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Retrospective review of uveal melanoma patients treated with fractionated stereotactic radiotherapy

Fraksiyone stereotaktik radyoterapi ile tedavi edilen uveal melanom hastalarının retrospektif olarak değerlendirilmesi

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SUMMARY

Objective: Last decades, radiotherapy displaced surgery as an effective organ preserving option for uveal melanoma treatment if tumor diameter and localisation permits. We aimed to report our experience about the management of uveal melanoma treated with CyberKnife fractionated stereotactic radiotherapy.
Method: We retrospectively evaluated 31 uveal melanoma patients treated with CyberKnife fractionated stereotactic radiotherapy. 29 was medium and 2 was large sized tumor.
Results: The median follow-up was 26 months. Overall survival, metastasis free survival, local control and eye retention rates for 2- and 4-year were 97.4%, 94.7%; 89.1%, 81%; 92.9%, 81.3% and 82.1%, 61.9%, respectively.
Conclusions: In view of our experience, it may be preferable to use CyberKnife fractionated stereotactic radiotherapy for patients with uveal melanoma as a noninvasive, precise radiotherapy technique.
Keywords: CyberKnife, radiosurgery, uveal melanoma

ÖZET

Amaç: Son yıllarda, radyoterapi uveal melanom tedavisinde tümör çapı ve yerleşimi uygunsa etkili bir organ koruyucu yöntem olarak cerrahinin yerini almıştır. CyberKnife fraksiyone stereotaktik radyoterapi ile tedavi edilen uveal melanom olgularındaki deneyimimizi rapor etmeyi amaçladık.
Yöntem: CyberKnife fraksiyone stereotaktik radyoterapi ile tedavi edilen 31 uveal melanom olgusu retrospektif olarak değerlendirildi. 29 hastada tümör boyutu orta, 2 hastada ise büyük boyutluydu.
Bulgular: Ortanca takip süresi 26 aydı. Genel sağkalım, metastazsız sağkalım, lokal kontrol ve göz korunma oranları 2- ve 4- yıl için sırasıyla %97.4, %94.7; %89.1, %81; %92.9, %81.3 ve %82.1, %61.9'du.
Sonuç: Deneyimlerimiz ışığında, uveal melanom hastalarında CyberKnife fraksiyone stereotaktik radyoterapi kullanımı noninvaziv, hassas bir radyoterapi yöntemi olarak tercih edilebilir.
Anahtar sözcükler: CyberKnife, radyocerrahi, uveal melanom

INTRODUCTION

Uveal melanoma (UM) is the most common intraocular malignancy of adulthood with 1500 newly diagnosed patients annually [1,2]. Traditionally orbitis enucleated surgically with permanent organ and thereby vision loss [3]. This modality has not proven survival benefit in different series that lead the investigators seek other organ preserving approaches [4-6]. Primary goal of the treatment is to prevent metastatic dissemination and save the vision as much as possible. Last decades, radiotherapy displaced surgery as an effective organ preserving option if tumor diameter and localisation permits [7-11].

Episcleral plaque brachytherapy (EPB), heavy ion radiotherapy (HIRT) are the frequently used radiotherapy options for eye preservation [3,7-9,12,13]. Recent years, stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) are becoming new therapeutic choices alternative to EPB and HIRT [10,11,14-18].

Data about the efficacy of CyberKnife as a FSRT device for UM treatment are scarcy [19-21]. We aimed to evaluate our experience about the management of UM treated with CyberKnife FSRT. Our objective was to report overall survival, metastasis free survival, local control and eye retention rate.

MATERIAL AND METHODS

We retrospectively evaluated 31 UM patients treated at CyberKnife unit of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Radiation Oncology Clinic from 2010 to 2014. Disease and patient characteristics are detailed in Table 1. Eligibility criteria for management with CyberKnife FSRT were as follows; lesions without scleral invasion and neovascular glaucoma, that are not amenable to EPB because of tumor diameter and localisation, patients who are with good health status of Karnofsky Performance Status > 70 and lesions without distant spread respectively. Patients who are refused enucleation also are included to study.

