Long term outcomes of Ru-106 brachytherapy for choroidal melanoma in Korean patients

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ABSTRACT

Long term outcomes of ruthenium-106 brachytherapy for choroidal melanoma in Korean patients

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Purpose: The purpose of this study was to report long-term outcomes of ruthenium-106 (^{106}Ru) brachytherapy for choroidal melanoma in Korean patients.

Methods: A retrospective review was conducted of 155 consecutive patients that underwent ^{106}Ru brachytherapy for uveal melanoma from 2006 to 2017 with a follow-up period of over 3 years. Baseline clinical characteristics and prognostic indicators such as rates of survival, local recurrence, metastasis, and loss of useful visual acuity (VA) were investigated. Additional analysis was done to determine whether there were any predictive factors for prognosis.

Results: The median follow-up was 68 months after brachytherapy. The estimated five-year survival rate was 85.5%, metastasis-free rate was 79.7%, eye preservation rate was 79.7%, and the rate of recurrence-free disease was 86.1%. The rate of losing useful VA (to below 20/200) was 54.6% at 5 years. Initial apical height, radiation dose to the optic nerve and incidence of retinal detachment were found to significantly correlate with loss of VA. Additional local tumor resection did not influence prognosis in very large tumors with apical heights over 8mm.

Conclusion: Medium-sized choroidal melanomas show favorable response to ^{106}Ru brachytherapy and additional local treatment does not seem to influence prognosis.

Key words: choroidal melanoma, uveal melanoma, brachytherapy, ruthenium radioisotopes

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I. INTRODUCTION

Choroidal melanoma is the most common intraocular malignancy in adults. The Collaborative Ocular Melanoma Study (COMS) study published in 2001 was a landmark study in the management of choroidal melanomas. It proved the efficacy of plaque brachytherapy by demonstrating that Iodine-125 (^{125}I) brachytherapy was noninferior to enucleation in survival in medium-sized choroidal melanomas (defined as 2.5-10.0 mm in apical height and 5-16 mm in largest basal diameter).[1] Brachytherapy has since become the favored treatment method because of its potential for preservation of vision and the eye. However further studies have reported that eventually 50% of patients treated with brachytherapy lose their visual acuity (VA) after 3~5 years, mainly due to radiation-related complications.[2-4]

While the COMS study was conducted with ^{125}I brachytherapy, comparable outcomes have been reported with Ruthenium-106 (^{106}Ru) brachytherapy. ^{106}Ru brachytherapy is the mainstay in most countries in Europe, and it is used at our institution. ^{106}Ru is a β-radiation emitter with a steeper dose fall-off and therefore lower penetration depth compared to ^{125}I. Thus, while there have been suggestions of it being less effective in larger sized tumors, previous studies still report a high local control and survival rate.[5] It has been suggested that it may cause less radiation-related complications.[6]

Choroidal melanomas are known to be very rare in Asian populations with an incidence of 0.42 per million compared to 6.02 in Caucasians.[7] It is also generally thought to have a worse prognosis in Asians, with a younger patient population, larger

sized tumors and a higher rate of the epithelioid cell type.[8,9] However the rarity of these tumors in Asians make large-scale studies difficult. In South Korea, brachytherapy for choroidal melanomas was first started in October 2006 and to date is only conducted at our institution. We have previously reported good early clinical outcomes of ^{106}Ru brachytherapy with 88 patients that underwent treatment from 2006 to 2012.[10] With an almost twice as larger pool of patients accrued since then, we aimed to identify long-term prognosis and predictive factors for prognosis.

II. METHODS

1. Patient selection

We conducted a retrospective review of a total of 176 consecutive patients that underwent ^{106}Ru plaque brachytherapy for uveal melanoma from October 2006 to July 2017 at Severance Hospital. We excluded 21 patients that had a follow-up period of less than 3 years after brachytherapy, making the total number of subjects included in this study 155. This investigation was approved by the Institutional Review Board (IRB No. 4-2020-0953).

2. Data collection

Baseline characteristics such as age, sex, concomitant ocular or medical conditions, and initial VA were recorded. Tumor characteristics such as largest basal diameter (LBD), height, shape and internal reflectivity as measured by B-scan, tumor location, PET-CT uptake, and pathology type were reviewed. The radiation dose to the tumor apex, sclera, optic nerve (ON), and macula were recorded as well as whether additional local treatment was performed. Tumor control parameters including overall survival (OS), rate of local control, rate of metastasis and eye-preservation rate were analyzed. Loss of useful VA was defined as deterioration of VA to below 20/200. To assess visual acuity, only patients that presented with a pre-treatment VA of over 20/200 were included, and patients that underwent enucleation at any point were excluded. Data on the type and timing of radiation or

tumor-related complications arising upon follow-up was also collected. Radiation retinopathy was defined as the appearance of any of the following on fundus photography: microaneurysms, telangiectases, neovascularization, vitreous hemorrhage, exudates, cotton wool spots or macular edema.

