Original paper

Ruthenium-106 brachytherapy for thick uveal melanoma: reappraisal of apex and base dose radiation and dose rate

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Abstract

Purpose: To evaluate the outcomes of ruthenium-106 (^{106}Ru) brachytherapy in terms of radiation parameters in patients with thick uveal melanomas.

Material and methods: Medical records of 51 patients with thick (thickness ≥ 7 mm and < 11 mm) uveal melanoma treated with ^{106}Ru brachytherapy during a ten-year period were reviewed. Radiation parameters, tumor regression, best corrected visual acuity (BCVA), and treatment-related complications were assessed.

Results: Fifty one eyes of 51 consecutive patients including 25 men and 26 women with a mean age of 50.5 ± 15.2 years were enrolled. Patients were followed for 36.1 ± 26.5 months (mean ± SD). Mean radiation dose to tumor apex and to sclera were 71 (± 19.2) Gy and 1269 (± 168.2) Gy. Radiation dose rates to tumor apex and to sclera were 0.37 (± 0.14) Gy/h and 6.44 (± 1.50) Gy/h. Globe preservation was achieved in 82.4%. Preoperative mean tumor thickness of 8.1 (± 0.9) mm decreased to 4.5 (± 1.6) mm, 3.4 (± 1.4) mm, and 3.0 (± 1.46) mm at 12, 24, and 48 months after brachytherapy (p = 0.03). Four eyes that did not show regression after 6 months of brachytherapy were enucleated. Secondary enucleation was performed in 5 eyes because of tumor recurrence or neovascular glaucoma. Tumor recurrence was evident in 6 (11.8%) patients. Mean Log MAR (magnification requirement) visual acuity declined from 0.75 (± 0.63) to 0.94 (± 0.5) (p = 0.04). Best corrected visual acuity of 20/200 or worse was recorded in 37% of the patients at the time of diagnosis and 61.7% of the patients at last exam (p = 0.04). Non-proliferative and proliferative radiation-induced retinopathy was observed in 20 and 7 eyes.

Conclusions: Thick uveal melanomas are amenable to ^{106}Ru brachytherapy with less than recommended apex radiation dose and dose rates.

J Contemp Brachytherapy 2016; 8, 1: 66–73
DOI: 10.5114/jcb.2016.57818

Key words: brachytherapy, radiation, ^{106}Ru plaque, uveal melanoma.

Purpose

Uveal melanoma (UM) is the most common primary malignant intraocular tumor in adults [1]. It is a life and sight threatening malignancy that is treatable if diagnosed in time and treated appropriately. The treatment modality of choice is mostly determined by the size and the location of the tumor. While small and medium sized UMs can be successfully treated with a variety of methods, no consensus exists about the optimum management for thick (≥ 7 mm) UMs [2,3,4]. Enucleation has traditionally been the treatment of choice for the majority of large UMs [5], however, in certain situations such as the presence of a tumor in the only remaining eye, poor vision in the fellow eye, or whenever a patient insists on avoiding enucleation, conservative treatment modalities aimed at preserving the diseased eye can be considered [3]. Although improving patient survival has been claimed as the most important rationale to support enucleation as the standard of care for large UM, the Collaborative Ocular Melanoma Study (COMS) results (report No 28) as well as publications by independent groups show that different treatment options, either conservative or radical (enucleation), are not associated with a definitive survival benefit [6,7,8,9]. This is one of the reasons that enucleation has been largely replaced by conservative modalities such

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Received: 02.10.2015
Accepted: 20.01.2016
Published: 26.02.2016

as brachytherapy, proton beam radiation, stereotactic radiotherapy, and tumor resection in recent years [4,5]. Of these, ruthenium-106 (^{106}Ru) brachytherapy is one of the most commonly used treatments [10].

Localized radiation therapy of UM by ^{106}Ru plaques has been the treatment of choice particularly in Europe for medium sized UMs since its introduction in the 1960s [11]. ^{106}Ru emits a spectrum of β-particles that, compared to gamma-radiation of ^{125}I plaques, imposes lower untoward radiation to nontumoral eye structures such as the optic disc, macula, and lens. A major concern for the use of ^{106}Ru plaques is its steep dose gradient in large tumors, meaning that the radiation dose falloff is quick, and in large UMs, the apex dose may not reach the recommended dose of 85 Gy [11]. Thus, some authors believe that ^{106}Ru plaques are not suitable for tumors with a thickness of 7 mm or more because the high dose to the outer sclera is a concern [12,13,14]. In contrast, multiple clinical studies have shown that ^{106}Ru brachytherapy can result in a favorable clinical outcome and complete regression even in large tumors [15,16]. Thus, more data is needed to determine the UM thickness limit and the optimum radiation dose for ^{106}Ru plaque application.