Pre-Radiotherapy Evaluation

All patients were examined by an experienced ophthalmologist in detail. Visual acuity, intraocular pressure and anterior segment findings were recorded. Localisation and shape of tumor, proximity to other critical structures were determined with fundoscopic examination and orbital magnetic resonance images (MRI). Tumor diameter and height was measured by ultrasonography (USG) A and B. Physical examination, blood test, chest X-ray and abdominal USG were done to rule out distant metastasis. All patients were informed about CyberKnife FSRT and were obtained informed consent.

Treatment Preparation

Retrobulbar Anesthesia

Forty five minutes before simulation ophthalmologist applied retrobulbar anesthesia with 5 cc 2% lidocain to the patient in supine position looking across. This was repeated before every fraction and computed tomography (CT) images of the orbita was fused with the planning CT for confirmation.

CyberKnife image guided radiotherapy was done with 6D-Skull X-ray techniques that bony structures from snap shots of X-rays were matched with digitally reconstructed radiograph images of planning CT. Although retrobulbar anesthesia was done with the same amount of anesthesia by the same ophthalmologist before every treatment, exophthalmos was differed and target could be missed. This observation beginning from the first few fractions, lead us to take orbital CT images to see whether the target was matched and geographic misses more than 1 mm was unacceptable.

Simulation and Planning

After retrobulbar anesthesia, CT simulation (Philips MX 6000 Dual CT-simulator) was done to the patients immobilized on supine position with a thermoplastic head mask. Axial scans of 1.5 mm slice thickness were taken including orbital structures. Post-gadolinium contrast T1-weighted axial images were obtained using brain MRI. These images were transferred to the Multiplan Treatment System for fusion and target volumes and bilateral organ at risk (orbit, lens, optic nerve, chiasma, retina, macula, optic disc, lacrimal gland and brainstem) were contoured. MRI scans were used especially if there is retinal detachment. Gross tumor volumes (GTV) were expanded 1 mm in all directions to form planning target volumes (PTV). A total dose of median 60 Gy (range 30-60 Gy) was administered in median 3 (range 3-7) fractions with the CyberKnife robotic radiosurgery system (Accuray, Sunnyvale, CA, USA).

Follow-up

Ophthalmologic eye exam and diagnostic workup were done every 2-3 months for the 1st year and every 3-6 months for following time. No

recurrence during follow-up was defined as local control and ≥25% increase in tumor volume in two sequential follow-ups defined as recurrence. Tumor without fibrotic band left behind assessed as complete response, ≥25% slimming of thickness as partial response and <25% as stable disease. Tumor volume was calculated according to ellipsoidal solid model (π/6XlengthXwidthXheight) [22]. Pretreatment and posttreatment visual acuity was performed by using Snellen chart. Visual acuity was categorized according to a value of 0.1, which was accepted as severe visual impairment. Newly developed adverse effects with respect to Common Terminology Criteria for Adverse Events v. 4.0 were noted [23].

Statistical Analysis

Analysis were done using Statistical Package for Social Sciences Version 21.0 (SPSS V 21). Median, medium and percent values were calculated using descriptive. Kaplan-Meier survival curves were studied using log-rank statistics to assess age, gender, localisation, thickness, American Joint Committee on Cancer (AJCC TNM) and The Collaborative Ocular Melanoma Study (COMS) stage of tumor, total radiotherapy dose as independent variables affected overall survival, metastasis free survival, local control and eye retention rates. Difference between pretreatment and posttreatment (last follow-up for each patient) tumor measurements were assessed with paired-t test. Visual acuity variations evaluated with McNemar test. Values ($p<0.05$) accepted as statistically significant.

RESULTS

Medical records of 16 female (51.6%) and 15 male (48.4%) UM patients (n=31) were retrospectively reviewed. Median age at presentation was 54 (range 24-75). Tumor was located at choroid in 23 (74.2%) patients, at ciliochoroid in 7 (22.6%) and at ciliary body in 1 (3.2%). According to COMS 93.5% (n=29) was medium and 6.5% (n=2) was large sized. AJCC classification assessed T1 (n=7, 22.5%), T2 (14, 45.1%) and T3 (n=10, 32.4%) with respect to tumor diameter and thickness. Median distance from macula, optic disc and fovea were found to be as 0 mm (range 0-12 mm), 3 mm (range 0-16 mm) and 3 mm (range 0-14mm) respectively. All patient and tumor characteristics in detail are shown in Table 1. Median diameter of tumor with reference to x, y coordinates and thickness were 11 mm (range 5.5-17 mm), 10 mm (range 4.5-17.4 mm) and 6.5 mm (range 3-12.8 mm) respectively. Median volume was 402.9 mm^3 (range 50.3-1189.5 mm^3). A total dose of median 60 Gy (range 30-60 Gy) was administered in median 3 (range 3-7) fractions to a median 89% isodose.