3. Treatment methods

All patients underwent ^{106}Ru plaque brachytherapy (Eckert & Ziegler BEBIG, Berlin, Germany) with a target dose of approximately 85Gy to the tumor apex. In the early period after introduction of brachytherapy at our institution, addition of transpupillary thermotherapy (TTT) and/or local excision was performed routinely. However, in the later study period, these adjunctive treatments were not a routine part of the treatment protocol.

Local excision consisted of either sclerouvectomy or internal choroidectomy, and was conducted before or on the same day as brachytherapy. For patients undergoing local excision, the radiation dose was planned as approximately 100Gy to 2~3mm from the sclera, adjusted for how much tumor was left after excision. Protocol for TTT was 1 minute of exposure time with a stepwise adjustment in energy size until the tumor surface turned slightly gray at the end of treatment.

4. Statistical analysis

Survival curves were estimated using the Kaplan-Meier method. Comparison of estimated survival rates between two groups were done by the log-rank test. Prognostic factors found to be significant on Cox's univariate proportional hazard model were entered into Cox regression analyses, and eliminated with a backward-stepwise procedure. Comparison between two subgroups were done either by the independent t-test, chi-square test or the Fischer's exact test. Statistical analyses were performed using SPSS ver. 25.0 (SPSS Inc., Chicago, IL).

III. RESULTS

1. Patient and tumor characteristics

A total of 155 patients were included in the analysis. The median follow-up period after brachytherapy was 68 months (range 1 – 156 months). Mean age was 51.3±12.6 months. Before treatment, 38.7% of the subjects had a good VA of over 20/30, 46.5% had moderate VA of between 20/200 – 20/30, and 14.8% had low VA of below 20/200. Mean initial tumor LBD was 9.9±2.7 mm and mean height was 6.0±2.5 mm. Most of the tumors were dome-shaped (61.2%) with medium internal reflectivity (75.2%) and located in the mid-peripheral or peripheral retina (57.8%). Biopsy was performed before or at the same time as brachytherapy in 45 patients. The epithelioid type was the most common (47.4%) of those whose pathology results specified a cell type. Initial patient and tumor characteristics are summarized in **Table 1**. Additional local treatment consisting of either TTT, local excision or trans pars plana vitrectomy (TPPV) was combined in 83.2% of the patients. Treatment characteristics are summarized in **Table 2.**

Table 1. Baseline patient and tumor characteristics

Characteristic	Total (N = 155) ¶	Small (N = 7)	Medium (N=132)	Large (N = 14)
Age (years)	51.3±12.6 (17 - 77)	47.1±18.6 (17 - 74)	51.3±12.1 (25 - 77)	52.6±12.4 (31 - 73)
Sex				
Male	70 (45.2%)	1 (14.3%)	58 (43.9%)	5 (35.7%)
Female	85 (54.8%)	6 (85.7%)	74 (56.1%)	9 (64.3%)
Initial VA category*				
Good	60 (38.7%)	1 (14.3%)	55 (41.7%)	4 (28.6%)
Moderate	72 (46.5%)	3 (42.9%)	62 (47%)	6 (42.9%)
Low	23(14.3%)	3 (42.9%)	15 (11.4%)	4 (28.6%)
Initial foveal OCT	**N = 117**	**N =5**	**N = 106**	**N = 5**
Normal	47 (40.2%)	0	44 (41.5%)	2 (40%)
SRF	52 (44.4%)	3 (42.9%)	48 (45.3%)	1 (20%)
CME	5 (4.3%)	0	5 (4.7%)	0
Both SRF and CME	4 (3.4%)	0	4 (3.8%)	0
ERM	8 (6.8%)	1 (14.3%)	5 (4.7%)	2 (40%)
Macular atrophy	1 (0.9%)	1 (14.3%)	0	0
Initial SFCT (μm)	277.8±101.2	196±178.1	275.9±92.8	356.6±151.4

