


## Outcomes of fractionated CyberKnife radiosurgery in patients with choroidal malignant melanoma

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### ABSTRACT

**Objective:** The aim of this study was to evaluate local tumor control and complication development rates of fractionated CyberKnife radiosurgery (CRS) in patients with choroidal melanoma.

**Methods:** A total of 29 patients with choroidal melanoma were treated with fractionated CRS at Ankara Oncology Research and Training Hospital, Department of Radiotherapy between May 2009 and December 2013. Patients were treated with CRS if the initial height of the choroidal melanoma was  $\geq 6$  mm, or juxtapapillary and/or juxtamacular tumors with a height of  $>2.5$  mm. Ophthalmic examinations were performed at baseline and at months 3, 6, 9 and 15 after radiotherapy. Assessment of visual acuity and measurement of tumor base dimension and height using A-scan and B-scan echography were done at each visit.

**Results:** The mean age was 56 (27–75) years. Tumor was located on choroid in 23 and on ciliochoroid in 6 patients. 86.2% of all melanomas were classified as medium sized and 23.8% as large sized. A median total dose of 5000 cGy was applied. Median tumor height decreased from 7.5 mm at baseline to 4.4 mm at the last follow-up visit ( $p < 0.001$ ). Median visual acuity decreased from 0.4 at baseline to hand motion ( $p < 0.001$ ). One patient had been lost to the metastatic disease and one patient had been treated with enucleation due to recurrent tumor growth.

**Conclusion:** CRS is an effective and reliable local treatment modality in uveal melanoma.

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### Introduction

Uveal melanoma is the most common primary intraocular tumor in adults with an incidence of about six cases per 1 million population [1,2]. Approximately 90% of uveal melanomas involve choroid. Several modes of treatment are available for choroidal melanoma [3,4]. Radioactive plaque brachytherapy and proton-beam therapy provide 85–98% local tumor control rates in selected patients. They both require an invasive surgical approach that involves opening the conjunctiva and tenon capsule and suturing surgical clips or a metal plaque. Apart from invasiveness, another setback is the frequently seen complications due to direct exposure of the surrounding tissues to radiation, such as radiation retinopathy, optic neuropathy, cataract and corneal damages [5].

Stereotactic radiotherapy delivers high doses of radiation precisely targeting the tumoral lesion. This modality provides less damage to the surrounding structures compared to results of proton radiotherapy or plaque brachytherapy techniques. The effectiveness of one of the stereotactic radiosurgery instruments, the CyberKnife robotic radiosurgery system (CRS) (Accuray, Sunnyvale, CA), was evaluated in our study. We aimed to assess the results of fractionated CyberKnife

radiosurgery (CRS) of uveal melanoma for local tumor control and complication rates.

### Materials and methods

Details of patients treated with CRS between May 2009 and December 2013 at Ankara Oncology Research and Training Hospital; Department of Radiotherapy were retrospectively retrieved from hospital records. Cases that had previous failed radiotherapy or laser therapy as well as melanomas of the iris and other tumors were excluded. Diagnosis of a uveal melanoma was made by means of slit-lamp examination, indirect ophthalmoscopy, B scan ultrasonography and fluorescein angiography, if required. A total of 29 patients treated for posterior choroidal melanoma that had at least 15 months of follow-up records were identified as eligible for the study.

Patients were treated with CRS if the initial height of the choroidal melanoma was  $\geq 6$  mm, or juxtapapillary and/or juxtamacular tumors with a height of  $>2.5$  mm. Patients were not treated with CRS if they had any evidence of extrascleral tumor extension, neovascular glaucoma, or metastatic disease at the time of diagnosis.

After positioning each patient in the supine position; a thermoplastic mask (Radon<sup>®</sup> Thermoplastic IMRT-A Head

**Table 1.** Demographical and clinical properties of the patients.

Variables	Values
Age, mean (year)	56 (27–75)
Gender	
Male	17 (58.6%)
Female	12 (41.3%)
Uveal melanoma types	
Choroidal	23 (79.3%)
Ciliochoroidal	6 (20.7%)

