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Comparative Outcomes and Toxicities for Ruthenium-106 versus Palladium-103 in the Treatment of Choroidal Melanoma

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Abstract

PURPOSE—For treatment of choroidal melanoma, Palladium-103 (¹⁰³Pd) and Ruthenium-106 (¹⁰⁶Ru) plaque brachytherapy demonstrates reduced toxicity compared to the historical standard Iodine-125 (¹²⁵I). No report has directly compared clinical outcomes between ¹⁰³Pd and ¹⁰⁶Ru, and reasons for selection of one over the other remain purely theoretical.

MATERIALS/METHODS—Patients with choroidal melanoma with apical tumor height ≤ 5 mm were included. Patients from Emory University were treated with ¹⁰³Pd between 1993 and 2012. Patients from Cleveland Clinic were treated with ¹⁰⁶Ru between 2005 and 2010. Medical records were retrospectively reviewed. We compared post-treatment visual acuity (VA), toxicity, and oncologic outcomes.

RESULTS—¹⁰³Pd patients (n = 124) and ¹⁰⁶Ru patients (n = 42) had median follow up of 4.2 and 5.0 years, respectively. Radiation retinopathy-free survival was similar for both radioisotopes but ¹⁰⁶Ru had lower grades of retinopathy (p=0.006). ¹⁰³Pd was associated with worse VA preservation (20/40) by year 3 (OR 3.8, 95% CI 1.01–14.31, p=0.048). ¹⁰³Pd was associated with higher distant metastases-free survival (DMFS) in multivariate analysis (MVA) (HR 0.10, 95% CI 0.02–0.38, p<.001).

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CONCLUSIONS— ^{106}Ru had lower grades of radiation retinopathy and improved long-term VA preservation, but also inferior DMFS, compared to ^{103}Pd . Due to the inherent limitations of a retrospective analysis, the significance of the inferior DMFS for ^{106}Ru remains unclear, although the suggestion of a slight inferiority in terms of DMFS for ^{106}Ru is consistent with the other limited literature. Based on this study, we believe both radioisotopes remain appropriate for the treatment of small choroidal melanomas ≤ 5 mm in apical height.

Keywords

choroidal melanoma; plaque brachytherapy; radioisotope selection; visual acuity preservation; radiation toxicity; palladium; ruthenium

BACKGROUND

Ocular melanoma is the most common primary intraocular tumor in adults and the second most common type of melanoma after cutaneous, accounting for 3.7% of all cases. It arises from melanocytes, usually in the uvea (82.5%), or less frequently in the conjunctiva. Within the uveal tract, 86.3% occur in the choroid; iris and ciliary body melanoma are much less common. The incidence of choroid melanoma in the United States is approximately 4.3 cases per million persons; melanoma of the iris and ciliary body contribute another 0.7 cases per million persons. Patients are typically diagnosed between ages 50–80 with peak incidence in the seventh decade.¹

Plaque radiation therapy (RT), with proper tumor selection, achieves local control and survival outcomes similar to those achieved by enucleation, as demonstrated in the Collaborative Ocular Melanoma Study (COMS). In this trial, which enrolled from 1986 to 2003, patients with medium-sized tumors were randomized to enucleation versus ^{125}I plaque brachytherapy. Long-term analysis showed no difference in overall survival or distant metastases.^{2–4} However, despite 70% of patients having baseline visual acuity 20/40 or better, only 34% of patients demonstrated 20/40 vision or better at 3 years.⁵ Some of the factors that influence post-treatment VA include tumor characteristics (mainly size and distance from the fovea), age, and ocular comorbidities such as diabetes. Secondary effects of radiation on normal ocular structures—namely radiation retinopathy (ischemic, exudative, hemorrhagic, or atrophic), radiation choroidopathy, radiation optic neuropathy, and radiation induced cataract—are also implicated as contributors to loss in VA.⁶