	(14 - 606)	(14 – 370)	(94 – 558)	(195 – 606)
Initial PET uptake	**N = 108**	**N = 5**	**N = 91**	**N = 10**
No uptake	61 (56.5%)	4 (80%)	53 (58.2%)	2 (20%)
Minimal uptake	34 (31.5%)	1 (20%)	27 (29.7%)	6 (60%)
Uptake	13 (12%)	0	11 (12.1%)	2 (20%)
Tumor color				
Pigmented	134 (86.5%)	7 (100%)	111 (84.1%)	14 (100%)
Amelanocytic	21 (13.5%)	0	21 (15.9%)	0
LBD (mm)	9.9±2.7 (2.4-18.5)	6.8±2.5 (2.68 – 10)	9.7±2.3 (2.4 – 15.97)	13.0±3.4 (5.49 – 18.50)
Height (mm)	5.9±2.5 (1.37-12.18)	1.9±0.3 (1.37 – 2.23)	5.7±2.0 (2.5 – 9.93)	10.7±1.0 (8.65–12.18)
Tumor shape				
Dome	90 (61.2%)	5 (71.4%)	79 (62.2%)	6 (50%)
Mushroom	26 (17.7%)	0	22 (17.3%)	3 (25%)
Lobulated	9 (6.1%)	0	7 (5.5%)	2 (16.7%)
Irregular	7 (4.8%)	1 (14.3%)	6 (4.7%)	0
Peaked	12 (8.2%)	0	11 (8.7%)	1 (8.3%)
Flat	3 (2.0%)	1 (14.3%)	2 (1.6%)	0
Internal reflectivity[§]				
Low	6 (4%)	0	6 (4.7%)	0
Medium	112 (75.2%)	4 (57.1%)	95 (74.2%)	12 (92.3%)
High	31 (20.8%)	3 (42.9%)	27 (21.1%)	1 (7.7%)
Pathology	**N = 45**	**N = 1**	**N = 31**	**N =12**
Spindle	3 (6.7%)	0	1 (3.2%)	2 (16.7%)
Mixed	7 (15.6%)	0	4 (12.9%)	3 (25%)
Epithelioid	9 (20%)	0	6 (19.4%)	2 (16.7%)
Cell type nonspecified	21 (46.7%)	1 (100%)	17 (54.8%)	4 (33.3%)
Inconclusive	5 (11.1%)	0	3 (9.7%)	1 (8.3%)
Tumor location				
Periphery	54 (34.8%)	2 (28.6%)	49 (39.8%)	4 (28.6%)
Mid-periphery	35 (22.6%)	2 (28.6%)	25 (20.3%)	2 (14.3%)
Peripapillary	24 (15.5%)	0	22 (17.9%)	2 (14.3%)
Macular	33 (21.3%)	3 (42.9%)	22 (17.9%)	3 (21.4%)
Ciliary body	9 (5.8%)	0	5 (4.1%)	3 (21.4%)
Initial presence of RD				
None	129 (83.2%)	6 (85.7%)	112 (85.5%)	9 (64.3%)
< 1 Quadrant	9 (5.8%)	1 (14.3%)	6 (4.6%)	1 (7.1%)

1~2 Quadrants	15 (9.7%)	0	12 (9.2%)	3 (21.4%)
> 3 Quadrants	2 (1.3%)	0	1 (0.8%)	1 (7.1%)

OCT = optical coherence tomography, SRF = subretinal fluid, CME = cystoid macular edema, ERM = epiretinal membrane, SFCT = subfoveal choroidal thickness, PET = positron emission tomography, LBD = longest basal diameter, RD = retinal detachment
¶Two patients could not be sorted into the size categories because B-scan size measurements in milimeters were not available.
*Good vision (≥ 20/30), moderate vision (≥ 20/200, < 20/30), low vision (< 20/200)
§Low reflectivity (< 5%), medium reflectivity (≥ 5%, < 60%), high reflectivity (≥ 60%)

Table 2. Treatment characteristics

Characteristic	**N = 155**
Plaque time (hours)	102.48±57.36 (12-237)
Apex dose (Gy)	89.29±13.15(21.31-142.1)
Scleral dose (Gy)	562.5±794.67(100.8-9208.0)
Macular dose (Gy)	115.70±144.57 (0-680.7)
Optic nerve dose (Gy)	49.49±106.50 (0-1168)
Myectomy during plaque insertion	N = 73
One muscle	57(36.8%)
≥ 2 muscles	16(10.3%)
Additional local treatment	N = 129
TTT	104 (67.1%)
Internal choroidectomy	7 (4.5%)
Sclerouvectomy	20 (12.9%)
TPPV	34 (21.9%)

