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 (106Ru) 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 106Ru 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 106Ru brachytherapy with less than recommended apex radiation dose and dose rates.

Key words: brachytherapy, radiation, 106Ru 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 as...
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 UM since its introduction in the 1960s [11]. \(^{106}\)Ru emits a spectrum of \(\beta\)-particles that, compared to gamma-radiation of \(^{125}\)I plaques, imposes lower up-toward 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 fall off is quick, and in large UM, 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 Gafchromatic 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.

Corrected apical dose rate at the day of application (Gy/h) = Apical dose rate at the time of plaque construction (mGy/min) × decay factor × 60

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

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.

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 extracocular 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. 106Ru 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 106Ru brachytherapy.

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 106Ru 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 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%)  |
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 106Ru 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).

| 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, 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     |

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

### Table 3. Kaplan-Meier analyses estimate the likelihood of developing poor final outcome at 2, 5, and 10 years of follow-up after 106Ru 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%           |

Journal of Contemporary Brachytherapy (2016/volume 8/number 1)
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 trans-sphincter 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 pars-plana 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, pars-plana 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.

Table 4. Predictors of enucleation, tumor recurrence, and poor visual acuity in 51 patients with thick choroidal melanoma (7 mm ≤ thickness < 11 mm) after 106Ru 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 statusa                       | 0.037   | 11.12        | 1.160-107.889           |
| Tumor overhanging on optic nerveb     | 0.022   | 5.35         | 1.160-22.493            |
| Plaque shapec                         | 0.004   | 10.83        | 2.180-53.845            |
| Radiation hoursd                      | 0.046   | 1.02         | 1.000-1.032             |
| **Tumor recurrence predictors**       |         |              |                         |
| History statusa                       | 0.012   | 8.74         | 1.595-47.923            |
| Plaque shapec                         | 0.005   | 3.37         | 1.109-11.294            |
| **Poor visual acuity predictors**     |         |              |                         |
| Tumor shapeb                          | 0.022   | 2.45         | 1.138-5.258             |
| Distance to optic nervef              | 0.035   | 0.45         | 0.214-0.944             |
| Plaque shapec                         | 0.005   | 2.81         | 1.356-5.831             |

aHypertension present or absent; bpresent vs. absent; cCOB vs. CCB vs. CGD; dmean radiation hours; emushroom vs. dome-shaped; fless than vs. ≥ 3 mm

**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 125I brachytherapy, published studies from European countries [14,22,23] indicate that 106Ru 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 106Ru 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
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 ($\geq$ 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 $\leq$ 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].

Table 5. Predictors of radiation maculopathy, radiation papillopathy, and radiation retinopathy in patients with thick choroidal melanoma ($7 \text{ mm} \leq \text{ thickness} < 11 \text{ mm}$) 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 | 0.005 | 1.83 | 1.001-3.402 |
| Radiation dose rate at tumor apex | 0.016 | 1.04 | 1.008-1.085 |
| Radiation dose rate at tumor base | 0.041 | 1.40 | 1.007-2.430 |
| Predictors (radiation papillopathy) | | | |
| Radiation at tumor base | 0.006 | 0.80 | 0.683-0.939 |
| Tumor shape | 0.004 | 4.45 | 1.609-12.327 |
| Radiation dose rate at tumor apex | 0.027 | 1.03 | 1.004-1.067 |
| Radiation dose rate at tumor base | 0.040 | 1.04 | 1.030-1.931 |
| Predictors (retinopathy) | | | |
| Tumor location | 0.047 | 3.39 | 1.018-11.285 |
| Tumor thickness | 0.019 | 0.55 | 0.331-0.907 |
| Plaque shape | 0.041 | 4.76 | 1.065-21.304 |

*aRadiation dose (in Gy), *bradiation dose rate (in Gy/hr), *ctumor diameter (in mm), *dmushroom vs. dome-shaped, *echoroidal vs. ciliochoroidal, *fmean tumor thickness (in mm), *gCOB vs. CCB vs. CGD
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 Kaiser 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.