Herein, we report the functional and anatomical outcomes of ^{106}Ru brachytherapy for thick UM with focus on prescribed apex and base radiation dose and dose rate.

Material and methods

Using a historical cohort design, we reviewed the clinical data from all patients with a diagnosis of UM who were treated with ^{106}Ru plaques at the Ocular Oncology Services of Rassoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran and Noor Eye Hospital, Tehran, Iran between October 2002 and March 2013. Fifty one consecutive patients with the diagnosis of thick choroidal or ciliochoroidal melanoma (7 mm ≤ thickness < 11 mm) with no history of distant metastasis who were treated by ^{106}Ru brachytherapy were included in this study. Patients with less than 12 months follow-up were excluded. Chart data included patient demographics, best corrected visual acuity (BCVA), slit-lamp, and fundus examination findings including tumor location, pigmentation, distance between the posterior border of the tumor and fovea and optic disc, the presence of retinal invasion, and the presence of subretinal fluid at initial exam. The largest basal diameter and apical height at initial and follow-up examinations were recorded by an experienced ophthalmic ultrasonographer. The tumor size was measured on ultrasound images; clinical target volume (CTV) was determined as basal tumor diameter plus a 2 mm safety margin and an extra 1 mm on tumor height to account for scleral thickness. Calibration of the plaques was done in a homemade Perspex eye phantom in orthogonal planes perpendicular to the central axis of the plaques using Gafchromic EBT2 film (ISP, Wayne, NJ, USA) [17]. The manufacturer's specifications on point dose levels in water were measured. Isodose planes perpendicular and parallel to the applicator central axis were determined and used to evaluate the CTV coverage. The size of the eye plaques was determined to be at least 3 mm larger than the tumor basal diameter to account for inactive rim and safety margin. Three plaques, namely CCB, CGD, and COB were used. At the time of the treatment, the plaques' dose rate was corrected based on ^{106}Ru decay factor and the time since its manufacture.

$$\text{Corrected apical dose rate at the day of application (Gy/h)} = \frac{\text{Apical dose rate at the time of plaque construction (mGy/min)} \times \text{decay factor} \times 60}{1000}$$

To calculate the overall treatment time, the apical dose covering the CTV thickness (prescription dose) is divided by the corrected apical dose rate at the time of surgery.

$$\text{Overall treatment (h)} = \frac{\text{Total prescribed dose (Gy)}}{\text{Dose rate (Gy/h)}}$$

In few instances where scleral maximum dose could surpass the 1500 Gy limit, implementation time was calculated differently, i.e. the scleral tolerance dose of 1500 Gy was divided by dose rate at a point 0.6 mm distant from the surface of the plaque. As such, the apical dose could be less than the recommended 100 Gy for uveal melanomas [18].

Radiation parameters (plaque shape and size, total radiation dose to apex and base, radiation dose rate for apex and base, and duration of radiation) were documented. Complications such as radiation related retinopathy and papillopathy, cataract, vitreous hemorrhage, neovascular glaucoma (NVG), and scleral necrosis were noted. The treatment protocol in both centers required us to offer enucleation as the first and standard treatment modality for all patients with UM equal to or larger than 7 mm in thickness. Patients who rejected enucleation were considered for ^{106}Ru brachytherapy. The off-label use of ^{106}Ru brachytherapy for a tumor height ≥ 7 mm and the safety concerns were discussed extensively with the patient and family, and an informed consent was obtained. Patients with a tumor height ≥ 11 mm, any evidence of large extraocular extension (> 3 mm in largest diameter), systemic metastasis of the tumor, and a history of prior treatment for UM were not considered for brachytherapy. Tumor thickness and tumor diameters were measured by standardized A-scan and B-scan ultrasonography (Aviso, Quantel Medical SA, Le Brezet, France). A comprehensive systemic workup including physical examination, liver enzyme tests, liver ultrasound and abdominal CT scan (if needed), and chest X-ray were performed for all patients to rule out the possibility of distant metastasis. The study was approved by the Ethics Committee of the Eye Research Center at Rassoul Akram Hospital and Noor Eye Hospital.