TTT = transpupillary thermotherapy, TPPV = trans pars plana vitrectomy

2. Local control, distant metastasis, and OS

Local progression was diagnosed in a total of 24 patients. The estimated 3-year local control rate was 88.6% and 5-year local control rate was 85.5% **(Fig 1A**The estimated 3-year OS was 91.6% and 5-year OS was 85.5% (**Fig 1B**). Estimated cancer-specific survival rates were 93.4% at 3 years and 87.9% at 5 years. The estimated median survival was not reached for our patient group. Of the total of 24

patients that died, median time from treatment to death was 34 months (range 1 – 78 months). Distant metastasis was diagnosed in 36 patients, and 19 of these patients died. The estimated metastasis-free rate was 84.7% at 3 years and 79.7% at 5 years (**Fig 1C**).

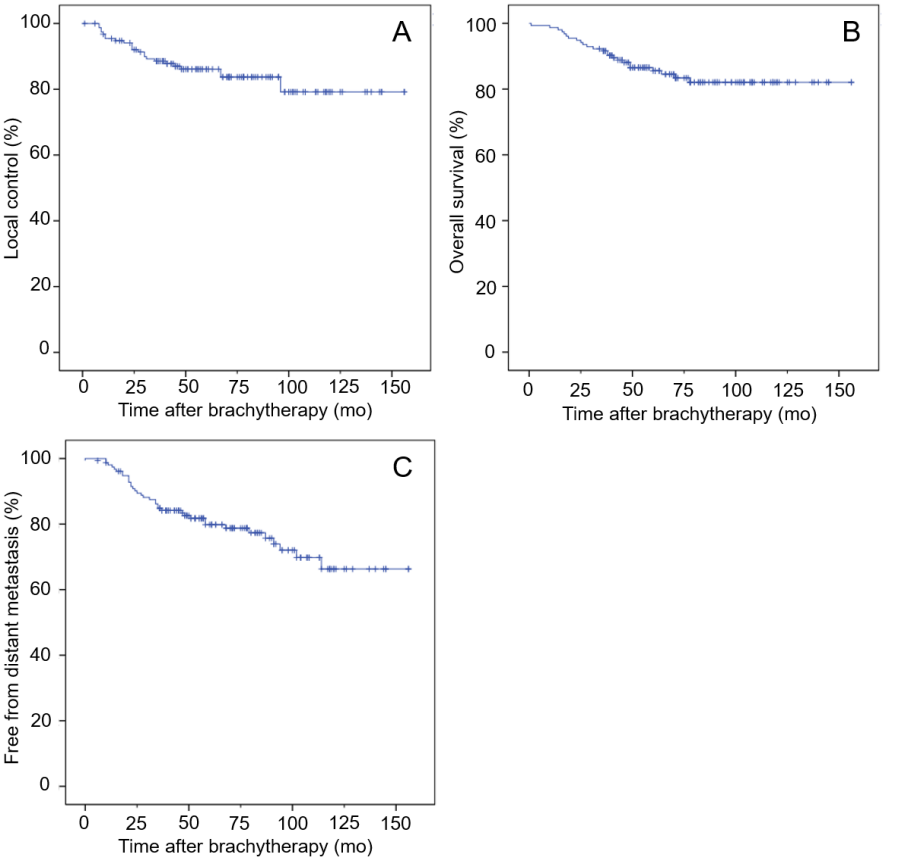

Figure 1. Kaplan-Meier curves estimating local recurrence (A), overall survival (B) and distant metastases (C).

The median time from diagnosis of distant metastasis to death was 12 months (range 0 – 48 months). Liver was the most common site of distant metastasis, with all but 3 patients having metastasis involving the liver. The metastasis sites are

summarized in **Table 3**. Cox's univariate proportional hazard model was used to evaluate prognostic factors for distant metastasis. High pre-treatment PET uptake, large size, and local recurrence were found to be significant, but after multivariate Cox regression analysis, high initial PET uptake was the only significant factor (Hazard ratio 5.206 compared to no uptake, 95% confidence interval 1.63-16.63, p=0.05).

Table 3. Sites of distant metastasis

Site	**N = 36**
Liver	21 (58.3%)
Liver + 1 site	10 (27.8%)
Lung	4
Bone or spine	5
Kidney	1
Liver + 2 sites	2 (5.6%)
Spleen, spine	1
Lung, bone	1
Other	3 (8.3%)
Lung, spine	1
Neck node	1
Stomach	1

Regression rate was measured as the amount of decreased height at each follow-up point compared to baseline height, as the percentage of the baseline height. The median regression rate was 12.8% at 6 months, 12.9% at 12 months, 18.5% at 24 months and 25.7% at 36 months. Regression in tumor height reached a plateau at around 36 months with nearly the same median regression rate at last follow-up (27.8%). Regression rate was not a predictive factor for any of the prognostic indicators such as loss of VA, OS, distant metastasis, local recurrence or eye preservation.