The most commonly used radioisotopes for ocular melanoma brachytherapy are ^{106}Ru , ^{103}Pd , and ^{125}I [please see Table 1 for a summary of the characteristics of these radioisotopes]. Due to relatively gradual dose fall off, ^{125}I delivers higher dose to critical eye structures including the macula, lens, and optic discs. Finger et al report that compared to ^{125}I , ^{103}Pd offers an opportunity for radiation sparing of ocular structures while maintaining better VA and equivalent rates of local control.^{7–9} ^{103}Pd , due to its lower energy resulting in steeper isodose fall off, has been shown to decrease dose to the macula and optic nerve relative to the ^{125}I .⁹ We recently reported an analysis of patients treated with plaque brachytherapy at Emory with either ^{103}Pd vs ^{125}I , which showed that ^{103}Pd is independently associated with superior long term VA preservation and lower incidence of radiation

retinopathy compared with ^{125}I .¹⁰ ^{106}Ru , a beta emitter rather than a gamma emitter, has even sharper dose fall off than even ^{103}Pd . Dosimetric comparison of ^{106}Ru and ^{125}I for tumors 5mm shows translation of this sharp dose fall off to a clinically relevant reduction in radiation dose to normal eye structures.¹¹ Additionally, a recent retrospective report from MD Anderson demonstrates equivalent overall survival, improved enucleation free survival, and reduced radiation retinopathy in patients receiving ^{106}Ru compared with patients receiving ^{125}I plaque brachytherapy.¹²

To date, there are no comparative reports of ^{106}Ru and ^{103}Pd brachytherapy for choroidal melanoma. Such a report may provide further insight into outcome implications of plaque brachytherapy radioisotope selection, particularly with respect to quality of life, vision preservation, and toxicities. Therefore, in this multi-institutional study, we compare the visual acuity (VA), toxicity, and oncologic outcomes for patients with choroidal melanoma treated with ^{103}Pd versus ^{106}Ru plaque brachytherapy.

METHODS

Patient Selection

We obtained approval from the institutional review boards of Cleveland Clinic and Emory University for this study. We reviewed the medical charts of all patients treated for choroidal melanoma with definitive intent with ^{103}Pd plaque brachytherapy at Emory University between 1993 and 2012 and ^{106}Ru plaque brachytherapy at Cleveland Clinic between 2005 and 2010. Inclusion criteria were apical tumor height 5 mm and age greater than 18 years. Tumors with apical height of > 5mm are not normally treated with ^{106}Ru , since the sharp dose falloff of this isotope would necessitate high dose to the sclera in order to achieve proper dose distribution to the tumor in the choroid, and such a dose to the sclera could result in scleral necrosis. We excluded patients with incomplete demographic data, pre-treatment visual acuity (VA) data, RT treatment data, tumor located in the iris or ciliary body, metastatic disease at initial presentation. We also excluded patients who had undergone transpupillary thermotherapy.

Patients were treated at both institutions with prescribed RT dose of 85 Gy, as per the COMS trial.¹³ We have previously published the detailed treatment protocols for Emory University and Cleveland Clinic.^{10, 14} Briefly, plaque size was chosen based on tumor size, allowing for a 2 mm margin around the circumference of the tumor. For tumors > 5 mm in height, RT dose was prescribed to a height of 5 mm.

Medical Record Review

Baseline patient data included age at time of treatment, gender, presence or absence of diabetes mellitus, best corrected VA prior to treatment, and tumor characteristics including laterality, location (o'clock), largest radial dimension, area, and height. Treatment data included date of plaque placement, radioisotope (^{106}Ru or ^{103}Pd), plaque size, RT dose, and distance of the tumor to the optic nerve (measured edge of tumor to center of disc) and macula (measured edge of tumor to fovea). We also determined the grade of radiation retinopathy, if any, per the Finger Classification.¹⁵ Follow-up data included length of follow-

up, VA at annual follow-up visits, date of diagnosis of complications of radiotherapy (e.g. radiation retinopathy), development of distant metastases, secondary enucleation, and date of death from all causes of mortality. Baseline and follow-up VA measurements were recorded using a Snellen VA scale. Count fingers VA was converted to a Snellen VA recording value.¹⁶ Hand motion only and light perception only vision were recorded as a decimal acuity of 0.005, and no light perception and enucleation were given a decimal acuity of one line worse than the lowest decimal VA (0.0015).¹⁷