Surgical procedure

All surgeries were performed under general anesthesia by one surgeon (MNP). Tumor outlines over the sclera were identified by intraoperative transillumination for pigmented tumors and indirect ophthalmoscopy for non-pigmented tumors. Acrylic dummies checked

tumor location before selecting and suturing the radioactive plaque. Extraocular muscles were temporarily disinserted by hang-back suture if needed. ^{106}Ru plaques were supplied by BEBIG Company (BEBIG Isotopen und Medizintechnik GmbH, Berlin, Germany) in different shapes and sizes. The target radiation dose for the tumor apex was 100 Gy provided that the scleral doses did not exceed 1500 Gy. The dose rate correction has been applied for different dose rates [19]. We included a lateral safety margin of 2 mm around the tumor base [20]. Using 5-0 Mersilene sutures, plaques were secured to the sclera for the duration of calculated radiation time. The plaque was removed, and conjunctiva was sutured with 7-0 Vicryl sutures at the end of the radiation period. After initial biweekly visits for four weeks, patients were followed every 3 months during the first year after surgery, every 4 months up to 2 years, and every 6 months thereafter. The follow-up examinations included BCVA, slit lamp biomicroscopy, dilated fundus examination, applanation tonometry, and A- and B-scan ultrasonography. Color fundus photography, OCT, and fluorescein angiography were performed if any evidence of proliferative radiation retinopathy was suspected. Liver enzymes were checked and a liver ultrasound was performed every 6 months. A chest x-ray was obtained annually for all patients. Transpupillary thermotherapy was performed using a commercial 810 nm laser (Iris Medical, Instruments, Inc. Mountain, CA, USA) as an adjuvant therapy in patients with insufficient reduction in thickness at least 6 months after ^{106}Ru brachytherapy.

Table 1. Demographics and tumor characteristics of 51 patients with thick uveal melanoma (thickness ≥ 7 mm)

Features	Values
Number	51
Age (years); median (mean, range)	48 (50.5, 17-84)
Gender (male, female)	(25, 26) (49%, 51%)
Medical history	
None	40 (78.43%)
Diabetes mellitus	3 (5.88%)
Hypertension	8 (15.69%)
Eye	
Right, left	22, 29 (43.1%, 56.9%)
Tumor	
Choroidal melanoma	42 (82.35%)
Ciliochoroidal melanoma	9 (17.65%)
Tumor dimensions (mm)	
Base 1 (min, max, mean, median)	(7.00, 19.00, 13.83, 14.00)
Base 2 (min, max, mean, median)	(6.00, 18.00, 12.20, 12.00)
Thickness (min, max, mean, median)	(7.00, 10.50, 8.12, 8.00)
Shape	
Dome shaped	38 (74.5%)
Mushroom shaped	13 (25.5%)
Subretinal fluid	
Yes	39 (76.5%)
No	12 (23.5%)
Distance to optic disc (mm); median (mean, range)	3.00 (3.92, 0.00-13.00)
Distance to foveola (mm); median (mean, range)	3.00 (3.85, 0.00-11.00)
Overhanging on the disc	
0	46 (90.20%)
< 50%	4 (7.84%)
≥ 50%	1 (1.96%)

Analysis of data was done using SPSS version of 20.0 (SPSS Inc., Chicago, Il, USA). Paired *t*-test was used to compare changes of numeric variables during follow-up times. We used univariate analyses and estimated crude hazard risks using Cox proportional hazard model. The study endpoints of globe preservation, visual outcome, and radiation induced complications were entered in multivariate Cox proportional hazard models to estimate the adjusted hazard risks (AHR). Time-to-event analyses for patients free of enucleation, tumor recurrence, and complications were assessed using Kaplan-Meier estimate. In these analysis, each endpoint entered separately and for each endpoint, if at the end of follow-up the event did not occurred, or the patient was dropped out of the study due to any reason during the follow-up, considered as "censored". A statistically significant level was defined at ≤ 0.05.

Results

Fifty one eyes of 51 patients with thick uveal melanoma including 25 men and 26 women with a mean (± SD) age of 50.5 (± 15.2) years (range: 17-84 years) were treated with ^{106}Ru brachytherapy. Patients were followed for a median time of 29.5 months (mean ± SD: 36.1 ± 26.5 months, range: 12-112 months). Table 1 shows patient demographic data and tumor characteristics.

