^{106}Ruthenium eye plaque brachytherapy in the management of medium sized uveal melanoma

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Abstract

Background: To evaluate ^{106}Ruthenium Brachytherapy in management of medium sized uveal melanoma, with emphasis on 5-year outcome and toxicity.

Methods: From 2007 to 2015, 39 patients were treated with ^{106} Ru eye plaques brachytherapy. At the time of diagnosis, the median tumor depth was 3.0 mm (CI: 1.6-8.9 mm). Median dose at the apex of the tumor was 145 Gy (± SD: 12.1Gy). The median sclera dose was 444.0Gy (±SD: 257.3 Gy).

Results: Median follow-up was 61.5 months (CI: 8.1-138 mon.). 34 patients (87.1%) remained free of recurrence. In 26 (66.7%) patients a total regression was achieved after a median period of 12 months (CI: 3-60 mon.). By the final examination, the visual acuity of 26 (66.7%) patients was better than 20/200. 12 (30.7%) patients had a visual acuity better than 20/40.

Retinopathy was detected in 11 (28.2%) patients. After treatments only 1 (5.1%) patients had active vascular changes by the last examination. Moderate optic neuropathy was observed in 4 (10.3%) patients. Cataract development was diagnosed in 21 (53.8%) patients, although 16 (41%) of them had bilateral cataract development.

Special emphasis was made on patients with larger tumors. Twelve out of the 39 patients had a tumor with a depth of 5mm or more. There was no significant difference neither in local control (75 % in tumors ≥5mm versus 92.6 % in tumors <5mm) nor in side effects between both groups.

Conclusions: Our study proved ^{106} Ru -brachytherapy to be an excellent treatment option with regard to tumor control and preservation of the visual acuity in well-selected patients. The data suggest that this treatment is also suitable for tumors with a depth of more than 5mm.

Background

Plaque brachytherapy has been well accepted for decades as an efficient treatment modality in the management of medium sized uveal melanoma. The largest prospective randomized trial with over 1300 patients, the Collaborative Ocular Melanoma Study (COMS), found no prognostic benefits in patients who had undergone enucleation in comparison with plaque brachytherapy. (1) As an organ sparing treatment, plaque brachytherapy has psychological benefits and improves the quality of life (QoL) for patients substantially. However, the optimal treatment strategies for plaque brachytherapy are under discussion. Different isotopes such as ^{125}I, ^{103}Pd, ^{106}Ru, ^{90}Sr and ^{131}Cs were used for plaque brachytherapy and the treatment concepts varied considerably between the different institutes.

As a beta emitter, the radiation gradient surrounding ^{106} Ru is steeper than the gradient surrounding a gamma emitter like ^{125}I or ^{103}Pd. The radiation to distal critical eye structures such as macula and optic nerve is therefore decreased during treatment with ^{106}Ru plaque therapy. Traditionally, the use of ^{106}Ru

plaque therapy is preferred in Europe and Asia. However, the treatment was commonly used to treat uveal melanomas with tumor depth of up to 5 mm (2, 3).

The ^{106} Ru plaque brachytherapy treatment strategy has been established for more than 20 years in our clinic and has also been used to treat medium sized uveal melanomas. We recently reviewed our treatments of ^{106} Ru brachytherapy in the past 10 years with emphasis on 5-year outcome and toxicity.

Methods

The diagnosis, localization and measurement of size of the uveal melanoma were performed using transilumination, fundoscopy, ultrasound and other presurgical ophthalmologic examinations. Patients whose visual acuity could no longer be saved underwent an enucleation. Patients with small or medium sized uveal melanoma up to 8 mm Tumor depth were treated with ^{106} Ru eye plaques brachytherapy after ruling out contact with the optic disc or macular, while those in the same group but with optic disc contact or macular involvement were referred for proton beam therapy. Other treatment strategies, such as endoresection, transpupillary thermotherapy, photodynamic therapy or chemotherapy were only considered in cases of recurrence or metastasis.

Brachytherapy treatment:

Patients remained hospitalized in appropriate rooms during the brachytherapy treatment period. General anesthesia was administered during the surgical procedures. Ocular muscles would be relocated when they interfered with plaque position, and then stitched back in the original position after remove the plaque.

