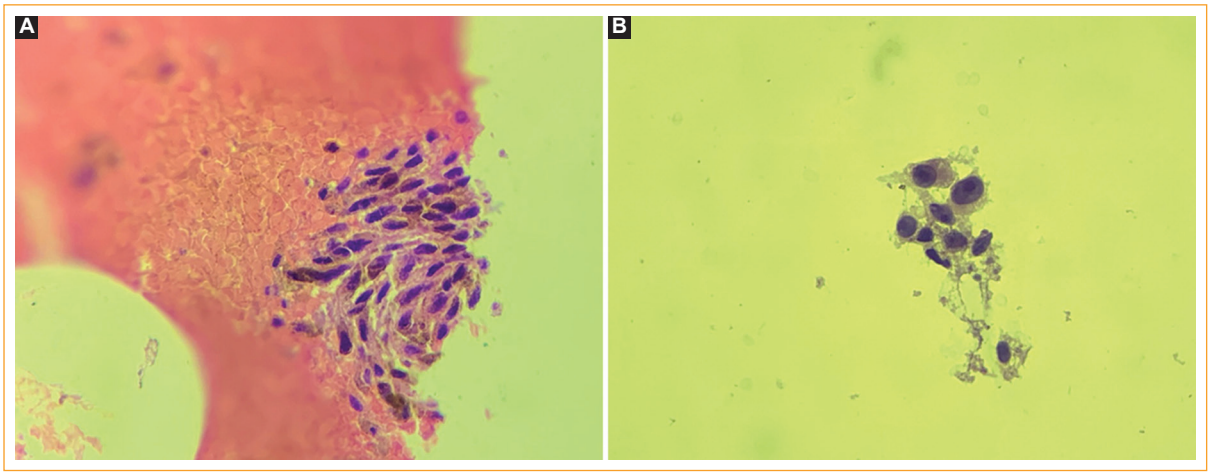

Figure 4. **A:** fine-needle aspiration biopsy of intraocular ciliochoroidal melanoma in patient #1 showed spindle cells with atypical, hyperchromatic nuclei, and abundant eosinophilic cytoplasm and intracellular melanin pigment. **B:** in contrast, a biopsy from patient #4 showed epithelioid cells with large nucleoli, abundant eosinophilic cytoplasm, and abundant inter-cell extracellular space.

follow-up of 13 months. Long-term results of the Munich group confirmed LTC in 87.4% and 70.8%, with overall survival rates of 84.8% and 78.4% in 217 patients, at 3 and 5 years, respectively[19]. Twenty-six patients (11.9%) required enucleation. Interestingly enough, the eye retention rate achieved was similar to the LTC rate (86.7% and 73% at 3 and 5 years, respectively)[19]. Krema et al.[13] studied the efficacy of stereotactic radiosurgery in juxtapapillary choroidal melanoma in 94 patients; 7% of tumors relapsed, 21% required secondary enucleation, and 16% developed systemic metastasis at a median of follow-up of 50 months. Özcan et al.[29] reported an LTC rate of 84% and an overall eye retention rate of 83.3% with a median of follow-up of 17.2 months in 36 patients. In this report, all four patients with simultaneous involvement of two adjacent uveal structures achieved LTC, and none required secondary enucleation. However, longer follow-up may show similar results to other reports.

The CK® system reduces the side effects of radiation based on multiple radiation beams, exceedingly precise dosage administration, and beam-collimation[23]. Main setbacks are radiation side effects, and the possibility of secondary enucleation. Radiation-induced retinopathy (RIR) is characterized by a progressive vasculopathy of retinal capillaries after vascular endothelium damage from ionizing radiation[32]. Radiation toxicity seems to be more common in larger tumors like the one seen on CBCh melanomas due to the need for higher radiation doses[26,33-35]. In addition, radiation doses (25-35 Gy) commonly used in CK to treat uveal melanoma are lower to known RIR limits of 35-45 Gy, which may translate into less radiation toxicity[36,37]. Admittedly, toxicity differences need to be further explored in larger comparative studies.

Eibl-Lindner et al.[19] (mean radiation dose [MDR] 20.3 Gy) reported on the outcomes of 217 patients

treated with CK robotic radiosurgery. A total of 29 patients out of the entire cohort (13.4%) developed RIR, 33 (15.2%) treatment induced glaucoma, 26 (11.9%) vitreous hemorrhage, and 7 (3.2%) macular edema.