The mean prescription dose to the apex and sclera was 71 Gy (range: 31-104 Gy) and 1269 Gy (range: 809-1560 Gy), respectively. The mean radiation dose rate at the tumor apex and sclera was 0.37 Gy/h (range: 0.13-0.79) and 6.44 Gy/h (range: 3.75-9.34), correspondingly. Generally, because of the scleral limit of 1500 Gy, 33.3% of patients received an apex dose less than 60 Gy, 29.4% received a dose between 60 and 80 Gy, and 37.3% received a dose more than 80 Gy. Regarding the base dose, all of the tumors have been irradiated with a dose more than 800 Gy (mean dose of 1269 Gy) and 48 eyes (94%) have been irradiated more than 1000 Gy. Table 2 shows dosimetric characteristics of this 51 patients.

The total number of patients for calculation were 47, 45, and 40 at 12, 24, and 48 months after treatment. Two patients had not thickness examinations at 48 month follow-up. Preoperative average tumor thickness of 8.1 ± 0.9 mm decreased to 4.5 (± 1.6), 3.4 (± 1.4), and 3.0 (± 1.46) mm at 12, 24, and 48 months after brachytherapy, respectively.

Table 2. Dosimetric characteristics of ^{106}Ru plaque treatment of 51 patients with thick choroidal and ciliochoroidal melanoma and two subgroup of patients with and without recurrent lesions

Parameter	51 patients	45 patients without recurrence	6 patients with recurrence
Radiation hours (range, mean, median)	101-314, 209, 215	101-314, 210, 215	135-281, 211, 212
Apex dose rate (Gy/h) (range, mean, median)	0.13-0.79, 0.37, 0.37	0.13-0.79, 0.36, 0.34	0.2-0.6, 0.36, 0.33
Apex dose (Gy) (range, mean, median)	31-104, 71, 74	31-104, 71.4, 74.3	40-93.5, 69, 73
Scleral dose rate (Gy/h) (range, mean, median)	3.8-9.3, 6.4, 6.0	3.7-9.3, 6.4, 6.1	5-9, 6.3, 5.6
Scleral dose (Gy) (range, mean, median)	809-1560, 1269, 1306	809-1560, 1277, 1341	1105-1350, 1232, 1243

Evidence of regression was not seen in 4 eyes (7.8%) during the first 6 months of brachytherapy, so early enucleation was performed. In these patients, the average tumor thickness was 8.9 mm and mean apical and scleral radiation dose was 55.3 and 1337 Gy, respectively.

Secondary enucleation was done in an additional 5 (9.8%) eyes due to the recurrence of the tumor or due to neovascular glaucoma development. The median time to late enucleation was 31 (range: 12-71) months. Based on Kaplan-Meier estimates, enucleation was essential in 13.7% and 17.6% of patients at 5 and 10 years follow-up, respectively (Table 3).

The overall anatomical success rate (preserving the eye) was 82.4% (42 out of 51 cases) in our study. Recurrence of tumor in 6 patients in this study was managed with enucleation in 3 patients, transpupillary thermotherapy in one patient, and secondary ^{106}Ru plaque insertion in two other patients. Enucleation was indicated in two patients with severe post-treatment tumor necrosis and extensive intraocular hemorrhage 38 and 25 months after brachytherapy. Kaplan–Meier survival analysis showed 11.8% and 13.7% tumor recurrence at 5 and 10 years, respectively (Table 3). The median time to recurrence was 12 (range 2-71) months.

Factors predicting enucleation, poor visual acuity (VA less than 20/200), and tumor recurrence are listed in Table 4. Although in the univariate model, the history of hypertension, tumor overhanging on optic nerve head, notched plaque shape, and radiation hours were predictors of enucleation ($p < 0.05$), in multivariate analysis, the only predictor of enucleation was past medical history of hypertension. (Cox proportional hazard estimate, HR = 3.60, $p = 0.02$). Since in bi-variate analyses, the radiation hours was significant – not the radiation dose, so we just entered the radiation hours factor in multivariate analyses. The location of recurrence was at the margin in 3 (5.8%) eyes and at the center in 4 (7.8%) tumors. History of hypertension and notched plaque shape were predictors for tumor recurrence in univariate analysis.