Table 1: Patient Demographics

Characteristics	Value (n)	Percent (%)
Gender		
Female	16	51.6
Male	15	48.4
Age	54 (24-75)	54 (24-75)
Shape		
Dome	25	80.6
Mushroom	3	9.7
Other	3	9.7
Place		
Choroid	23	74.2
Ciliochoroid	7	22.6
Ciliary	1	3.2
T stage		
T1	7	22.6
T2	14	45.2
T3	10	32.3
Distance from macula		
0	19	61.3
1-3	5	16.1
>3	7	22.6
Distance from optic disk		
0	8	25.8
1-3	10	32.3
>3	13	41.9

Distance from fovea		
0	13	41.9
1-3	8	25.8
>3	10	32.3

During a follow-up of median 26 months (range 14-54) after CyberKnife FSRT, local control was assessed in 28 (90.3%) patients but one was lost due to metastatic disease. Overall survival was 96.8%, with 2- and 4-year rate of 97.4% and 94.7% (Figure 1). Survival was not influenced significantly by age (p=0.497), gender (p=0.394), tumor localisation (p=0.550), stage (0.695), tumor thickness (p value was not calculated), radiotherapy dose (p=0338) and local control existence (p=0.732) on univariate analysis. Statistically significant good prognostic factor for overall survival was lack of metastasis (p=0.021).

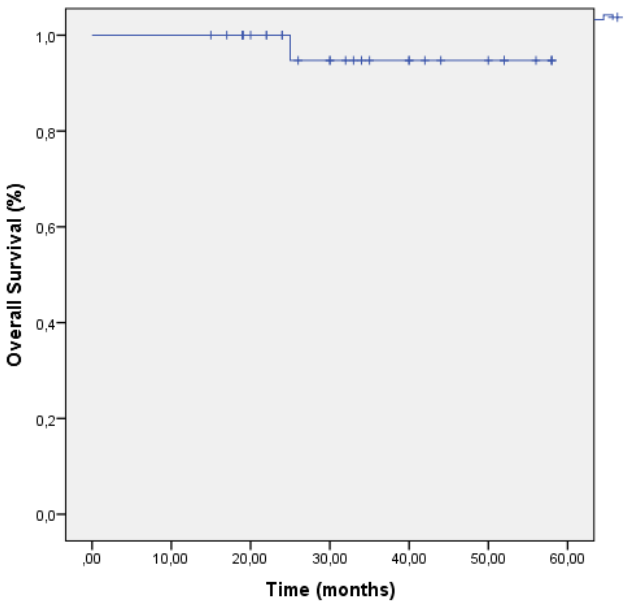

Figure 1: Kaplan-Meier survival curve, overall survival.

Metastasis free survival was 87.1% with 2- and 4-year rate of 89.1% and 81% (Figure 2). During the follow-up, 4 patients (12.8 %) developed metastatic disease, 3 in liver and 1 in lung at 12^{th}.,19^{th}., 22^{th}. and 38^{th} months respectively. Age (p=0.587), gender (p=0.104), tumor localisation (p=0.189), tumor thickness (p=0.376), radiotherapy dose (p=0.085) were not found statistically significant on univariate analysis.