Three types of ^{106} Ru eye applicators were used in our institute (Eckert & Ziegel BEBIG GmbH, Berlin, Germany): CCA, CIB, CCB. To ensure that a safety margin of at least 2 mm was added on all margins of the GTV, the chosen plaque diameter was 4 mm more than the largest tumor diameter.

Two patients with large tumor diameters of 17 × 12 × 6 mm and 18 × 5.1 × 3.8 mm were treated with two applicators sequentially, the CCB and CIB applicators. After the prescribed dose of the first implanted applicator (CCB) was attained, the second applicator (CIB) was attached near the CCB applicator before its removal.

A pretreatment plan was calculated with a prescribed dose of 150 Gy at the apex of the tumor, taking into consideration that a dose of not more than 1200 Gy should delivered to the sclera. A depth of 1 millimeter corresponding to the sclera thickness was added to the real depth measured. After the treatment, the applied plan was calculated and documented.

Treatment evaluation:

Follow-up examinations were performed in intervals of 3 months in the first year and in six-months-intervals thereafter up to 5 years. Sixteen patients had further examinations annually.

Tumor response was evaluated using fundoscopy and ultrasound. Metastases were investigated routinely and in symptomatic patients the additional use of imaging methods was applied. Tumor size and visual acuity were documented on each follow up examination. Glaucoma was defined as intraocular pressure (IOP) ≥ 21 mm Hg. Recurrence was defined as the tumor growth more than 1 mm in any directions. Hemorrhagic or exudative tumor enlargement was observed for regression prior to being considered growth.

All statistical analysis was performed with SPSS software, version 24.0 (SPSS, Chicago, IL).

Results

Patient characteristics

From April 2007 through October 2015, 39 patients were treated with ^{106}Ru eye plaque brachytherapy in our institute. Twenty-six of these patients were female and 13 were male. The median age at diagnosis was 71.1 years (CI: 37–88 years). At the time of diagnosis, the median tumor depth was 3.0 mm (CI: 1.6–8.9 mm). For tumors depths less than 2 mm, documented growth before intervention was a prerequisite. The median distance to papilla and macula were 6.0 mm (± SD: 2.8 mm) and 3.5 (± SD: 2.7 mm). Two patients had received ^{106}Ru brachytherapy with 140 Gy and 150 Gy previously.

Initially 38 (97.4%) patients had a visual acuity better than 20/200. Twenty-three (59.0%) patients had visual acuity better than 20/40. Median dose at the apex of the tumor was 145.0 Gy (± SD: 12.1 Gy). The median sclera dose was 444.0 Gy (± SD: 257.3 Gy) (Table 1). Median follow-up was 61.5 months (± SD: 53.8 months).

Table 1
Patient characteristics:

Patient variables	Median	No. of patients	%
Age (years)	71.1 (CI: 37–88 y)		
Male		13	33.3%
Female		26	66.7%
Visual acuity > 20/40		23	59.0%
20/40 – 20/200		15	38.5%
< 20/200		1	2.6%
Tumor depth (apical height mm) < 2.5		9	23.1%
2.5-5.0		18	46.2%
5.0-8.9		12	34.3%
Minimum distance to the papilla (mm)	6.0 (± SD:2.8)		
Minimum distance to the macula (mm)	3.5 (± SD:2.7)		
Plaque type CCB		20	51.3%
CIB		6	15.4%
CCA		15	38.5%
Administered dose (Gy)	145 (± SD:12.1)		
Treatment time (hours)	96.5(± SD 73.7)		
Scleral dose (Gy)	444.0 (CI: 185–1271)		

Tumor response and visual acuity:

Thirty-four cases (87.1%) remained free of recurrence. Five (12.8%) patients developed metastatic disease. 3 patients died during the follow-up of the melanoma.

In 26 (66.7%) patients a total regression was achieved after a median period of 12 months (CI: 3–60 mon.). By the final examination, 26 (66.7%) patients had visual acuity better than 20/200. Twelve of 23 patients (52.2%), whose initial visual acuity was better than 20/40, preserved it after the treatment (Table 2).