Preoperative BCVA (mean ± SD) of 0.75 ± 0.63 Log MAR dropped to 0.94 ± 0.50 at last follow-up ($p = 0.04$). Thirty-seven percent (12 eyes) of the patients at the time of diagnosis and 61.7% (29 eyes) of the patients at last exam had BCVA of 20/200 or worse ($p = 0.04$). Using

Table 3. Kaplan-Meier analyses estimate the likelihood of developing poor final outcome at 2, 5, and 10 years of follow-up after ^{106}Ru plaques radiotherapy

Outcomes	At 2 years (*n*, %)	At 5 years (*n*, %)	At 10 years (*n*, %)
Poor visual acuity (20/200 or worse)	15, 31.9%	27, 57.4%	29, 61.7%
Complications			
Retinopathy			
Proliferative	5, 10.6%	6, 12.8%	7, 13.7%
Non-proliferative	13, 25.5%	19, 37.2%	20, 39.2%
Maculopathy	8, 15.7%	10, 19.6%	10, 19.6%
Papillopathy	9, 19.1%	15, 31.9%	15, 31.9%
Cataract	15, 31.9%	18, 38.3%	19, 40.4%
Neovascular glaucoma	2, 3.9%	2, 3.9%	3, 5.9%
Vitreous hemorrhage	5, 9.8%	8, 15.7%	9, 17.6%
Enucleation	6, 11.8%	7, 13.7%	9, 17.6%
Tumor recurrence	5, 9.8%	6, 11.8%	7, 13.7%

Table 4. Predictors of enucleation, tumor recurrence, and poor visual acuity in 51 patients with thick choroidal melanoma (7 mm ≤ thickness < 11 mm) after ^{106}Ru brachytherapy (poor visual acuity was defined as VA less than or equal to 20/200)

Variable	*p* value	Hazard ratio	95% confidence interval
Enucleation predictors			
History status[a]	0.037	11.12	1.160-107.889
Tumor overhanging on optic nerve[b]	0.022	5.35	1.160-22.493
Plaque shape[c]	0.004	10.83	2.180-53.845
Radiation hours[d]	0.046	1.02	1.000-1.032
Tumor recurrence predictors			
History status[a]	0.012	8.74	1.595-47.923
Plaque shape[c]	0.005	3.37	1.109-11.294
Poor visual acuity predictors			
Tumor shape[e]	0.022	2.45	1.138-5.258
Distance to optic nerve[f]	0.035	0.45	0.214-0.944
Plaque shape[c]	0.005	2.81	1.356-5.831

[a]Hypertension present or absent, [b]present vs. absent, [c]COB vs. CCB vs. CGD, [d]mean radiation hours, [e]mushroom vs. dome-shaped, [f]less than vs. ≥ 3 mm

Kaplan-Meier estimates, poor visual acuity (VA ≤ 20/200) was evident in 31.9% and 57.4% of the cases at 2 and 5 years follow-up, respectively (Table 3). Mushroom-shaped tumor and a less than 3 mm distance to optic nerve were significant predictors of poor visual acuity (Table 4).

Adjuvant transpupillary thermotherapy was performed in 9 (19.4%) eyes. Tumor related metastasis was observed in 3 (5.9%) patients, and one of these patients died of liver metastasis during the follow-up time.

Non-proliferative radiation retinopathy was observed in 20 eyes (39.2%) and proliferative retinopathy in 7 other eyes (13.7%). Of all patients who had radiation retinopathy (proliferative and non-proliferative), macular involvement was evident in 10 (19.6%) patients. Vitreous hemorrhage developed in 9 eyes (17.6%) after treatment. Non-clearing vitreous hemorrhage in 5 eyes (9.8%) was successfully managed with parsplana vitrectomy. Radiation papillopathy and cataract progression was detected in 15 eyes (29.4%) and 19 eyes (37.2%), respectively. Predictors of radiation maculopathy, radiation papillopathy, and radiation retinopathy are summarized in Table 5. All predictors had significant effects on radiation complications in univariate analysis. We were not able to show any significant effects after adjusting these variables in multivariate analysis.

Postoperative temporary increase in subretinal fluid (SRF) was managed conservatively in all except one patient who was monocular and experienced bullous, exudative retinal detachment followed by neovascularization of the iris (NVI) during the first month after brachytherapy. Because of the absence of response to oral corticosteroids, parsplana vitrectomy with endolaser photocoagulation and silicone oil tamponade was performed for this patient. Postoperative NVI was managed with an intravitreal bevacizumab injection in 4 (7.8%) patients.