Özcan et al.[29] (MRD, 24.5 Gy) reported that ten out of 36 patients (27.7%) developed RIR. The mean time of appearance was 12 months. However, RIR was not associated significantly with MRD (p = 0.53). Dunavoelgyi et al.[21] (MRD, 50 Gy, fractionated in five) reported that after a 60-month follow-up, only 24 out of 91 patients (26%) remained RIR-free. Yazici et al.[30] (MRD, 54 Gy, fractionated in three) reported that 76 out of 181 eyes (42%) developed RIR with a mean time of appearance of 12 months. MRD was significantly higher in patients with RIR compared to those without it (63 Gy vs. 52 Gy; p = 0.04). Due to the short follow-up (median of 9.5 months), long-term morbidity and patient survival may not be well-established in our series.

In this case series, it was notable that three out of four patients presented with vitreous hemorrhage. Eskelin et al.[38] have studied this mode of presentation in uveal melanoma. Only one out of 104 patients reported had vitreous hemorrhage as the sign of presentation. Shields et al.[1] reported 8033 cases of uveal melanoma (98% Caucasian). A total of 821 cases (10%) from all ages had intraocular hemorrhage at the early examination. Other studies conducted among the Asian population conclude that retinal detachment, acute glaucoma, uveitis, cataracts, or vitreous hemorrhage may occur as signs of presentation of uveal melanoma. However, no exact percentage of occurrence of vitreous hemorrhage was provided[39]. The higher incidence rate of vitreous hemorrhage in this short case series may be attributed to the clinical diversity seen among several ethnicities[2,40], delayed diagnosis of uveal melanoma in our country or the slightly higher percentage of intraocular hemorrhage reported in large case series among the Hispanic population[2].

Other radiation side effects are cataracts, limbal stem cell deficiency, and glaucoma[41,42]. The rate of cataracts as a complication of radiotherapy is somewhere between 43% and 64%[41]. The rate of limbal stem cell deficiency has been reported in between 2% and 33% of the patients treated with radiotherapy on the anterior segment[43,44]. Glaucoma is also prevalent after radiotherapy with an incidence rate between 3% and 92%. This variation depends on tumor seeding into the anterior chamber angle[41]. Several studies report rates of corneal complications as low as 3-9%. However, dry eye after radiotherapy is highly prevalent[45].

Furthermore, despite radiotherapy is covered by the national health insurance system, there are only 3 CK® systems available in Mexico, and patient costs for travel and lodging are not covered, which limits the choices of treatment and puts a financial burden on most patients[46,47]. These may cause delays in diagnosis and treatment leading to increased morbidity and mortality rates. Plaque brachytherapy also has limited availability in our country so all options that may help avoid primary enucleation need to be thoroughly explored to deliver better outcomes. Further studies assessing the cost-effectiveness of CK over other radiotherapy options in a real-world context may help address this issue. Although carbon fiducial markers or tantalum rings may optimize the 3D imaging of intraocular tumors and allow enhanced radiation plans[48], they are not currently available in Mexico.

Finally, between 15% and 26% of cancer survivors experience clinically significant levels of depression and anxiety after 2-5 years of medical treatment, which can negatively impact adherence to treatment, recovery, and quality of life[49]. Addressing psychopathological symptoms in survivors as part of a multidisciplinary approach may help prevent, detect, and perform prompt interventions in patients at risk.

Limitations of this study are the short follow-up period, the small number of patients included, and the study retrospective nature. The follow-up time was admittedly short to observe most radiotherapy-related toxicity. Larger case series with longer follow-ups may support the long-term safety of CK.

As shown in our preliminary results[50], CK® is an effective therapeutic alternative for medium to large CBCh melanomas. Furthermore, this outpatient treatment may help decrease hospital services during the current pandemic of SARS-CoV-2, where reduced hospital admissions may help battle the rising demand for medical care[49,51-53].

Conclusion

This preliminary retrospective study suggests that CK® may be a feasible and effective option in the therapeutic armamentarium to treat CBCh melanoma since it provides adequate tumor control. Furthermore, CK is a straightforward option that allows eye preservation and spares enucleation. The small percentage of early treatment associated adverse events was managed with known therapeutic options such as steroids, and antiangiogenic agents. Larger prospective comparative studies with longer follow-ups are needed to support the long-term efficacy and safety profile of CK. As discussed, a

multidisciplinary team is also of paramount importance regarding patient care in a radiosurgery unit.

Funding

None.

Conflict of interests

None.

Ethical disclosures

Protection of people and animals. The authors declare that the procedures followed were in accordance with the ethical to the ethical standards of the responsible human experimentation and in accordance with the World Medical Association and the Medical Association and the Declaration of Helsinki.

Confidentiality of data. The authors declare that they have followed the protocols of their centre of protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is held by the author of correspondence.

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