Shoulder Mask) was used for the immobilization of the head. The eye was stabilized with retrobulbar injection of 5 cc 2% lidocaine 30 min before planning computed tomography (CT)/magnetic resonance imaging (MRI) and every fraction. The planning CT scan (Philips MX 6000 Dual CT-simulator) was followed by Post-gadolinium contrast T1-weighted brain MRI where axial images were obtained with 1-mm slice thickness. A network transferred the acquired images to the CyberKnife® (MultiPlan; Accuray Inc., Sunnyvale, CA) treatment planning workstation. The target volume and organ at risk were delineated on the basis of these two imaging data sets (CT/MRI). While gross tumor volume (GTV) was defined on magnetic resonance images, bilateral organ at risk (orbit, lens, optic nerve, chiasma, retina, macula, optic disk, lacrimal gland and brainstem) were delineated on CT images. Clinical target volume was equal to GTV. A margin of 1 mm was added in all directions to the clinical target volume to obtain the planning target volume (PTV). The treatment plan was generated by means of a nonisocentric inverse treatment planning algorithm. Dose was prescribed to the median 83% isodose line. Same radiation oncologist (E.A.A) noted the PTV, total dose given, prescribed isodose line, fraction number, conformity index (CI), homogeneity index (HI) together with ipsilateral eye, lens, optic nerve, and optic disk doses for each patient.

Ophthalmic examinations were performed at baseline and 3, 6, 9 and 15 months of radiotherapy. Assessment of visual acuity, routine ophthalmic examinations, and measurement of tumor base dimension and height using standardized B-scan ultrasonography were done at each visit.

Analysis of the data was conducted using SPSS 25.0 software. Normal distribution of the data was analyzed with the Kolmogorov-Smirnov test. Wilcoxon Signed Ranks Test was used to determine a difference between groups. P-values represent the difference of measurements of each visit from the previous one. A value of  $p < 0.05$  was accepted as statistically significant.

## Results

Twenty-nine patients (12 females, 17 males) with uveal melanoma were treated according to this procedure. The mean age was 56 (27–75) years and right eyes were involved in 19 of the patients. Regarding the uveal melanoma types, 23 (79.3%) had choroidal and 6 (20.7%) had ciliochoroidal localization (Table 1). According to the Collaborative Ocular Melanoma Study tumor size classification, 25 (86.2%) of all melanomas were classified as medium sized and 4 (23.8%) as large sized. All of the patients had stage T4A choroidal

**Table 2.** Lesion height measurements before treatment and during follow up.

		p Value*
Median pretreatment lesion height (mm) (range)	7.5 (2.7–15)	<0.001
Median first control lesion height (3 months) (mm) (range)	6.5 (2–11.3)	<0.001
Median second control lesion height (6 months) (mm) (range)	6.1 (1–11)	<0.001
Median third control lesion height (9 months) (mm) (range)	5 (1–12)	<0.001
Median fourth control lesion height (15 months) (range)	4.4 (1–12)	<0.001

\*p-Value represents the significance of difference compared to the previous control.

melanoma according to the AJCC (American Joint Committee on Cancer, 8th edition). None of the patients had ciliary body involvement, extrascleral extension, lymph node involvement and distant metastasis.

Median radiotherapy values calculated were as follows: 1117 mm<sup>3</sup> (range 275–4546 mm<sup>3</sup>) for PTV, 5000 cGy (range 1200–6250 cGy) for total dose, 84% (range 67–96) for prescribed isodose line, 3 (range 3–7) for fraction number, 1.26 (range 1.10–1.81) for CI, 1.19 (range 1.04–1.49) for HI, 6000 cGy (range 1445–7333 cGy) for ipsilateral eye dose, 1933 cGy (range 172–6374 cGy) for ipsilateral lens dose, 2719 cGy (range 176–6354 cGy) for ipsilateral optic nerve dose and 2274 cGy (range 133–6566 cGy) for ipsilateral optic disk dose.

Median tumor height decreased from 7.5 mm at baseline to 4.4 mm at the last follow-up ( $p < 0.001$ ). At each visit, a significant decrease in median tumor height was detected (6.5 mm, 6.1 mm, 5.0 mm, 4.4 mm respectively) ( $p < 0.001$ ). The tumor height measurements were shown in Table 2. Median visual acuity decreased from 0.4 at baseline to hand motion at the last visit ( $p < 0.001$ ). Pretreatment and post-treatment visual acuity values are demonstrated in Table 3. A prominent decrease in visual acuity values was encountered after the treatment in comparison to pretreatment values. Mortality was reported due to the metastatic disease in one patient and enucleation was required in another patient due to recurrent tumor growth. During the follow-up period eight patients (27.5%) had serious retinal detachment. We detected cataract in 10 (34.4%), dry eye syndrome in 15 (51.7%), maculopathy in 16 (55.1%), optic neuropathy in 3 (10.3%), secondary glaucoma in 4 (13.7%), neovascular glaucoma in 3 (10.3%), vitreous hemorrhage in 5 (17.2%) and synechia in 2 (6.8%) patients (Table 4).

