• Clinical Research •

High-dose ruthenium-106 plaque therapy for circumscribed choroidal hemangioma: a retrospective study of 25 Chinese patients

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Abstract

● **AIM:** To evaluate the efficacy and safety of ruthenium-106 (^{106}Ru) plaque radiotherapy at a dose (>50 Gy) higher than recommended (29-50 Gy) for treatment of circumscribed choroidal hemangioma (CCH) in Chinese patients.

● **METHODS:** This retrospective study included 25 symptomatic CCH patients undergoing ^{106}Ru plaque brachytherapy involving 25 eyes between January 2005 and August 2016. Ophthalmic examination was performed at the baseline and at each post-treatment follow-up visit, using best-corrected visual acuity (BCVA), dilated fundus examination, and B-scan ultrasonography. The primary efficacy outcome measures included the changes in BCVA and hemangioma dimensions at the last followup visit from the baseline.

● **RESULTS:** The mean follow-up duration was 28.0±26.6 (range, 12-110)mo. All the hemangiomas were located in the posterior pole except for two involving the fovea. The mean apex dose of ^{106}Ru plaque radiotherapy was 84.4±19.7 Gy. The mean BCVA improved from 41.4±29.3 (0-97) at the baseline to 53.0±33.8 (0-97) ETDRS letters at the last visit (P=0.01). The mean hemangioma height declined from 3.98±0.88 (2.40-5.50) mm to 0.84±1.63 (0-6.47) mm (P≤0.001), and the greatest linear diameter (GLD) reduced from 9.36±2.23 (6.80-15.00) to 7.40±2.45 (0-13.00) mm (P≤0.001). Hemangioma size increased in one (4%) eye with a worsened vision, and subretinal fluid completely resolved in all but one patient (4%). Radiation-related retinopathy was observed in two patients at post-treatment 9 and 11mo, respectively.

● **CONCLUSION:** ^{106}Ru plaque brachytherapy at a dose (>50 Gy) higher than recommended (29-50 Gy) is an effective treatment regimen for symptomatic CCH associated with significantly improved visual acuity and a favorable safety profile in Chinese patients.

● **KEYWORDS:** circumscribed choroidal hemangioma; radiotherapy; ruthenium-106; Chinese patients; retrospective study

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INTRODUCTION

Circumscribed choroidal hemangioma (CCH) is a rare benign vascular hamartoma and generally arises unilaterally in the choroidal tissue of the posterior pole[1]. Accumulation of serous subretinal fluid (SRF) and intraretinal cystoid edema result in visual loss. Approximately 40% of CCH cases will become progressively symptomatic, while no intervention is generally required for asymptomatic cases[2]. For symptomatic CCH cases, effective treatment modalities include transpupillary thermotherapy, laser photocoagulation, photodynamic therapy, radiotherapy, and anti-vascular endothelial growth factor (VEGF) medication[3-6].

Radiation therapy has been recommended for treating choroidal hemangiomas, especially for patients with extensive subretinal exudation and retinal detachment refractory to photodynamic therapy[7]. Multiple radiation therapies, including plaque radiotherapy (brachytherapy), external beam, proton beam radiation and stereotactic radiosurgery, have been reported to be effective for treating symptomatic CCH[5,7-9]. Among these modalities, plaque brachytherapy is thought to

be a more targeted treatment for hemangioma, as a higher dose acts on the base of the hemangioma rather than the apex with minimized radiation-induced side effects[5,8].

As a safe and effective therapeutic approach for choroidal hemangiomas, the efficacy and safety ruthenium-106 (^{106}Ru) plaque brachytherapy has been studied in Caucasian CCH patients[5,9], with a knowledge gap in Eastern Asian populations including Chinese patients. Therefore, the objective of the present study is to evaluate the efficacy and safety of ^{106}Ru plaque brachytherapy at a dose (>50 Gy) higher than recommended (29-50 Gy) for treating symptomatic CCH in Chinese patients, aiming to decrease hemangioma recurrence without increasing radiation retinopathy, in comparison with those in Caucasian population reported from previous literature.