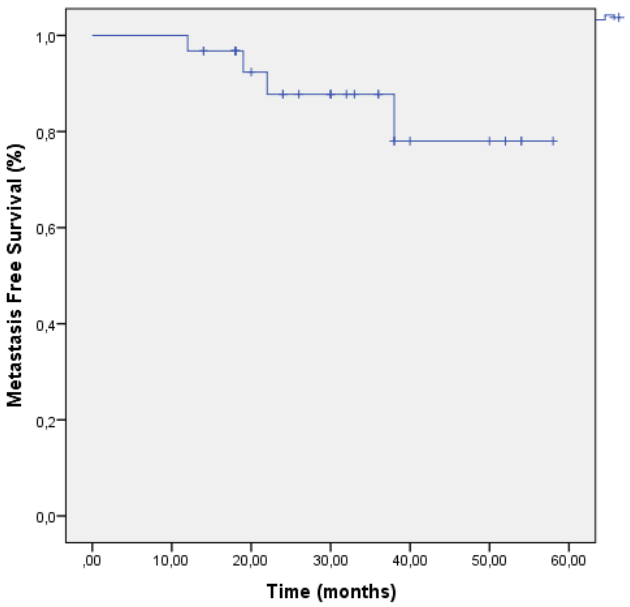

Figure 2: Kaplan-Meier survival curve, metastases free survival.

Local control was achieved in 28 (90.3%) with 2- and 4-year local control of 92.9% and 81.3% (Figure 3). Recurrence was seen in 3 patients on 12th.,15th. and 36th. months after radiotherapy (Figure 4). In univariate analysis, age (p=0.905), gender (p=0.466), tumor localisation (p=0.890), TNM stage (p=0.625), tumor thickness (p=0.480) and radiotherapy dose (p=0.138) remained insignificantly associated with local control. Response rates evaluated according to last follow-up; 5 and 22 patients reached complete and partial response respectively, 1 remained stable (Figure 5).

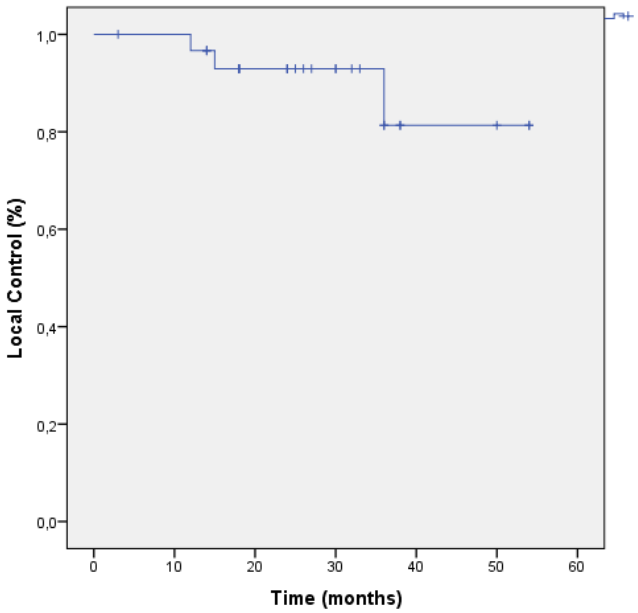

Figure 3: Kaplan-Meier survival curve, local control.