## Discussion

The primary aim for the treatment of uveal melanomas, essentially, is the destruction of the tumor. Preservation of the eye and the visual function are the secondary goals. There are several treatment options available including plaque brachytherapy, proton beam irradiation, stereotactic radiosurgery, local resection, and primary enucleation [4,6]. The Collaborative Ocular Melanoma Studies (COMS)

**Table 3.** Visual acuity values of the patients before and after treatment with CyberKnife radiosurgery.

Visual acuity Snellen chart (decimal equivalent)	Number of patients (%)	Visual acuity Snellen chart (decimal equivalent)	Number of patients (%)
<i>Pretreatment</i>		<i>Posttreatment</i>	
20/80 (0.2)	6 (20.7)	20/200 (0.1)	3 (10.3)
20/63 (0.3)	5 (17.2)	20/400 (0.05)	4 (13.8)
20/50 (0.4)	6 (20.7)	20/1000 (counting fingers)	6 (20.7)
20/40 (0.5)	6 (20.7)	20/11,600 (counting fingers)	8 (27.6)
20/32 (0.6)	4 (13.8)	20/2500 (hand movements)	8 (27.6)
20/25 (0.7)	2 (6.9)		

**Table 4.** Complication rates encountered after treatment of uveal malign melanomas with CyberKnife radiosurgery.

Complications	Number of patients (percentage)
Retinal detachment	8 (27.5%)
Cataract	10 (34.4%)
Dry eye syndrome	15 (51.7%)
Maculopathy	16 (55.1%)
Optic neuropathy	3 (10.3%)
Secondary glaucoma	4 (13.7%)
Neovascular glaucoma	3 (10.3%)
Vitreous hemorrhage	5 (17.2%)
Synechia	2 (6.8%)

examined the role of radiotherapy in the treatment of uveal melanoma and the results suggested no difference in mortality of the melanoma patients treated with either brachytherapy or enucleation [7,8]. Since then, eye-preserving radiotherapy methods gradually gained popularity. Particle radiotherapy is generally accepted as a standard approach for the management of choroidal melanoma due to its ability to deliver radiation with similar accuracy to plaque brachytherapy techniques [9]. Stereotactic radiotherapy enables fractionation without implanting radio-opaque markers and minimizes dose to the surrounding critical structures. We aimed to report our uveal melanoma treatment results with fractionated CyberKnife (Accuray, Sunnyvale, CA) radiosurgery which provided favorable results with good local tumor control and decreased morbidity.

Choroidal tumors up to 5 mm thickness and not extending close to the optic disk are generally treated with ruthenium plaque radiotherapy as the first choice. For tumors > 6 mm thickness, controversy starts whether proton beam radiotherapy, Iodine-125 plaque brachytherapy, stereotactic radiosurgery, transscleral local resection, endoresection, or enucleation should be considered. Our study population consisted of patients who had  $\geq 6$  mm tumor thickness and we evaluated the results of CRS. Enucleation is the final choice of treatment indicated when there is diffuse melanoma at presentation, extra ocular extension, or progressive disease after treatment [10]. In our study, only one patient has been treated with enucleation during the overall follow-up period.

The current gold standard for the treatment of uveal melanomas is the proton beam radiotherapy [11]. However, it is not a readily available and easily accessible radiotherapy option in many centers and even in many countries due to the high costs [12]. Therefore, radioactive plaque brachytherapy is generally the first choice of treatment. Radioactive plaque brachytherapy is performed by using isotopes

Iodine-125, ruthenium-106, or palladium-103. Iodine plaques emitting gamma radiation are effective for tumors in the range of 8–10 mm and ruthenium plaques emitting beta radiation for up to 5 mm [4,13,14]. Especially in large tumors, it might not be possible to deliver large doses of radiotherapy (80–100 Gy) to the tumor site. That is why, higher local recurrence rates (10.3%) were reported with plaque brachytherapy [15] than with proton-beam radiotherapy (3%).<sup>16</sup> Moreover, conventional plaque radiotherapy can be technically difficult in both insertion and placement of the plaques, especially when treating juxtapapillary tumors because of the proximity to the optic nerve. Williams *et al.* [17] reported cases in which the posterior edge of the juxtapapillary plaque was displaced away from the optic nerve, as demonstrated by MRI, in cadaver eyes. Harbor *et al.* [18] reported that after initial plaque placement by transillumination and indirect ophthalmoscopy, echography identified that 14% of the plaques were decentered by more than 2 mm with at least one tumor margin uncovered by the plaque. In a more recent study, regardless of the radio-isotopes used and plaque designs (notched vs non-notched), a two to threefold increased risk of treatment failure with plaque brachytherapy has been reported for choroidal melanomas touching the optic disk [19]. Therefore, the need for safer and noninvasive treatment modalities for uveal melanomas caused rising interest in stereotactic radiosurgery which provided promising results [20].