SUBJECTS AND METHODS

Ethical Approval This study retrospectively reviewed a cohort of 25 symptomatic patients undergoing ^{106}Ru plaque brachytherapy for unilateral CCH at the Ophthalmology Center of Peking University People's Hospital between January 2005 and August 2016. All the included patients were consecutively followed up for 1y or more. The study protocol was approved by the Ethics Committee at Peking University People's Hospital, Beijing, China in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient before receiving ^{106}Ru plaque brachytherapy.

CCH was diagnosed using a combination of binocular indirect ophthalmoscopy by a single board-certified ophthalmologist (Liang JH), B-scan ultrasonography (USG), optical coherence tomography (OCT), fluorescein angiography (FA) and indocyanine green angiography (ICGA) prior to plaque brachytherapy. The inclusion criteria were presence of CCH with extensive subretinal exudation and/or retinal detachment and receiving no treatment for CCH, regardless of baseline best-corrected visual acuity (BCVA). Patients with complicating ophthalmic conditions, including glaucoma, diabetic retinopathy, rhegmatogenous retinal detachment, and macular hole, were excluded from analysis.

Plaque Brachytherapy A ^{106}Ru ophthalmic applicator (BEBIG Isotopen und Medizintechnik GmbH, Berlin, Germany) was used for plaque brachytherapy with the size and shape adjusted to the dimension and location of the CCH. The hemangioma location and dimension were determined using a combination of indirect binocular ophthalmoscopy, USG, FA, and ICGA, and reconfirmed before implantation of the plaque. An additional 2-mm healthy margin was included for the choice of plaque size. Upon completion of the implantation, indentation and transillumination was done to confirm plaque placement and positioning. An in-house calibration protocol was used for plaque quality control. The target radiation dose for all the CCH patients was calculated by the single board-certified ophthalmologist (Liang JH), and the plaque was removed after delivering the target dose. Insertion and removal of the plaque was performed by Liang JH in all patients under general anesthesia.

Follow-up Visits Follow-up ophthalmic examination were performed at an interval of 3-6mo in the first year and every 6-12mo afterwards. The examination included BCVA, slit-lamp biomicroscopy, dilated funduscopy, USG, OCT, FA, and ICGA (HRA-2, Heidelberg Retina Angiograph System; Heidelberg Engineering Inc., Vista, CA, USA). Dilated fundus examination was performed by the single board-certified ophthalmologist (Liang JH) for a consistent clinical evaluation. USG was used to determine the greatest basal diameter and the apical height of the hemangioma. OCT was used to measure the foveal center thickness and the height of the SRF for hemangiomas located near the fovea.

Outcome Measures The primary efficacy outcome measures included the changes in BCVA and hemangioma dimensions at the last follow-up visit from the baseline. Significant improvement in BCVA was defined as an at least two-line improvement in visual acuity of letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) acuity chart at the last visit. Major safety outcome measures included occurrences of treatment-emergent radiation retinopathy and cataract formation.

Statistical Analysis All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). The paired *t*-test was used to compare the changes in BCVA and hemangioma dimension on USG between the baseline and the last follow-up visit. A two-sided *P* value of less than 0.05 was considered statistically significant unless otherwise specified.

RESULTS

Twenty-five symptomatic CCH patients were included for analysis in this study with 25 unilateral eyes involved. This cohort included 12 men and 13 women at a mean age of 41.1±12.3 (range 16-67)y, and the mean follow-up duration was 28.0±26.6 (range 12-110)mo. The hemangiomas were located under the retina in all patients, with 23/25 (92%) located in the posterior pole and 2/25 (8%) involving the fovea. The demographic and clinical characteristics are shown in Table 1 and individual patient characteristics are listed in Table 2. The situation before and after the treatment of a patient were exhibited including fundus photography, B-scan USG, and FA (Figure 1).