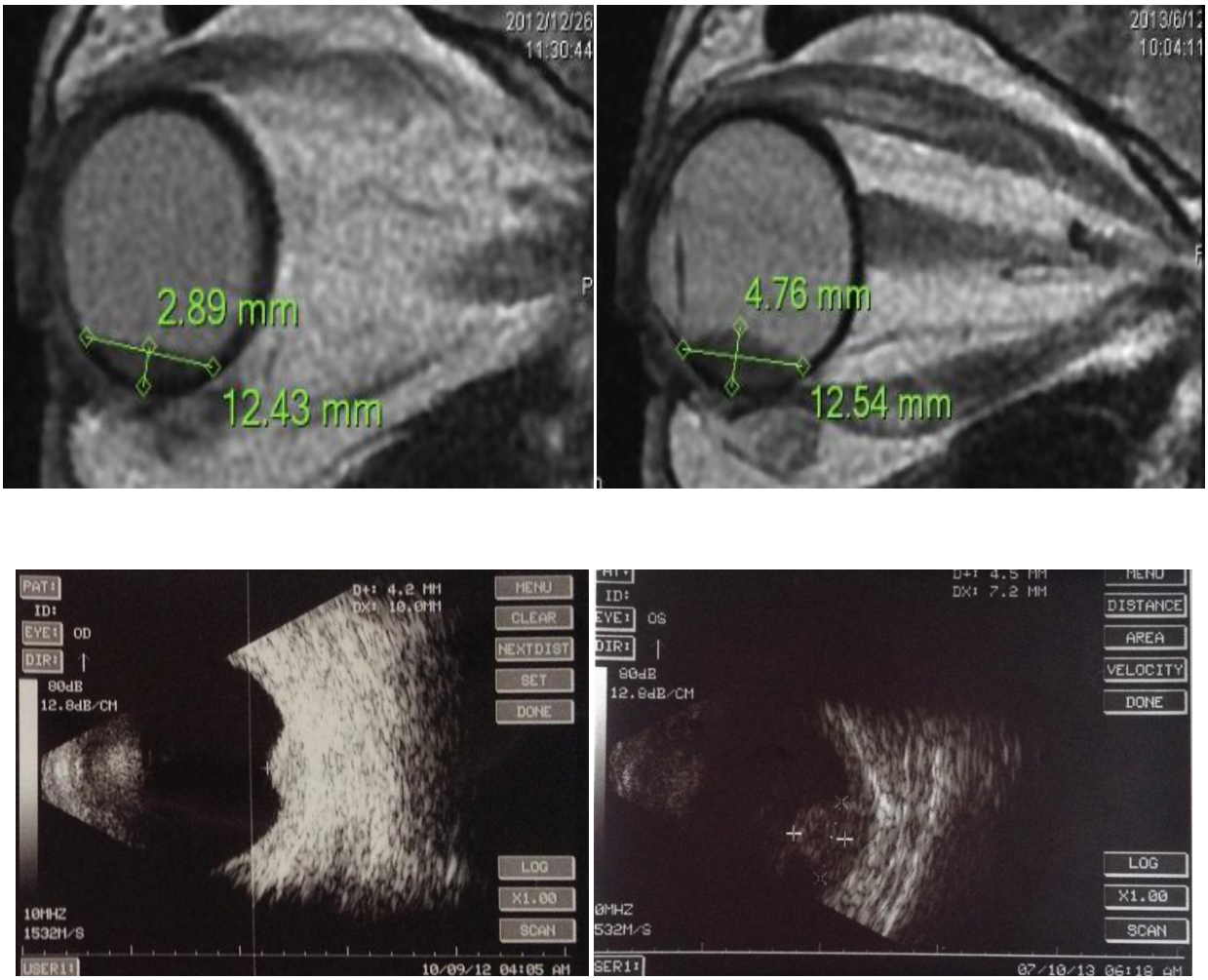

Figure 4: Local Recurrence. Sagittal MR imaging and USG imaging of patient 36th month post radiotherapy.

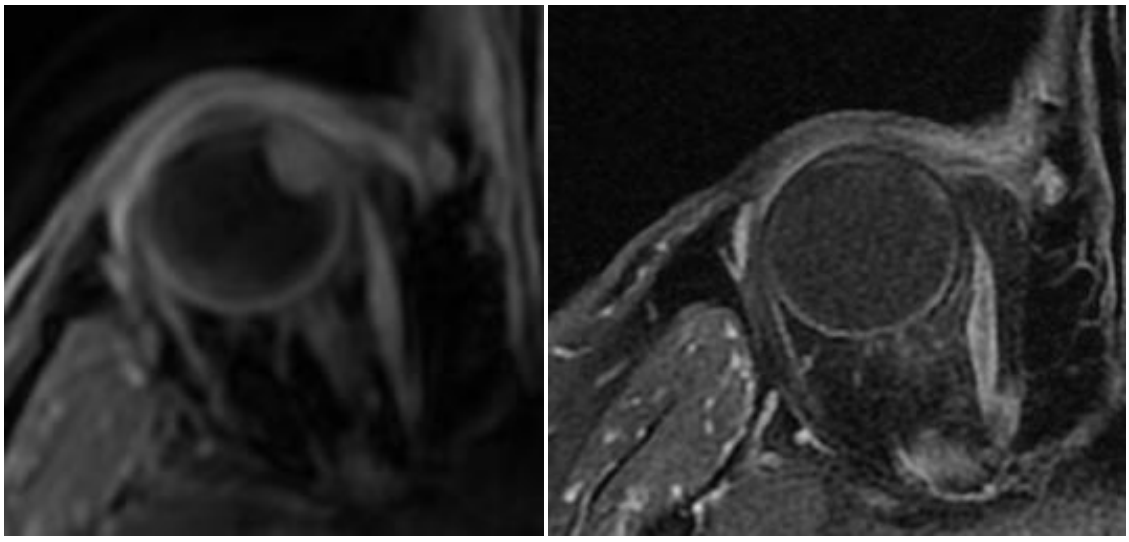

Figure 5: Complete Response. Axial MR imaging of patient 18th month post radiotherapy.