3. Preservation of useful vision and the eye

A total of 26 patients underwent either enucleation or exenteration. The estimated 3-year eye preservation rate was 87.4% and the 5-year rate was 84%. The median time to enucleation or exenteration was 28 months (range 11 – 90 months). The most common reason for enucleation was local recurrence (73.1%), defined as progressive growth of the tumor after treatment. Other reasons included a painful blind eye due to neovascular glaucoma (11.5%) and phthisis (11.5%). One patient experienced recurring, treatment-resistant uveitis in the fellow eye after treatment, and under the suspicion of sympathetic ophthalmia, the eye with melanoma was enucleated.

The mean logMAR VA of all patients whose eye was preserved was decreased to 1.40±1.10 from 0.52±0.64 at last follow-up (N=129). Also, the ratio of patients having low VA increased to 63.6%, while patients with good VA decreased to 11.6%. When patients that either lost their eye or presented with pre-treatment VA below 20/200 were excluded, 109 patients were left. Of those patients, 62 (56.9%) lost useful VA at some point in during their follow-up. The estimated 3-year visual loss rate was 42.9% and the 5-year rate was 54.6%. The median time to loss of useful VA was 10 months (range 0 – 115 months). The most common reason for loss of VA was macular atrophy and retinal detachment (RD) each responsible for 32.3% of the visual loss respectively. The characteristics of patients that lost their VA after treatment are summarized in **Table 4**.

Table 4. Characteristics of patients that lost useful vision following treatment. Only patients that did not undergo enucleation or exenteration were included. Patients that initially presented with a visual acuity (VA) below 20/200 were also excluded.

Characteristics	**N = 109**
Loss of useful VA to below 20/200	62 (56.9%)
Mean time to loss of VA (months)	20.7±28.7 (0 – 115)

3-year VA loss rate	42.9%	
5-year VA loss rate	54.6%	
Reason for loss of useful VA		N = 62
Macular atrophy	20 (32.3%)	
RD	20 (32.3%)	
Media opacity	5 (8.1%)	
Corneal opacity	1 (1.6%)	
Radiation maculopathy	7 (11.3%)	
NVG	5 (8.1%)	
Unknown	4 (6.5%)	

RD = retinal detachment, NVG = neovascular glaucoma

Cox's univariate proportional hazard model was used to evaluate prognostic factors for useful VA loss. Bigger pre-treatment tumor height, addition of local resection, higher radiation dose to the ON, occurrence of secondary RD or vitreous hemorrhage requiring TPPV were found to be significantly related to VA loss. After multivariate Cox regression with these variables, tumor height, ON radiation dose, and occurrence of RD were found to be significant (**Table 5**).

Table 5. Univariate and multivariate Cox hazard model for prognostic factors related to loss of useful visual acuity (VA).

Variable		**Univariate**			**Multivariate**		
		HR	**P**	**95% CI**	**HR**	**P**	**95% CI**
Age	Per 1 yr increase	0.933	0.58	0.97-1.02			
Initial logMAR VA	Per 1 increase	1.013	0.961	0.60-1.72			
Initial foveal OCT	Normal	1	-	-			
	SRF/CME	0.999	0.997	0.54-1.86			
	ERM	1.136	0.837	0.34-3.82			
SFCT	Per 1μm increase	1.002	0.271	0.998-1.006			
LBD	Per 1mm increase	1.093	0.067	0.994-1.202			
Height	Per 1mm increase	1.139	**0.013**	1.028-1.262	1.158	**0.018**	1.025-1.309
Tumor shape	Dome	1	-	-			
	Mushroom	1.793	0.089	0.95-3.51			
	Irregular	1.233	0.731	0.37-4.06			
	Flat	0.887	0.906	0.12-6.51			