Statistical Analysis

We analyzed three VA measures to determine the toxicity of the radioisotopes: visual preservation, loss, and change. VA preservation was defined as post treatment visual acuity of 20/40 or better. VA loss was defined impairment in vision to 20/200 or worse. Degree of change was categorized into stable/improved (e.g. VA change of logmar(0.1)≥0) or a decrease in lines (e.g. VA change of logmar(0.1)<0).

Survival was defined as time from date of plaque placement to one of the following: death (OS), distant metastasis (DMFS), enucleation (EFS), radiation retinopathy (RRFS), censored at last follow-up. Survival was estimated using the Kaplan-Meier method, and survival distributions were compared using log-rank tests. Firth's penalized maximum likelihood estimation was implemented for the DMFS and EFS models in order to reduce bias in the parameter estimates and confidence intervals due to the small number of events in each model. Treatment groups and vision endpoints were compared across categorical endpoints using chi-squared tests or Fisher's exact tests, where appropriate, and across continuous variables using ANOVA. Multivariable analysis (MVA) for time-to-event endpoints was performed using Cox proportional hazards modeling and included the following factors for OS, DMFS, and EFS: age at time of procedure, tumor area, tumor height, radioisotope. MVA for RRFS and VA endpoints (loss, preservation and change at 1 year, 2 years, and 3 years) included: radioisotope, pretreatment vision, distance from macula to tumor, distance from optic disk to tumor, tumor area, tumor height, and age at time of procedure. MVA for VA endpoints at each time point was performed using logistic regression modeling.

All analyses were carried out using the SAS 9.3 version statistical software package (SAS Inst., Cary, NC). All statistical analyses were 2-sided, and p-values <0.05 were considered statistically significant.

RESULTS

At Emory University, 124 patients were treated with ¹⁰³Pd plaque brachytherapy between 1993 and 2012 with a median follow up of 4.2 years. At Cleveland Clinic, 42 patients were treated with ¹⁰⁶Ru plaque brachytherapy between 2005 and 2010 with a median follow up of 5.0 years. Table 2 summarizes patient, disease, and treatment characteristics of each cohort. There were no significant differences in the cohorts except for a minor difference in prescribed dose, and also difference in radiation retinopathy grade per the Finger Classification.¹⁵ ¹⁰⁶Ru patients had lower grades of retinopathy compared to the ¹⁰³Pd cohort at latest follow up visit (p=0.006). At baseline, ¹⁰⁶Ru and ¹⁰³Pd patients had similar distribution of pre-treatment visual acuity.

EFS could not be analyzed, as there were too few events in the cohorts: 2 in the ^{106}Ru cohort and 1 in the ^{103}Pd cohort. Five-year DMFS was higher in the ^{103}Pd cohort, 96.5% vs 78.6% in the ^{106}Ru cohort ($p=0.0002$) [Figure 1]. Five-year OS was also higher in the ^{103}Pd cohort, 89.3% versus 80.2% in the ^{106}Ru cohort ($p=0.0347$).

Fifteen patients (35.7%) treated with ^{106}Ru and 56 patients (45.1%) treated with ^{103}Pd developed radiation retinopathy. Three-year RRFS was not statistically different between ^{103}Pd and ^{106}Ru (65.2% vs 50.6% respectively, $p=0.5420$) [Figure 2]. Table 3 summarizes rates of VA loss, preservation, and stability/improvement over 3 years for ^{106}Ru and ^{103}Pd .