Stereotactic radiotherapy could deliver the dose in a single fraction or in multiple fractions with the use of noninvasive fixation systems [21,22]. The fractionation of the dose gives the advantage of delivery of large doses to the tumor with lower ocular complications. The results of the studies about the local tumor control of the stereotactic radiotherapy is in line with the other radiotherapy procedures [23,24]. Stereotactic approach involves the Gamma Knife (Elekta, Stockholm, Sweden), Cyberknife or linear accelerator-based radiosurgery (LINAC) systems. CyberKnife, Gamma Knife, LINAC based radiosurgery were compared with proton beam radiotherapy dosimetrically. It was demonstrated that stereotactic approaches were an effective and safe alternative to proton beam radiosurgery [5]. All three radiosurgery techniques were effective and reasonable to limit the dose to the anterior structures, but the doses to the ciliary body and to the periphery of the lens were lower in CRS than with protons or Gamma Knife. Another study reported a significant decrease in tumor height and effective local tumor control

with CRS [9]. In our study, median tumor height significantly decreased from 7.5 mm at baseline to 4.4 mm at the last visit and this was compatible with the previous studies. Although relatively thicker and posteriorly located tumors were involved in our study population, a significant decrease in tumor height was detected at each visit indicating the effectiveness of the treatment.

The chronic complications are encountered less frequently in fractionated stereotactic radiotherapy compared to Gamma knife Stereotactic radiotherapy. Complication rates increase when the tumor approaches to optic disk and macula and also in doses higher than 50 Gy in 5 fractions in 80% isodose [25]. Anterior segment complications, such as neovascular glaucoma and cataract, are frequently reported with all forms of radiotherapy. Retinopathy, optic neuropathy, neovascular glaucoma, cataract, vitreous hemorrhage are the major complications [25–27]. Visual acuity usually decreases after treatment even in lower doses especially in the juxtapapillary tumors. Someni *et al.* [28] reported the incidence of neovascular glaucoma to be 28%, peaking between 1 and 2,5 years after irradiation, which is comparable to the 31% incidence reported after helium ion radiotherapy at 5-to-10 year follow-up [29]. The three most common complications were cataracts (34.4%), dry eye syndrome (51.7%), and radiation maculopathy (55.1%) in our study population. Overall median visual acuity decreased from 0.4 at baseline to hand motion at the last individual follow-up ( $p < 0.001$ ). Our complication rates are similar to the previous studies reporting complication rates of other irradiation modalities [26,30].

Stereotactic radiosurgery does not have a negative effect on patient survival. Thus, Someni *et al.* [28] reported a 94% survival rate at 26 months. Studies of other modalities with longer follow-up have found the tumor control rate and survival rate, at a median follow-up of 5 years, to be around 85% with brachytherapy treatment and 83% with helium ion irradiation of juxtapapillary melanoma [29,31]. In our study, one patient had been lost to the metastatic disease, one patient had been treated with enucleation due to recurrent tumor growth. Therefore, overall survival and tumor control rate is 93.1% for our study population. Despite the presence of relatively thicker and posteriorly located tumors in our study population, overall survival and tumor control rate is still in line with the literature. However, our study reports the results of patients who had a minimum of 15 months follow-up time over the study period, and therefore, the duration of follow-up in our study may not be sufficient to evaluate the late-stage toxicity of CRS.

Our study indicates that stereotactic radiotherapy offers a noninvasive, relatively nonexpensive management option in the treatment of uveal melanomas. It provides a high local tumor control rate, similar to the rates reported with other irradiation modalities at a similar median follow-up period. It seems to carry a similar incidence of anterior segment complications in comparison to other external beam radiotherapy options, and a higher incidence in comparison to brachytherapy. However, it is known that complication rates and the

preservation of visual acuity are generally not at the expected levels when dealing with thicker uveal melanomas.

## Conclusion

CyberKnife fractionated stereotactic radiosurgery seemed to be an effective and reliable local treatment modality in large and medium-sized uveal melanomas. It enabled the delivery of large doses of radiation to the target with a steep-dose gradient with good local control and acceptable morbidity rates.

## Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patients. Approval for the study was granted by the Ethics Committee of Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital. The permit number is 584.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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