Treatment outcomes are shown in Table 3. The mean apex dose of ^{106}Ru plaque radiotherapy was 84.4±19.7 Gy. The mean BCVA improved from 41.4±29.3 (0-97) at the baseline to 53.0±33.8 (0-97) ETDRS letters at the last visit (*P*=0.01). Visual acuity significantly improved in 14/25 (56%) eyes;

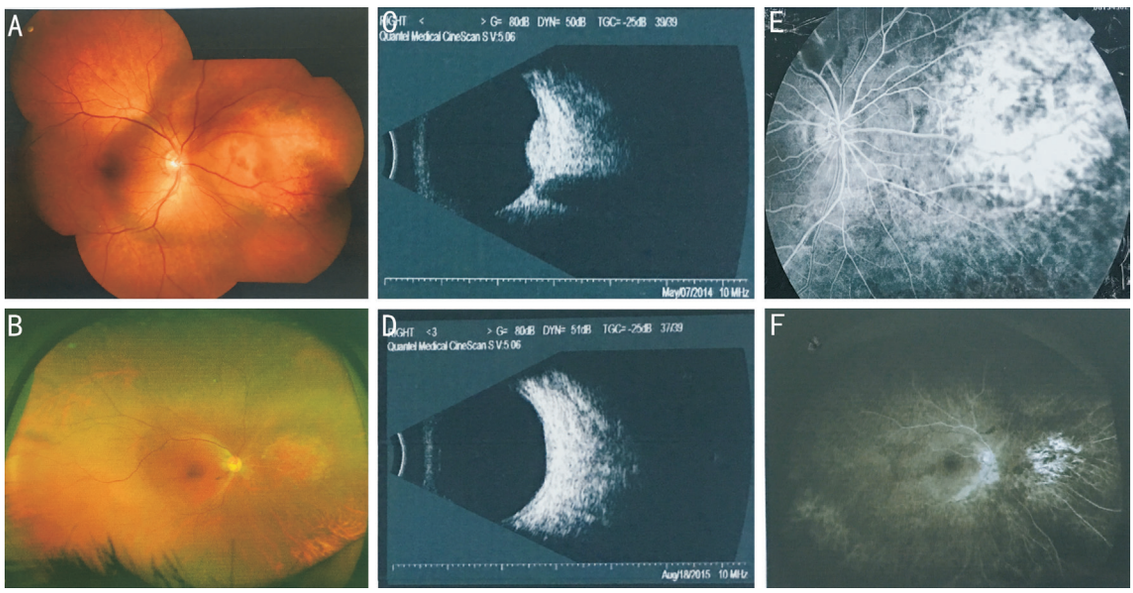

Figure 1 Treatment outcome in a patient with CCH pretreatment and post-treatment 15mo using ^{106}Ru plaque radiotherapy An orange-red colored (A), CCH located in the posterior polar and tumor reduction (B) in post-treatment 15mo on color funduscopy. C, D: Before and after treatment on B-scan USG. E, F: Before and after treatment on FA, in the same eye.

Table 1 Demographic and clinical characteristics of CCH patients

Characteristics	Statistics
No. of patients	25
No. of eyes	25
Male/female	12/13
Age (y, range)	41.1±12.3 (16-67)
Follow-up time (mo, range)	28.0±26.6 (12-110)
Hemangioma location, *n* (%)	
Foveal	2/25 (8)
Extra-foveal	23/25 (92)
Exudative retinal detachment, *n* (%)	25/25 (100)
Involvement of macular area, *n* (%)	24/25 (96)

CCH: Circumscribed choroidal hemangioma.