The significantly higher DMFS for ^{103}Pd persisted in MVA (HR 0.10, 95% CI 0.02–0.38, $p<.001$). Tumor height was significantly associated with worse DMFS in MVA (HR 3.07, 95% CI 1.60–5.90, $p<.001$); no other covariates were significantly associated with DMFS. The higher OS demonstrated for ^{103}Pd also persisted on MVA (HR 0.19, 95% CI 0.07–0.54, $p=0.002$). Increasing tumor height (HR 2.43, 95% CI 1.38–4.27, $p=0.002$) and older age at time of procedure (HR 1.15, 95% CI 1.07–1.23, $p<.001$) were significantly associated with lower OS on MVA; other covariates were not significantly associated with OS. In MVA of rates of RRFS, increasing distance from the optic disc to the tumor was demonstrated to have significantly higher RRFS (HR 0.83, 95% CI 0.74–0.93, $p<0.001$); no other covariates (including radioisotope used) were found to be significantly associated with RRFS in MVA. In MVA for VA preservation (post treatment vision 20/40 or better), the ^{103}Pd radioisotope was associated with worse outcomes (OR 3.8, 95% CI 1.01–14.31, $p=0.048$); no other covariates had significant associations with VA preservation. In MVA for VA loss (impairment in vision to 20/200 or worse), increasing distance from optic disk to tumor was associated with improved outcomes (OR 0.78, 95% CI 0.63–0.97, $p=0.023$); no other covariates had significant associations with VA loss. No covariates (including radioisotope used) were significantly associated with VA stability/improvement in MVA.

DISCUSSION

Since the initiation of the COMS study in 1986, there has been a sharp and steady increase in the use of radiation and decline in surgery for uveal melanoma. Surgery alone was used in 93.8% of cases for 1973–1975 compared to 28.3% for 2006–2008, with a corresponding increase in those treated with radiation from 1.8% of cases 1973–1975 compared to 62.5% for 2006–2008.¹⁸ This paradigm shift has likely improved patient quality of life through ocular preservation, while maintaining DMFS and OS. In the present analysis, we sought to compare, for the first time, the oncologic, toxicity, visual acuity outcomes of ^{106}Ru and ^{103}Pd episcleral plaque brachytherapy in the definitive treatment of choroidal melanoma with apical height $\leq 5\text{mm}$. In this multi-institutional analysis, we found that the ^{103}Pd group had improved DMFS at 5 years (96.5% vs 78.6%, $p=0.0002$). Three-year RRFS was equivalent in both cohorts but ^{106}Ru had lower grades of retinopathy. 3-year VA preservation was worse in the ^{103}Pd cohort in MVA. We report improved OS with ^{103}Pd ; however, we believe this significant difference is confounded by the competing comorbidities and selection bias inherent to a retrospective analysis of all-cause mortality.

Although a small number of patients (4%) present with distant metastases at diagnosis, about half of patients develop metastases in their disease course,¹⁹ which is significant because the prognosis of metastatic disease has been historically very poor. At 5 and 10 years of follow up, choroidal melanoma metastases have been reported in 15% and 25% patients, respectively.²⁰ Uveal melanoma has a high propensity for liver (94%) followed by lung (24%) and bone (16%).²¹ Memorial Sloan Kettering reviewed their experience with ¹⁰⁶Ru for definitive management of uveal melanoma and found 5 year DMFS of 88.6%.²² Their cohort had a median tumor diameter of 9.4 mm and height of 2.6 mm, which is similar to Cleveland Clinic's cohort which had median values for tumor diameter of 9.75 mm and height of 2.5 mm. Finger et al reported 5-year DMFS 92.7% for their ¹⁰³Pd cohort consisting of mainly medium-sized choroidal melanoma, which is similar to our Emory experience.⁷ Due to the inherent limitations a retrospective analysis, the significance of the inferior DMFS demonstrated for ¹⁰⁶Ru in our study remains unclear, although the suggestion of a slight inferiority in terms of DMFS for ¹⁰⁶Ru is consistent with the other limited literature.