Table 2

Treatment results in tumors with a depth of ≥ 5 mm versus < 5 mm

Tumor depth (apical height)	**< 5 mm**		**≥ 5 mm**		**p-Value**
Patient number	27		12		
Tumor recurrence	2 (7.4%)		3 (25%)		0.129
Retinopathy	9 (33.3%)		2 (16.7%)		0.286
Optic neuropathy	3 (11.1%)		1 (8.3%)		0.792
Cataract of treated eye	15 (55.6%)		6 (50%)		0.748
Cataract both sides	12 (44.4%)		4 (33.3%)		0.515
Hemorrhage	1 (3.7%)		0		0.499
Metastasis	1 (3.7%)		4(33.3%)		0.011
Visual acuity	initial	posttreatment	initial	posttreatment	
> 20/40	15(55.5%)	10(37.0%)	8(66.7%)	2 (16.7%)	
20/40 – 20/200	11(40.7%)	8 (29.6%)	4 (33.3%)	6 (50%)	
< 20/200	1 (3.7%)	9(33.3%)	0	4 (33.3%)	

Early and late treatment-related side effects:

Retinopathy was detected in 11 (28.2%) patients after a median period of 18 months (CI: 3–24 months). The changes due to retinopathy responded well to laser therapy. By the last examination, only 1 patient had active vascular changes.

Moderate optic neuropathy was observed in 4 (10.3%) patients, mild optic neuropathy in 2 additional (5.1%) patients. Cataract development was diagnosed in 21 (53.8%) patients, although 16 (41.2%) of them had bilateral cataract development. Despite three patients with incomplete documentation, no glaucoma patient was found.

Impact of tumor depth on treatment results:

Special emphasis was made on patients with larger tumors. Twelve of the 39 patients had a tumor with a depth of 5 mm or more. The treatment results depending on tumor depth of more than or less than 5 mm are shown in Table 2. We identified a better local control rate with 92.6% in tumors < 5 mm as that with 75% in tumors ≥ 5 mm. However, this difference is not significant (p = 0.129). There was no difference in side effects between both groups observed (retinopathy 16.7% vs. 33.3%, optic neuropathy 8.3% vs. 11.1%). Lager Tumors was significantly correlated with the risk of the metastases.

Discussion

Successful treatment of uveal melanomas with preservation of the eye and visual function is one of the great achievements in oncology in the 20th century. Plaque brachytherapy as well as external beam radiotherapy with charged particles therapy (CPT) like proton therapy and, especially in recent years, radiosurgery can achieve very high rates of local control and play an important role in eye preservation. However, it is still challenging to optimize radiation treatment especially in larger tumors with regard to tumor control and visual outcome and side effects.

In this study, the 5-year local control rate of uveal melanomas by ^{106} Ru eye plaques brachytherapy reached 87.1%, which is consistent with the local control rate of 89.7% reported by COMS report 19 [4]. However, the local control failure of COMS study was defined as the progression of the height of the tumor in 25%. When ^{125}I plaque therapy was applied, the rates of tumor controlling vary from 88.2–94% in diverse studies [5, 6, 7]. The 5-year local recurrence rate of CPT was around 5% [8, 9, 10]. Co-founding factors that affect treatment outcomes among different studies include the selection of patients, tumor characteristics and the definition of the recurrence rate. 5-year tumor control rate near to 90% is a good result and confirms the efficiency of ^{106} Ru eye plaque brachytherapy in our study.

Intraocular side effects observed in our study were rare. 28.2% patients developed retinopathy, although only 2.6% patients had active vascular changes after the treatment. 10.3% patients had optic neuropathy and 12.8% patients developed unilateral cataract. No enucleation due to complications was necessary. Recently studies indicated that ^{106} Ru eye plaque brachytherapy generally causes fewer late complications than ^{125}I therapy [11, 7]. A meta-analysis of CPT involving 7500 patients in 28 studies also revealed a low ocular toxicity similar to our study. The pooled rate of radiation retinopathy was 0.28 (95% CI, 0.15–0.41), 0.34 for cataract formation (95% CI, 0.15–0.53), 0.21 for optic neuropathy (95% CI, 0.04–0.38) and 0.02 for enucleation due to complications (95% CI, 0.00-0.04) [12] .