Discussion

Identification of a cut-off point as an optimal height for each isotope to manage the uveal melanoma with brachytherapy and avoid of enucleation is still unresolved issue.

Although based on the COMS recommendation [21] tumors, up to 10 mm can be treated with ^{125}I brachytherapy, published studies from European countries [14,22,23] indicate that ^{106}Ru radioactive plaques is a choice of treatment for uveal melanomas with tumor height of 5.4 to 7 mm because of its limited depth of penetration. Therefore, the cut-off point of 7 mm was considered for thick tumor implication and inclusion criterion in our study.

Our study showed that ^{106}Ru brachytherapy in selected eyes with thick uveal malignant melanomas (7 mm ≤ thickness < 11 mm) that would otherwise be managed with enucleation could result in a high local tumor control rate in spite of the less than recommended radiation dose and dose rate to the apex in the majority of our cases.

Enucleation with or without pretreatment radiation is classically recommended for UM thicker than 7 mm [24]. Alternative treatments include brachytherapy [14,25,26], gamma-knife radiosurgery [27], proton beam radiation [28,29], fractionated stereotactic radiotherapy [30,31], and partial lamellar sclerouvectomy [32]. However, none of these alternative therapies has been evaluated prospectively.

Published data regarding the impact of brachytherapy on UM generally support two schools of thought [33]. Some studies emphasize achieving 85 Gy of radiation to the tumor apex [16], provided no more than 1000 Gy is applied to the sclera [33]. Based on this concept, the tumor apex should receive enough of a tumoricidal radiation dose to kill the tumor cells directly. Others believe that

Table 5. Predictors of radiation maculopathy, radiation papillopathy, and radiation retinopathy in patients with thick choroidal melanoma (7 mm ≤ thickness < 11 mm) treated with ^{106}Ru brachytherapy

Variable	*p* value	Hazard ratio	95% confidence interval
Predictors (radiation maculopathy)			
Tumor thickness	0.032	0.28	0.088-0.899
Radiation dose at tumor apex[a]	0.005	1.83	1.001-3.402
Radiation dose rate at tumor apex[b]	0.016	1.04	1.008-1.085
Radiation dose rate at tumor base[b]	0.041	1.40	1.007-2.430
Predictors (radiation papillopathy)			
Radiation at tumor base[c]	0.006	0.80	0.683-0.939
Tumor shape[d]	0.004	4.45	1.609-12.327
Radiation dose rate at tumor apex[b]	0.027	1.03	1.004-1.067
Radiation dose rate at tumor base[b]	0.040	1.04	0.103-1.931
Predictors (retinopathy)			
Tumor location[e]	0.047	3.39	1.018-11.285
Tumor thickness[f]	0.019	0.55	0.331-0.907
Plaque shape[h]	0.041	4.76	1.065-21.304

[a]Radiation dose (in Gy), [b]radiation dose rate (in Gy/hr), [c]tumor diameter (in mm), [d]mushroom vs. dome-shaped, [e]choroidal vs. ciliochoroidal, [f]mean tumor thickness (in mm), [h] COB vs. CCB vs. CGD

indirect tumoricidal effects of radiation through obliterating tumor blood supply can justify lower doses to apex even when the tumor is very thick, and the apex of tumor will receive radiation less than the recommended dose [15,16,34]. Compatible with this theory, some authors [22] have recommended a minimal radiation dose of 300-400 Gy to the sclera for development of choroidal atrophy.

Our results showed 82.4% globe preservation with an average ^{106}Ru radiation dose of 71 Gy to the apex. This is similar to Kaiserman *et al.* [15] report, which indicated 71.4% globe preservation in patients with thick UM (≥ 8 mm in thickness) treated with ^{106}Ru brachytherapy at mean apex dose of 69.9 Gy.

Radiation complications are major causes of visual loss after brachytherapy. One of the most important approaches to reduce radiation complications secondary to brachytherapy is to prescribe a less than conventional therapeutic dose of 85 Gy to the tumor apex, without compromising local tumor control. In a retrospective review of 62 patients treated with ^{125}I plaque brachytherapy for choroidal melanoma, Saconn *et al.* [35] prescribed a lower dose of radiation to the apex. Although the mean apex dose was reduced to 62.5 Gy, the 5-year enucleation rate was 12.0%, which is comparable to the 13.7% enucleation rate at 5 years in our study with the mean apex dose of 71 Gy (median 73.6 Gy).