Tumor location	Periphery	1	-	-			
	Peripapillary	1.62	0.15	0.84-3.13			
	Macular	1.5	0.21	0.79-2.85			
	Ciliary body	1.34	0.55	0.51-3.54			
Initial RD	Present	1.63	0.26	0.70-3.83			
Resection	Performed	2.16	0.058	0.94-4.78			
Scleral dose	Per 1Gy increase	1	0.713	1-1			
ON dose	Per 1Gy increase	1.006	**0.009**	1.002-1.011	1.006	**0.021**	1.001-1.010
Macular dose	Per 1Gy increase	1.002	0.109	1-1.004			
TTT	Performed	0.61	0.062	0.363-1.026			
RD		2.78	**0.001**	1.59-4.87	2.80	**0.001**	1.49-5.23
VH		2.36	**0.004**	1.32-4.21			
Radiation retinopathy		0.89	0.7	0.49-1.62			
NVG		1.696	0.13	0.86-3.36			

HR = hazard ratio, CI = confidance interval, logMAR = logarithm minimum angle of resolution, OCT = optical coherence tomography, SRF = subretinal fluid, CME = cystoid macular edema, ERM = epiretinal membrane, SFCT = subfoveal choroidal thickness, LBD = longest basal diameter, RD = retinal detachment, ON = optic nerve, TTT = transpupillary thermotherapy, VH = vitreous hemorrhage, NVG = neovascular glaucoma

4. Secondary vitrectomy for retinal detachment

A total of 31 patients underwent TPPV for RD. Every patient in this subgroup had a final VA of under 20/200. Of these patients, 26 (83.8%) lost their VA during follow-up and 5 (16.2%) had an initial VA lower than 20/200. The mean initial LBD and height in this subgroup were both bigger than the total mean values. However, upon comparison with the patients with no RD, only the difference in height was significant. There was no difference in the tumor location and the rate of biopsy or local resection performed between the two groups (**Table 6**).

Table 6. Comparison of the patients that later developed retinal detachment (RD) needing trans pars plana vitrectomy after undergoing brachytherapy with those that did not.

Characteristic	**No RD**	**RD**	**P value**
Number of patients	124	31	

LBD	9.74±2.71	10.61±2.76	0.117§
Height	5.77±2.57	6.79±2.10	0.044§
Location			0.229*
Periphery	42 (48.3%)	11 (52.4%)	
Mid-periphery	13 (14.9%)	6 (28.6%)	
Juxtapapillary	16 (18.4%)	1 (4.8%)	
Macular	9 (10.3%)	3 (14.3%)	
Ciliary body	7 (8%)	0	
Biopsy	31 (25.2%)	10 (32.3%)	0.427¶
Local resection	18 (14.5%)	5 (16.1%)	0.783¶

§Independent t-test, *Fischer's exact test, ¶Chi-square test
LBD = longest basal diameter

All patients undergoing surgery for RD also received silicone oil (SO) injection. Despite vitrectomy and SO tamponade, 12 patients experienced recurrent RD later, requiring re-operation and SO re-injection. Of the 15 patients that received SO removal, 6 patients (40%) experienced recurrent RD. Out of the 16 patients that did not receive SO removal, only 3 (18.8%) patients experienced recurrent RD. Silicone oil removal was a significant risk factor for recurrent RD with an odds ratio of 6.5 (p=0.018).

5. Efficacy of additional local therapy

In large tumors with a height over 6 mm, excluding patients that received local resection, patients who received TTT (n = 38) and those that underwent brachytherapy alone (n = 12) were compared. Despite the no-TTT group having a bigger pre-treatment tumor height, there were no significant differences in the outcomes between the two groups including OS, local recurrence, eye preservation, distant metastasis, and loss of useful VA (**Table 7**).

Table 7. Comparison of outcomes in relatively large tumors with an initial height over 6mm, according to whether or not transpupillary thermotherapy(TTT) was

added.

Characteristic	No TTT (N = 12)	TTT (N = 38)	P value
Height	8.37±1.79	7.39±1.20	0.099*
LBD	10.11±2.15	11.81±2.11	0.019*
3-year eye preservation rate	83.3%	85.3%	0.610§
3-year local control rate	83.3%	82%	0.806§
3-year metastasis-free rate	83.3%	69.6%	0.610§
3-year OS	91.7%	86.8%	0.430§

*independent t-test, §log-rank test
LBD = longest basal diameter, OS = overall survival

In very large tumors with an initial height of over 8 mm, patients that received local excision (n = 18) were compared with those that did not (n = 16). Again, there were no significant differences in all prognostic outcomes (**Table 8**).

Table 8. Comparison of outcomes in relatively large tumors with an initial height over 8 mm, according to whether or not local excision was added.