Pretreatment median x, y dimensions, thickness and volumes were 11 mm (range 5.5-17 mm), 10 mm (range 4.5-17.4 mm), 6.5 mm (range 3-12.8) and 402.9 mm^3 (range 50.3 mm-1189.6 mm^3) respectively. At the last follow-up these measurements were 9 mm (range 1.1-13.9mm), 7.3 mm (range 0.9-15.6 mm), 3.5 mm (range 1-10 mm) and 120.7 mm^3 (range 0.5-645.779 mm^3) respectively. Decrease in measurements across the time were statistically significant ($p<0.001$ for x and y, $p=0.001$ for thickness and $p<0.001$ for volume, figure 6).

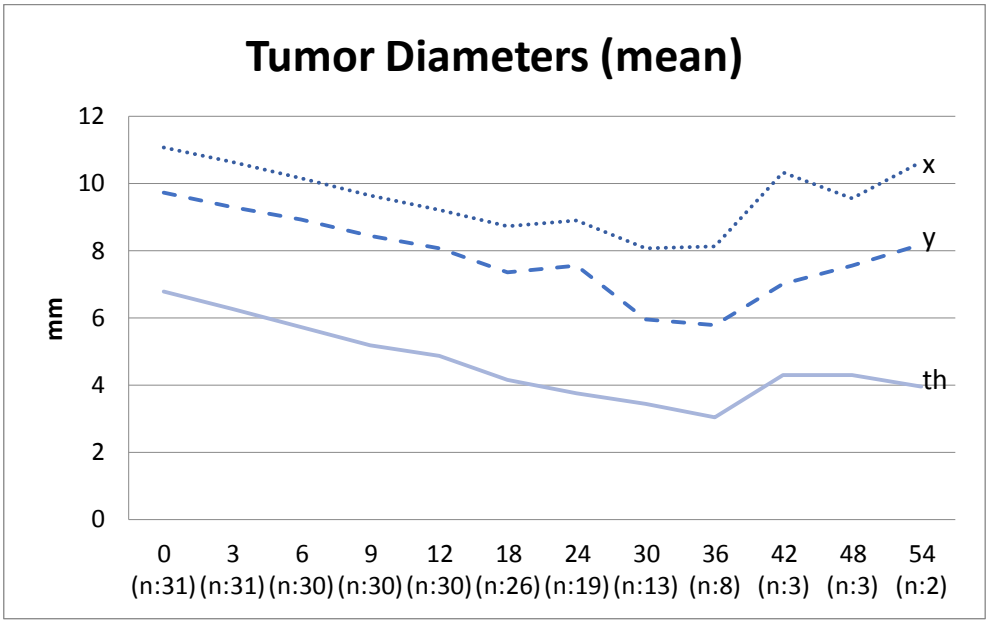

Figure 6: Decrease in measurements across the time were statistically significant (p=0.000 for x and y, p=0.001 for thickness)

During the follow-up enucleation was administered to 8 patients, 3 (9.7%) because of local recurrence and 5 (16.1%) for management of complications. Eye retention rates were 82.1% and 61.9% for 2- and 4-year respectively (Figure 7). Median time interval between radiotherapy and enucleation was 21 months (range 3-40 months). Age, tumor localisation, radiotherapy dose were statistically insignificant factors but gender (p=0.024), COMS stage (p=0.001), tumor thickness (p=0.035), tumor volume (p=0.028) were found statistically significant in univariate analysis.