Multiple reports from throughout the world have detailed the visual acuity and toxicity outcomes of ¹⁰⁶Ru, though it is somewhat difficult to compare these studies directly since each report contains unique baseline patient and tumor characteristics. In our ¹⁰⁶Ru cohort, 67% had VA 20/40 or better and 93% VA 20/200 or better at median 5.0 years follow up after treatment. Marconi et al reported in their cohort of 83 ¹⁰⁶Ru patients (median tumor height 4.3 mm and diameter 9.3 mm) with 3.25 year median follow up, 56% had VA 20/200 or better and 30% had VA 20/40 or better.²³ A Swedish study reported results of 579 eyes treated with ¹⁰⁶Ru. In their patients, median tumor height was 4.3 mm, median diameter was 10 mm, median distance from the macula was 2.0 mm and median distance from the optic disc was 3 mm. These tumors were thicker and closer to macula and optic disc than our ¹⁰⁶Ru cohort. The reported 5-year VA 20/40 or better was 31% and VA 20/200 or better was 49%.²⁴ A report of 458 patients in the UK with choroidal melanoma (median tumor height 3.2 mm and median diameter 10.6 mm) reported 80% had VA 20/40 or better and 93% had VA 20/200 or better at 2 years. In terms of toxicity, MD Anderson has reported that 50% of their ¹⁰⁶Ru patients have radiation retinopathy (median tumor height 3.05 mm and median diameter 9.6 mm) at median 67 months follow up.¹² At Helsinki University, 28% of ¹⁰⁶Ru patients (median tumor height 1.9 mm and median diameter 7 mm) experienced radiation maculopathy at 5 years.²⁵

As with any retrospective study, there are several limitations of the present analysis. There is potential for selection bias due to the non-randomized treatment cohorts. However, both Emory University and Cleveland Clinic have uniform follow up patterns, and most patients have detailed clinical records that have been meticulously maintained. Patient, tumor, and treatment characteristics were well documented at both institutions, and were well balanced between institutional cohorts. The quality of documentations made it possible to report grade of radiation retinopathy, a variable that is not frequently found in the literature. Once again, there may be confounding due to differences in surgeon experience between Emory University and Cleveland Clinic. Finally, we have relatively small cohorts especially for ¹⁰⁶Ru brachytherapy which is attributable due to the limited availability of ¹⁰⁶Ru in the United States during the last few decades.

CONCLUSIONS

We compared oncologic, toxicity, VA acuity outcomes of patients treated with episcleral plaque brachytherapy for choroidal melanoma 5mm in height, and found that ^{106}Ru yielded similar rates but lower grades of radiation retinopathy, and superior VA preservation at 3 years, compared to ^{103}Pd . This advantage in terms of toxicity is perhaps compromised by lower DMFS compared to ^{103}Pd , though the mechanism for this finding is unclear and most likely results from patient imbalances. At present, both radioisotopes remain appropriate for this population, and it seems a clear answer regarding superiority of one over the other will not be possible without prospective studies.

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SUMMARY

This is a retrospective study that compares outcomes for patients treated for choroidal melanoma with the plaque brachytherapy radioisotopes Ruthenium-106 or Palladium-103. Ruthenium-106 patients were treated at Cleveland Clinic, and Palladium-103 patients were treated at Emory University. Ruthenium-106 demonstrated lower grades of radiation retinopathy and improved 3-year visual acuity preservation--but also lower distant metastasis-free survival--compared to Palladium-103.