Characteristic	No resection (N = 16)	Resection (N = 18)	P value
Height	9.40±0.95	10.02±1.30	0.127*
LBD	11.42±2.61	12.50±2.68	0.253*
Additional TTT	10(62.5%)	2(11.1%)	0.003¶
3-year eye preservation rate	74%	71.1%	0.326§
3-year local control rate	74%	88.1%	0.917§
3-year metastasis-free rate	81.3%	64.7%	0.494§
3-year OS	87.5%	83.3%	0.355§

*independent t-test, §log-rank test, ¶chi-square test
LBD = longest basal diameter, TTT = transpupillary thermotherapy, OS = overall survival

6. Radiation-related complications

A total of 72 patients eventually experienced some form of radiation retinopathy. Treatment was only administered when there was hope for salvage of vision. Intravitreal anti-VEGF was the main treatment (n=13) for macular CME, and 4

patients underwent TPPV for vitreous hemorrhage. One patient received a triamcinolone injection to the posterior subtenon space and one received an intravitreal triamcinolone injection. Neovascular glaucoma (NVG) developed in 22 patients (14.2%). NVG was managed with medical treatment in 9 patients (40.9%), 5 patients (22.7%) received bevacizumab injections, 3 patients (13.6%) underwent enucleation, and 5 (22.7%) underwent glaucoma surgery.

IV. DISCUSSION

In this analysis, long-term outcomes of ^{106}Ru brachytherapy were evaluated in a large series of 155 East Asian patients with choroidal melanoma. In the previous report on ^{106}Ru brachytherapy outcomes from our institution in 2018, the estimated 3-year local control rate, free from distant metastases rate and OS were 80%, 84% and 90% respectively.[10] In this study, even with a much longer period of follow-up and almost twice as many subjects, prognosis remains relatively similar. The estimated 5-year local control rate, free from distant metastases rate and OS were 85.5%, 79.7% and 85.5% respectively, favorable compared to other Western studies on brachytherapy for medium-sized choroidal melanomas.[11-13] Our results confirm eye-preserving treatment with brachytherapy in East Asians does not impair OS. Our previous report established that a larger initial tumor height of over 6 mm is a significant risk factor for local recurrence, enucleation, distant metastases and death.

In this study, the median time to diagnosis of distant metastases was 31 months (range 10 - 114 months), comparable with a Dutch study that reported a median time of 30.4 months.[13] However, the Kaplan-Meier curve for metastasis-free survival did not plateau at 5 years. From the total of 36 patients that were eventually diagnosed with distant metastases, 7 patients were diagnosed after more than 5 years had passed from brachytherapy with one patient as late as 114 months after treatment. Therefore, long-term continuous screening for distant metastases is needed even if the tumor seems stable. We found that high FDG uptake on initial PET scans was a significant risk factor for distant metastases, which has already been reported previously with a

smaller number of subjects by our group in 2011.[14] Our subjects showed a median 12 months from diagnosis of distant metastasis to death, which is quite longer than reported by the COMS trial (3.6 months).[15] But other smaller trials report median survival of metastatic uveal melanoma as up to 15 months.[16,17]

Choroidal melanomas rarely regress completely after plaque brachytherapy. A faster, larger reduction in tumor height has actually been reported to be correlated with worse outcomes, possibly because highly mitotic and metabolically active tumors are more responsive to radiotherapy.[18-20] However in this study, the rate of tumor height regression was not correlated with any prognostic outcomes.

The estimated 5-year eye preservation rate was 84% in our study. However, at last follow-up, the majority of patients (63.6%) had a VA of less than 20/200. Even when excluding those that had a low VA at presentation, 56.9% eventually lost useful VA during follow-up.

One of the most common reasons for loss of VA was peritumor macular atrophy resulting from radiation or TTT. Previous reports have cited tumor distance from the macula, macular radiation dose and tumor height as risk factors for loss of VA.[21,22] In our study, we could not establish a definite relationship between the tumor location and loss of VA but increased radiation dose to the ON, and larger tumor height were significant risk factors. Some patients, even with a tumor as close as 2~3mm from the fovea maintained moderately good final VA, with very little peritumor atrophy in the posterior margins of the tumor. These findings suggest that careful placement of plaques, especially in regard to the posterior margin for maximal avoidance of the macular area, could result in better visual outcomes. Also, in our institution, intravitreal anti-vascular endothelial growth factor (VEGF) injections for macular edema after brachytherapy was used very conservatively until recently. The low rates of treatment for CME or SRF resulting from radiation may have resulted in higher rates of macular atrophy and vision loss.