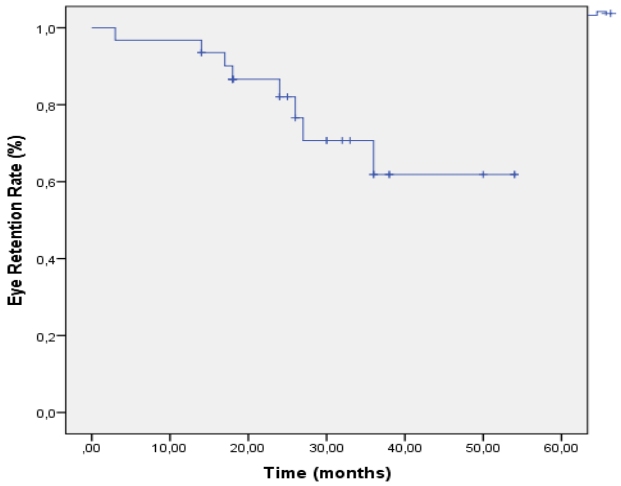

Figure 7: Kaplan-Meier survival curve, eye retention rate.

Visual acuity

Pretreatment visual acuity was ≥ 0.1 in 25 (80.6%) patients and < 0.1 in 6 (19.4%) patients. At the last follow-up these measurements were valid for 13 (41.9%) and 18 (58.1%) patients respectively. Decrease in visual acuity was statistically significant at 9 month (p=0.008).

Toxicity

Treatment related complications in order of frequency were cataract in 17 (54.8%), dry eye in 10 (32.2%), secondary glaucoma in 7 (22.5%), maculopathy in 6 (19.3%), vitreous hemorrhage in 6 (19.3%), retinopathy in 5 (16.1%), optic neuropathy in 4 (12.9%), neovascular glaucoma in 3 (9.6%), synechiae in 2 (6.4%) patients, rubeosis iridis in 1 (3.2%).

DISCUSSION

Because randomized and nonrandomized studies revealed no survival difference between radical surgery versus organ preserving approaches, radiotherapy became one of the first option in UM management in recent years for cases with suitable diameter and localization [3,7-9,23-26]. One of the most widely used radiotherapy method for UM is EPB, with a limited role in relatively big and adjacent to papilla and macula located tumors [3,27]. HIRT is another effective way but proton therapy centers are not common in worldwide [3,12,13]. SRS and FSRT are good alternatives especially in posteriorly located big lesions which plaque cannot reach [10,14-18]. Dosimetric comparison of stereotactic radiotherapy (SRT) systems (Gammaknife, CyberKnife, Linac-based) demonstrated similar outcome with proton radiotherapy in one study and in another study Linac-based FSRT revealed superior outcome in organ at risk doses but more inhomogenity in PTV compared to proton radiotherapy [28,29]. These studies made SRT techniques alternative to HIRT in UM treatment. Organ preserving approaches frequently require invasive procedures for optimal accuracy; for example EPB and HIRT needs surgical implementation for embedment and Gammaknife SRS needs sutures and invasive frame [30-33]. But CyberKnife FSRT is relatively a good option that eye is fixed with local anesthesia and head is fixed with thermoplastic mask for immobilization, so, this radiotherapy technique is more comfortable and acceptable than the others by patients during the preparation of the treatment [19,21].

Various approaches for the management of UM have been described previously, primary goal of the treatment is to prevent metastatic dissemination, in this respect there was no superiority between these approaches. Traditionally, before the 1980s, orbitis enucleated surgically with permanent organ and thereby vision loss [3]. In COMS trial report number 18, 1317 patients with medium-sized tumors were randomized brachytherapy versus enucleation, 5-year overall survival and metastases free survival rates were found 81% and 82%; 89% and 91%, respectively, without statistically significant difference [7]. COMS trial report number 28 showed equivalent survival rates between the two treatment groups after 12 years follow-up period (overall survival 57% vs 59%; metastases free survival 79% vs 83%) [8]. After a while, by rapid developments on SRS techniques, survival analyzes comparing enucleation with SRS in UM management were published, according to these studies, survival outcomes were not affected by treatment arms [25,26]. Overall survival and metastasis free survival rates were 72-94% and 65-91% respectively with SRT and results were similar with other radiotherapy techniques and enucleation [7-9,11,17,24-26,34,35]. In current study we found a 4-year overall survival and metastasis free survival of 94.7% and 81%.