Figure 1.
Distant Metastasis-Free Survival for ^{106}Ru versus ^{103}Pd

Figure 2.
Radiation Retinopathy-Free survival for ^{106}Ru versus ^{103}Pd

Table 1

Isotope Characteristics

Isotopes Used for Plaque Brachytherapy of the Eye

	¹²⁵ I	¹⁰³ Pd	¹⁰⁶ Ru
Energy	35.5 keV	21 keV	39.4 keV
Radiation type	Gamma	Gamma	Beta
Half Life	60 days	17 days	374 days
Cost	\$	\$\$	\$\$\$\$
Advantages	• easy to shield • treats thicker tumors	• high dose rate	• sharp dose fall off • reusable (longer implant duration over time)
Disadvantages	• higher radiation to normal tissues	• short half life	• only thin tumors <5mm

Table 2

Baseline Patient Characteristics

		¹⁰³ Pd N=124	¹⁰⁶ Ru N=42	P Value [*]
Gender	Male	59 (47.58%)	16 (38.1%)	0.286
	Female	65 (52.42)	26 (61.9)	
Age at time of procedure	Median	64.5	69.9	0.42
Diabetes	No	104 (85.95)	34 (80.95)	0.439
	Yes	17 (14.05)	8 (19.05)	
Pre-treatment vision (20/x)	20	30 (24.19)	9 (21.43)	0.334
	>20, 50	60 (48.39)	22 (52.38)	
	>50, 100	26 (20.97)	6 (14.29)	
	>100, 200	5 (4.03)	1 (2.38)	
	>200	3 (2.42)	4 (9.52)	
Laterality	Left	58 (46.77)	18 (42.86)	0.66
	Right	66 (53.23)	24 (57.14)	
Location Clock Hour	12–3	32 (25.81)	16 (38.1)	0.424
	3:30–6	24 (19.35)	5 (11.9)	
	6:30–9	44 (35.48)	14 (33.33)	
	9:30–11:30	24 (19.35)	7 (16.67)	
Largest dimension (mm)	Median	10.5 (range, 0.1 – 32.8)	9.7 (range, 4.5 – 16.5)	0.517
Tumor area (mm²)	Median	99.5 (0.01 – 1075.8)	65.9 (15.9 – 236.9)	0.121
Height of tumor (mm)	Median	2.5 (81.3 – 88.1)	2.5 (71.8 – 92.8)	0.839
Plaque size (mm)	Median	18 (14 – 24)	15.9 (15.9 – 20.4)	0.131
Dose (Gy)	Median	84.5 (81.3 – 88.1)	85.1 (71.8 – 92.8)	0.003
Distance from macula to tumor (mm)	Median	4.16 (0 – 21.1)	4.5 (0 – 18)	0.296
Distance from optic disk to tumor (mm)	Median	4.39 (0 – 17.4)	4.75 (1 – 15)	0.129
Radiation retinopathy grade (Finger Classification)	1	16 (28.57%)	12 (80%)	0.006
	2	13 (23.21)	0 (0)	
	3	20 (35.71)	2 (13.33)	
	4	6 (10.71)	1 (6.67)	
	no records	1 (1.79)	0 (0)	

* The p-value is calculated by ANOVA for numerical covariates; and chi-square test or Fisher's exact for categorical covariates, where appropriate.

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Table 3

Visual Acuity Outcomes for ^{106}Ru versus ^{103}Pd

^{106}Ru						^{103}Pd					
year	preservation (better than 20/40) (%)	loss (worse than 20/200) (%)	stable/improved (%)	n	preservation (better than 20/40) (%)	loss (worse than 20/200) (%)	stable/improved (%)	n	loss (worse than 20/200) (%)	stable/improved (%)	n
0	28 (67)	5 (12)	-	42	83 (67)	6 (5)	-	42	6 (5)	-	124
1	16 (50)	2 (6)	18 (56)	32	81 (66)	12 (10)	70 (57)	32	12 (10)	70 (57)	122
2	15 (68)	0 (0)	15 (68)	22	59 (56)	15 (14)	53 (50)	22	15 (14)	53 (50)	106
3	10 (67)	1 (7)	9 (60)	15	45 (48)	17 (18)	37 (40)	15	17 (18)	37 (40)	93