RD was another most common reason for loss of useful VA, and was found to be significantly correlated with visual loss by multivariate analysis. Even after TPPV,

and successful re-attachment of the retina, all of these patients ended up with a final VA of less than 20/200. Only tumor height was a significant risk factor in predicting RD occurrence. Local excision or tumor biopsy procedures did not seem to increase risk for RD. SO removal seemed to result in re-detachment of the retina in a significantly higher portion of cases. Even with successful SO removal, no patients resulted with a useful final VA of over 20/200. Therefore, leaving the SO tamponade and not considering SO removal unless strongly indicated may be recommended.

In the beginning of our experience with plaque brachytherapy, additional local therapy of either TTT or local excision was routinely performed in almost all cases. This patient group is well represented in earlier reports from our institution.[10,23] Later on, local therapy was not performed routinely with brachytherapy. Because the decision to perform adjunctive local therapy in most patients was not based on individual status of the tumor but rather the standard treatment protocol of our center at the time, selection bias in analyzing these patients is minimal.

Addition of TTT was based on the fact that ^{106}Ru brachytherapy, with a lower depth penetration compared to other radioisotopes, is thought to be less effective in tumors with heights exceeding 5 – 6 mm. With application of TTT, tumor necrosis is induced to a depth of about 2 -3 mm from the tumor surface. Therefore, a combination of TTT and ^{106}Ru brachytherapy was thought to be synergistic, especially in larger tumors.[24,25] However, our results found that there were no significant differences in all outcomes between the group that received additive TTT and those that did not. In very large tumors, with a height over 8 mm, local excision was often performed. Patients that did not receive resection mostly underwent TTT. We did not find any significant differences in the outcomes with or without local excision in these patients. Even though ^{106}Ru is thought to have insufficient doses to tumors with larger heights, our results show this is not necessarily the case. Even in very large tumors with height exceeding 8mm, when local resection can't be performed, combined brachytherapy and TTT can be a good option.

The limitations of this study are due to its retrospective nature. While the brachytherapy protocol was relatively homogenous among the study subjects, the indications for additional local therapy such as TTT or local excision were not consistent and changed over time as our experience with brachytherapy and choroidal melanoma grew. Therefore, while there was the advantage of being able to compare the outcomes between patients that received adjunctive TTT and those that did not without bias, this limited the number of statistically significant conclusions our study was able to make. Another limitation was the inconsistency in the follow-up and management of radiation retinopathy. Because rates of eye preservation and survival after brachytherapy seem to be excellent, the next goal in the development of choroidal melanoma management should be preservation of vision. Therefore, future studies directed towards strategies to reduce radiation dose and to avoid complications such as macular atrophy and RD are needed.

V. CONCLUSION

^{106}Ru is effective as an eye-preserving treatment for medium-sized choroidal melanoma in Korean patients. Even in cases with larger heights over 6 ~ 8mm, adjunct local therapy such as TTT and resection should not be performed routinely.

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ABSTRACT(IN KOREAN)

한국인에서 Ruthenium-106 근접방사선치료 후 맥락막 흑색종의 장기 예후

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목적: 맥락막 흑색종 환자에서 Ruthenium-106 근접방사선치료 후 장기 예후를 연구해보고자 하였다.
방법: 2006년부터 2017년까지, 맥락막 흑색종 진단 하 Ruthenium-106 근접방사선치료를 시행 받은 후 3년 이상의 추적관찰 기간을 가진 155명의 환자들에 대한 후향적 의무기록 분석을 시행하였다. 기본적 임상 정보 및 종양 관련 정보를 조사하였으며, 사망률, 재발률, 전이율, 실명율 등 예후를 분석하였다.
결과: 환자들의 추적관찰 기간의 중앙값은 68개월이었다. 5년 생존률은 85.5%, 전이없는 생존률은 79.7%, 안구 보존률은 79.7%, 재발 없는 생존률은 54.6%였다. 5년째 시력이 0.1 이하로 떨어지는 기능적 실명률은 54.6% 였다. 기능적 실명의 예측인자로는 높은 치료 전 종양의 높이, 시신경에 대한 큰 방사선 조사량, 망막박리 발생이 있었다. 크기가 큰 종양에서도 경동공 온열치료나 국소적 절제법을 추가하여도 예후의 차이가 없었다.
결론: 한국인에서 중간 크기의 포도막 흑색종은 Ruthenium-106 근접방사선치료에 반응을 잘 하며, 추가적인 국소 치료는 예후에 영향이 적은것으로 보인다.

핵심되는 말: 맥락막 흑색종, 포도막 흑색종, 근접방사선치료, 루테늄