In a study of proton beam therapy involving 2413 patients, Desjardins and coworkers reported that 42% of patients preserved visual acuity of more than 20/200 after a median follow-up of 98 months. The median size of treated tumor depth was 4.7 mm and additional treatment to improve final visual results were used [13]. The 3-years visual acuity of more than 20/200 was reported from 45%-73% in several studies after ^{125}I plaque brachytherapy [14, 15, 16]. In our study, the preservation of useful vision (more than 20/200) was achieved in 66.7% of patients after a median follow-up of 61.5 months. 52.2% of patients (total number of 12) kept their initial visual acuity better than 20/40 after the treatment.

Brachytherapy offers a variety of practical advantages. It is a cost-effective treatment technique and can be offered in a large number of radiotherapy centers. During brachytherapy, the plaque is attached to the eye wall so that the intrafraction motion is reduced and neglectable, which is, in our opinion, an important advantage compared to external beam techniques. Moreover, plaque brachytherapy results in less anterior segment complications due to the short distance between the brachytherapy plaque and the target. Unlike charged particle therapy, where patient cooperation and comprehension are necessary,

plaque brachytherapy can be carried out without these pre-requisites. The good visual outcome and low intraocular side effects revealed by our study prove that ^{106} Ru brachytherapy is an excellent treatment option in well-selected patients.

Barker and coworkers reported a high tumor recurrence rate by ^{106}Ru treatments with 75.5 Gy radiation doses delivered to the tumor apex [17]. Barker also suggested that the brachytherapy-planning protocols used for ^{125}I, for example COMS, were not sufficient for ^{106}Ru plaque brachytherapy due to the dosimetric difference between ^{125}I und ^{106}Ru. Three large ^{106}Ru treatment series with a mean dose of 100 Gy to the apex reported 5-year local control rates at 78%, 82% and 84% [18, 19, 20]. Another prospective study of ^{106}Ru brachytherapy on 450 patients reported that a 5-year local control rate of 97.9% could be achieved if a minimal-scleral radiation dose of 300–400 Gy was used. It was estimated that 96% of those patients received more than 100 Gy apex dose, while 73% of them received more than 125 Gy and 54% with more than 150 Gy [21]. More studies are needed to determine the optimal treatment radiation dose of ^{106}Ru brachytherapy. What we reported in this study showed that our protocol with up to 150 Gy at the tumor apex was feasible, effective and safety.

In North America, ^{106}Ru brachytherapy is normally considered for tumors with a depth of less than 5 mm. Our results showed that treatment of uveal melanomas with an apex depth more than 5 mm (up to 8 mm in this series) was also possible. There was no correlation between tumor depths with neither local control rates nor late toxicity in our study.

Like other studies involving ^{106}Ru brachytherapy, our study has some limitations. First of all, the sample size is small and the outcome is based on retrospective analysis. Secondly, there have been changes in the whole treatment concept over the past years; the use of additional therapies like transpupillary thermotherapy, photodynamic therapy and other therapy modalities varied over time and might have had an impact on the results. Moreover, direct comparisons of ^{106}Ru brachytherapy with other therapies in randomized trials are lacking.

Conclusions

The major findings in our study were the high local control rate with ^{106}Ru brachytherapy even in tumors with a depth of more than 5 mm and the overall low acute and long-term toxicities. Despite the limited number of patients, these results prove ^{106} Ru brachytherapy to be an excellent treatment option in clinical practice for uveal melanoma and should be promoted in well-selected patients. The treatment is also suitable for tumors with a depth of more than 5 mm.

Abbreviations

COMS: Collaborative Ocular Melanoma Study; ^{106}Ru: ^{106}ruthenium; ^{125}I: ^{125}iodine; ^{103}Pd: ^{103}palladium; ^{90}Sr: ^{90}strontium; ^{131}Cs: ^{131}cesium; CPT: charged particles therapy

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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The study did not receive any funding.

Authors' contributions

PJ, KP performed data acquisition and participated in patient treatment, statistical analysis and in drafting the manuscript. GK participated in treatment of the patients and statistical analysis. DK, FAS treated the patients and participated in data acquisition. UL participated in statistical analysis and revised the manuscript critically. JR participated in patient treatment and revised the manuscript critically. JD participated in treatment of the patients, drafting the manuscript and critically reviewed the data and the manuscript. All authors read and approved the final manuscript.

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