Our results are also similar to those reported by Shields *et al.* [26] who reported a 24% enucleation rate at 5 years in 354 patients with large posterior UM treated with median apex dose of 80 Gy. The lower enucleation rate in our study might be explained by higher radiation dose to the base of the tumors and less median tumor thickness. The median base dose in our cases was 1306 Gy, which is three times more radiation than scleral dose of patients treated with ^{125}I plaques in Shields' study [26]. It is of interest that none of our patients developed scleral necrosis, reported in 1% [36] of patients following brachytherapy. This could be explained, by either a lower number of ciliochoroidal tumors, a known risk factor for scleral necrosis, or the short follow-up time in our cases.

The median apex dose rate in our patients was 0.37 Gy/h, which is less than the American Brachytherapy Society recommended dose rate of 0.60-1.05 Gy/h. In contrast to Quivey *et al.* [37] who reported that a dose rate of less than 0.50 Gy/h could be associated with a 4.75 fold increase in local failure using ^{125}I, we did not find any statistical difference between preserved and enucleated eyes regarding the apex dose rate. This may be due to small numbers of events (enucleation) in our study or more radiation dose to the base of tumors.

Poor visual function (VA ≤ 20/200) was evident in 31.9%, 57.4%, and 61.7% of cases at 2, 5, and 10 years follow-up, respectively. In a large analysis of 579 patients with posterior UM of all sizes treated with ^{106}Ru brachytherapy by Bergman *et al.* [14], poor visual acuity at 2, 5, and 10 years was reported in 32.5%, 39.2%, and 44.8% of the patients. The higher rate of vision loss in our patients could be explained by greater tumor thickness as well as higher radiation dose to the sclera. All patients in our study had thick tumors, however, only 9.5% of enrolled patients reported by Bergman *et al.* [14] had a tumor thickness more than 7 mm. The importance of tumor thickness on ultimate final visual acuity after brachytherapy has been emphasized in multiple reports [38,39].

Although the comparison of our results and other published outcomes regarding the VA is complicated because of differences in patient demographics, tumor characteristics, and radiation parameters, the percentage of our patients with a final vision of 20/200 or less is comparable to those of Shields *et al.* [26] and Kaiserman *et al.* [15].

Several studies have addressed UM recurrence following brachytherapy. Lommatzsch *et al.* [11] evaluated 141 eyes with small, medium, and large UMs treated with ^{106}Ru brachytherapy and reported a cumulative 15-year tumor recurrence in 37% of patients. Wilson and Hungerford reported a 5-year tumor recurrence of 4%, 11%, and 5% following ^{125}I brachytherapy, ^{106}Ru brachytherapy, and proton beam radiotherapy, respectively. This is in accordance with an 11.8% and 13.7% recurrence rate at 5 and 10 years in our patients.

Neovascular glaucoma is not uncommon after radiotherapy for large UM. We detected early (less than 6 months post-operation) NVI without NVG in 7.8% of patients with thick UM. All of these patients developed total exudative retinal detachment immediately following brachytherapy. Neovascularization of the iris was treated with single or multiple intravitreal bevacizumab injections. The incidence of late neovascular glaucoma (developed after 6 months) was 3.9% during the first 5 years of follow-up. This complication was successfully treated with intravitreal bevacizumab injections and medication in the majority of cases.

Lower complications rate in our series of thick UMs may be a result of a lower radiation dose of apex and/or a possible selection bias due to a tendency to enucleate very thick tumors. Therefore, tumors with a greater chance of receiving higher radiation and developing radiation-related complications were enucleated before entering our study. Also, the small sample size and retrospective nature of the study may limit generalization of our conclusions.

Conclusions

In summary, ^{106}Ru brachytherapy is a successful alternative for enucleation for thick uveal melanoma. Lower doses of radiation to tumor apex, provided that enough radiation doses is delivered to the sclera, can successfully treat the tumors possibly because of the effects of radiation on tumor blood supply. Randomized prospective studies are warranted to find the optimum ^{106}Ru plaque radiation dose and dose rate balancing local tumor control and radiation complications.

Disclosure

Authors report no conflict of interest.

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