References

1. Strickland D, Lee JA. Melanomas of eye: stability of rates. Am J Epidemiol 1981; 113: 700-702.
2. Robertson DM. Changing concepts in the management of choroidal melanoma. Am J Ophthalmol 2003; 136: 161-170.
3. Damato BE. Treatment selection for uveal melanoma. Dev Ophthalmol 2012; 49: 16-26.
4. Shields CL, Shields JA. Recent developments in the management of choroidal melanoma. Curr Opin Ophthalmol 2004; 15: 244-251.
5. Bell DJ, Wilson MW. Choroidal melanoma: natural history and management options. Cancer Control 2004; 11: 296-303.
6. Adams KS, Abramson DH, Ellsworth RM et al. Cobalt plaque versus enucleation for uveal melanoma: comparison of survival rates. Br J Ophthalmol 1988; 72: 494-497.
7. De Potter P, Shields CL, Shields JA et al. Impact of enucleation versus plaque therapy in the management of juxtapapillary choroidal melanoma on patient survival. Br J Ophthalmol 1994; 78: 109-114.
8. Seddon JM, Gragoudas ES, Albert DM et al. Comparison of survival rates for patients with uveal melanoma after treatment with proton beam irradiation or enucleation. Am J Ophthalmol 1985; 99: 282-290.
9. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28. Arch Ophthalmol 2006; 124: 1684-1693.
10. The American Brachytherapy Society – Ophthalmic Oncology Task Force, The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. Brachytherapy 2014; 13: 1-14.
11. Lommatzsch P, Vollmar R. A new way in the conservative therapy of intraocular tumors by means of beta-irradiation (Ruthenium 106) with preservation of vision. Klin Monbl Augenheilkd 1966; 148: 682-699.
12. Nag S, Quivey JM, Earle JD et al. The American Brachytherapy Society recommendations for brachytherapy of uveal melanomas. Int J Radiat Oncol Biol Phys 2003; 56: 544-555.
13. Damato B, Patel I, Campbell IR et al. Visual acuity after Ruthenium (106) brachytherapy of choroidal melanomas. Int J Radiat Oncol Biol Phys 2005; 63: 392-400.
14. Bergman L, Nilsson B, Lundell G et al. Ruthenium brachytherapy for uveal melanoma, 1979-2003: survival and functional outcomes in the Swedish population. Ophthalmology 2005; 112: 834-840.
15. Kaiserman N, Kaiserman I, Hendler K et al. Ruthenium-106 plaque brachytherapy for thick posterior uveal melanomas. Br J Ophthalmol 2009; 93: 1167-1171.
16. Kreusel KM, Bechrakis N, Riese J et al. Combined brachytherapy and transpupillary thermotherapy for large choroidal melanomas: tumor regression and early complications. Graefes Arch Clin Exp Ophthalmol 2006; 244: 1575-1580.
17. Heilemann G, Nesvail N, Blackner M et al. Multidimensional dosimetry of 106 Rureau plaques using EBT3 films and its impact on treatment planning. Med Phys 2015; 42: 5798-5808.
18. Pötter R, Van Limbergen Erik. In: GEC ESTRO Handbook of Brachytherapy. Brussels 2002; 591-610.
19. Gérard JP, Grange JD, Romestaing P et al. Curietherapy using a ruthenium and iridium disk in the treatment of choroidal melanoma. Augen heilkd Klin Monbl (Ruthenium 106) with preservation of vision. Klin Monbl Augenheilkd 1966; 148: 682-699.
20. Gagne NL, Rivard MJ. Quantifying the dosimetric influences of radiation coverage and brachytherapy implant placement uncertainty on eye plaque size selection. Brachytherapy 2013; 12: 508-520.
21. Diener-West M, Earle JD, Fine SL et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings. COMS Report No. 18. Arch Ophthalmol 2001; 119: 969-982.
22. Damato B, Patel I, Campbell IR et al. Local tumor control after 106Ru brachytherapy of choroidal melanoma. Int J Radiat Oncol Biol Phys 2005; 63: 385-391.
23. Wilson MW, Hungerford JL. Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma. Ophthalmology 1999; 106: 1579-1587.
24. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma II: initial mortality findings. COMS report no. 10. *Am J Ophthalmol* 1998; 125: 779-796.