10/25 (40%) eyes remained unchanged but 1/25 eye (4%) worsened. At the last visit, 22/25 (88%) eyes with the disease located in the posterior pole had an improved or unchanged visual acuity, while 2/25 (8%) eyes with the disease involving the foveal area showed no improvement. The mean hemangioma height declined from 3.98±0.88 (2.40-5.50) to 0.84±1.63 (0-6.47) mm (P≤0.001), and the greatest linear diameter reduced from 9.36±2.23 (6.80-15.00) to 7.40±2.45 (0-13.00) mm (P≤0.001). In one patient, the hemangioma height increased from 5.50 mm at the baseline to 6.47 mm at the last visit with a worsening BCVA. SRF completely resolved in all cases except for one patient.

Radiation-related retinopathy on funduscopy was observed in two (8%) patients at post-treatment 9 (dose=60 Gy) and 11mo (105 Gy), respectively. These two patients with radiation related retinopathy responded to treatment with between two and three intravitreal bevacizumab injections with one having resolved two years after occurrence and the other lost to follow-up. None of patients developed any other complications, such as glaucoma, choroidal ischemia, or secondary choroidal neovascularization.

DISCUSSION

The present study demonstrated the efficacy and safety of ^{106}Ru plaque brachytherapy at a dose (>50 Gy) higher than recommended (29-50 Gy) for treating symptomatic CCH in Chinese patients. The clinical benefits included improvement in visual acuity and reduction in hemangioma dimension, without significantly increasing the risk of radiation-induced retinopathy. To the best of our knowledge, the present work was the first report regarding ^{106}Ru aplaque brachytherapy for treating CCH in Chinese population.

Multiple treatment modalities have been available for treatment of symptomatic CCH. Laser photocoagulation has long been used as the first-line therapy for CCH but results in a limited visual recovery[10]. Transpupillary thermotherapy is more effective in pathologic response but requires repeated performance, which is therefore mainly indicated for hemangiomas with a large retinal detachment[11]. Use of oral propranolol may be partially effective for infantile hemangioma[12], and intravitreous injection with anti-VEGF medication and photodynamic therapy had also been used for treating CCH with complicating SRF[13]. Photodynamic therapy, however, showed no significant visual acuity improvement although the hemangioma became downsized only if a double-dose therapy was given[14].

Table 2 Summary of treatment and clinical characteristics of CCH patients *n*=25

Pt No.	Sex	Age (y)	Laterality	Location	Pre-treatment dimension (mm)		Post-treatment dimension (mm)		Plaque	Apex dose (Gy)	Follow-up (mo)	BCVA (ETDRS)		Complication
					D	H	D	H				BL	LFUV	
1	M	46	OS	F	9.26	4.28	7.32	0.12	CCA	95	12	53	90	None
2	F	67	OD	Ex-F	10.11	4.39	9.03	0.20	CCA	106	70	37	63	None
3	M	34	OS	Ex-F	10.86	5.33	7.8	0.22	CCA	95	13	47	47	None
4	M	53	OD	Ex-F	7.56	4.18	6.88	0.01	CCA	78	12	30	33	None
5	M	44	OD	Ex-F	9.7	4.3	8.13	2.61	COB	95	12	0	0	None
6	M	43	OD	Ex-F	6.8	3.6	5.88	0.03	CCA	83	12	47	83	None
7	F	36	OD	F	7.16	3.4	6.89	0.18	COB	75	39	5	5	None
8	M	29	OS	Ex-F	7.73	3.23	5.56	0.03	CCA	85	110	87	87	None
9	M	65	OS	Ex-F	8.1	3.5	7.44	0.06	CCA	73	12	33	33	None
10	F	35	OS	Ex-F	9.47	4.02	8.07	0.11	CCA	60	12	24	47	RP
11	M	49	OS	Ex-F	15	5.5	13	6.47	COB	93	12	63	5	None
12	F	24	OD	Ex-F	8.75	4.04	7.77	0.04	CCA	100	12	63	63	None
13	F	30	OS	Ex-F	7.8	3.1	7.00	0.05	COB	103	12	33	57	None
14	M	60	OD	Ex-F	7.1	2.4	6.99	0.08	CCA	73	30	33	47	None
15	M	42	OS	Ex-F	7.45	3.12	6.64	0.12	CCA	56	48	73	93	None
16	F	38	OS	Ex-F	11.44	4.97	10.08	0.19	COB	122	15	0	0	None
17	F	41	OD	Ex-F	6.95	3.01	5.88	0.01	CCA	56	87	77	97	None
18	M	37	OD	Ex-F	7.64	2.89	6.01	0.09	CCA	86	12	77	77	None
19	F	16	OD	Ex-F	13.79	5.32	10.11	0.11	COB	59	49	27	77	None
20	M	45	OS	Ex-F	9.07	4.04	6.4	2	CCA	69	12	5	30	None
21	F	30	OS	Ex-F	9.2	4.2	0	0	CCB	129	12	0	0	None
22	F	53	OS	Ex-F	11.2	5.2	11.3	3.4	CCA	67	12	5	30	None
23	F	39	OD	Ex-F	10.3	3.8	8.83	0.02	CCB	105	34	97	97	RP
24	F	42	OD	Ex-F	8.3	2.8	7.09	0.64	CCA	71	36	67	97	None
25	F	29	OD	Ex-F	13.36	5.03	3.9	4.05	COB	77	12	53	67	None