Experimental and clinic trials showed low radiosensitivity for UM [36-39]. Invitro studies demonstrated that UM cell needs a dose of at least 6 Gy for a meaningful antitumor effect [36,37]. Van den Aardweg et al advocated that a single dose of 17-20 Gy or a 3-4 fractions of 8-10 Gy must be applied in order to sterilize a 1 cm^3 tumor [38]. These radiobiological findings led clinicians to prescribe high doses for UM treatment, but this was with increased rate of complications. The optimal total dose and fraction scheme for SRT are not clear yet [11,14,16,40,41]. Reported curative marginal doses were 50-90 Gy for UM with Gammaknife SRS which caused increased radiotherapy related adverse effects. Langman et al determined that reduction in dose from 50 Gy to 40 Gy did not impair local control rates [14]. Mueller et al applied 25 Gy and the early results were promising [16]. Zehetmayer et al tried a total of 45-70 Gy in 1-3 fractions in order to decrease toxicity [41]. Dunavoelgyi et al implemented 50-70 Gy in 5 fractions and found no statistically significant difference in terms of recurrence, metastasis free survival and overall survival [11].

There are so many studies in the literature pointing the efficiency of Gammaknife and Linac-based SRT in UM treatment especially in medium and large sized lesions [10,11,14-18]. CyberKnife is a precise way of Linac SRT and studies about the use of CyberKnife in UM is relatively low [19-21].

Muacevic et al treated 20 UM patients with CyberKnife [19]. They applied 18-22 Gy to a 70% isodose and during a 13 months follow-up, local control was obtained in all patients without glaucoma as an adverse effect, authors concluded. Choi et al applied a total dose of 36-39 Gy in 3 fractions in 6 UM patients who require enucleation but refused to have it [20]. Tumor size decreased in 5 of them, all patients had toxicity but none had organ loss. Zorlu et al treated 5 UM patients with CyberKnife. Total dose was 60 Gy in 3 fractions prescribed to 80-85% isodose [21]. During a follow-up of 8 months, 3 of lesions regressed and 2 remained stable. Our study is unique in terms of patient number and relatively long follow-up period. In our study 4-year local control and eye retention rate was 81.4% and 61% respectively.

Although radiotherapy displaced surgery as an effective organ preserving option, enucleation is performed in progressive disease and in treatment of complications like exudative type retinal decolman, macular edema, neovascular glaucoma and glaucoma which do not respond to medical therapies such as steroid, anti-angiogenetic agents and phototherapy [11,42.] In this study enucleation was performed in case of progressive disease (n=3, 9.6%) and for treatment of complications like vitreous hemorrhage (n=1, 3.2%), rubeosis iridis (n=1, 3.2%), retinopathy (n=1, 3.2%), and glaucoma and synechiae (n=2, 6.4%). Serious complications of radiotherapy decrease quality of life. Langmann et al have found high neovascular glaucoma rate 9 % to 48% depending increased radiation doses (35-80 Gy) [10,14]. Retinopathy and neovascular glaucoma developed in 84 % and 47 % of patients in another Gammaknife SRS study [43]. In a report, 212 patients treated with Linac-based FSRT, 5-year retinopathy, optic neuropathy and neovascular glaucoma rates were 66.4%, 61.5%, 24.5%. We have found relatively low complication rate of neovascular glaucoma (9.6%), optic neuropathy (12.9%) and retinopathy (16.1) as compared to other stereotactic techniques [10,11,14,40,42,43]. This is probably because of fractionation, day between two fractions that enables normal tissues to recover and CT scanning before every fraction to check up local anesthesia for accurate targeting.

Big concerns on the decrease of visual acuity after treatment made UM patients to decline some of the treatment approaches. Unchangeable patient related factors like increased tumor thickness and proximity to fovea (≤ 5mm) are affected visual acuity bad regardless of the form of therapy [44,45]. On the other hand, treatment related factor like big fraction size is associated with decreased visual acuity [11,44,45]. Our results also confirm this finding so that visual acuity worsened significantly at 9 months (p=0.008).

CONCLUSION

In view of our experience, it may be preferable to use CyberKnife FSRT for patients with UM as a noninvasive, precise radiotherapy technique. Fused images before every fraction contribute accuracy of targeting thus increase treatment outcome.

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