25. Puusaari I, Heikkonen J, Summanen P et al. Iodine brachytherapy as an alternative to enucleation for large uveal melanomas. *Ophthalmology* 2003; 110: 2223-2234.

26. Shields CL, Naseripour M, Cater J et al. Plaque radiotherapy for large posterior uveal melanomas (> 8 mm thick) in 354 consecutive patients. *Ophthalmology* 2002; 109: 1838-1849.

27. Haas A, Pinter O, Papaefthymiou G et al. Incidence of radiation retinopathy after high-dosage single-fraction gamma knife radiosurgery for choroidal melanoma. *Ophthalmology* 2002; 109: 909-913.

28. Fuss M, Loredo LN, Blacharski PA et al. Proton radiation therapy for medium and large choroidal melanoma: preservation of the eye and its functionality. *Int J Radiat Oncol Biol Phys* 2001; 49: 1053-1059.

29. Marucci L, Ancukiewicz M, Lane AM et al. Uveal melanoma recurrence after fractionated proton beam therapy: comparison of survival in patients treated with reirradiation or with enucleation. *Int J Radiat Oncol Biol Phys* 2011; 79: 842-846.

30. Tokuyue K, Akine Y, Sumi M et al. Fractionated stereotactic radiotherapy for choroidal melanoma. *Radiother Oncol* 1997; 43: 87-91.

31. Dunavoelgyi R, Dieckmann K, Gleiss A et al. Local tumor control, visual acuity, and survival after hypofractionated stereotactic photon radiotherapy of choroidal melanoma in 212 patients treated between 1997 and 2007. *Int J Radiat Oncol Biol Phys* 2011; 81: 199-205.

32. Puusaari I, Damato B, Kivela T. Transscleral local resection versus iodine brachytherapy for uveal melanomas that are large because of tumour height. *Graefes Arch Clin Exp Ophthalmol* 2007; 245: 522-533.

33. Wilkinson DA, Kolar M, Fleming PA et al. Dosimetric comparison of 106Ru and 125I plaques for treatment of shallow (< 5 mm) choroidal melanoma lesions. *Br J Radiol* 2008; 81: 784-789.

34. Messmer E, Bornfeld N, Foerster M et al. Histopathologic findings in eyes treated with a ruthenium plaque for uveal melanoma. *Graefes Arch Clin Exp Ophthalmol* 1992; 230: 391-396.

35. Saconn PA, Gee CJ, Greven CM et al. Alternative dose for choroidal melanoma treated with an iodine-125 radioactive plaque: a single-institution retrospective study. *Int J Radiat Oncol Biol Phys* 2010; 78: 844-848.

36. Kaliki S, Shields CL, Rojjanaporn D et al. Scleral necrosis after plaque radiotherapy of uveal melanoma: a case-control study. *Ophthalmology* 2013; 130: 1004-1011.

37. Quivey JM, Augsburger J, Snelling L et al. 125I plaque therapy for uveal melanoma. Analysis of the impact of time and dose factors on local control. *Cancer* 1996; 77: 2356-2362.

38. Shields CL, Shields JA, Cater J et al. Plaque radiotherapy for uveal melanoma: long-term visual outcome in 1106 consecutive patients. *Arch Ophthalmol* 2000; 118: 1219-1228.

39. Melia BM, Abramson DH, Albert DM et al. Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years COMS report no. 16. *Ophthalmology* 2001; 108: 348-366.