F: Female; M: Male; F: Foveal; EX-F: Extra-foveal; D: Diameter; H: Height; BL: Baseline; LFUV: Last follow-up visit; RP: Retinopathy.

Table 3 Treatment outcomes of ^{106}Ru plaque therapy

Treatment outcomes	*n*=25
BCVA, ETDRS (letters)	
Baseline	41.4±29.3
The last follow-up visit	53.0±33.8
P[a]	0.01
BCVA improved or stable, *n* (%)	24 (96)
Tumor dimension on USG	
Height, mm	
Baseline	3.98±0.88
The last follow-up visit	0.84±1.63
P[a]	≤0.001
GLD, mm	
Baseline	9.36±2.23
The last follow-up visit	7.40±2.45
P[a]	≤0.001
Complete SRF resolution, *n* (%)	24 (96)
Recurrence, *n* (%)	0

BCVA: Best-corrected visual acuity; ETDRS: The Early Treatment Diabetic Retinopathy Study; USG: Ultrasonography; GLD: The greatest linear diameter; SRF: Subretinal fluid. [a]*P* value using the paired Student's *t*-test.

Multiple radiotherapy techniques have been used for treating symptomatic CCH with a high efficacy and a favorable safety profile[15-21]. Plaque brachytherapy achieves a more targeted delivery and results in less frequent radiation-induced retinopathy, using a variety of isotopes including palladium-103, cobalt-60, ^{106}Ru and iodine-125[2,17-20]. A low-dose radiation therapy achieves significantly improved visual acuity, complete SRF resolution and hemangioma regression in a high proportion of symptomatic CCH[15-16]. However, a major limitation regarding plaque brachytherapy is the inconsistence in radiation dose between the base and the apex of the hemangioma at a risk of recurrence from the base[21].

In this study, ^{106}Ru was given at a dose higher than recommended (normally at a dose range of 29-50 Gy) for plaque brachytherapy in a Chinese CCH population, due to the risk of disease recurrence from a low-dose radiotherapy, with patient demographic and clinical characteristics similar to those from previous studies (Table 4)[5,21]. A large proportion of patients showed significant (56%) improvement in visual acuity, similar to those (12/21, 57%) reported by Naseripour *et al*[9].

Table 4 Comparative treatment outcomes of ^{106}Ru plaque therapy for CCH

Parameters	Present study	Medraperla *et al*[5]	Naseripour *et al*[9]	Joshi *et al*[21]
No. of patients	25	8	21	8
Radioactive isotope	^{106}Ru	^{106}Ru and iodine-125	^{106}Ru	^{106}Ru
Dose, Gy, mean	84.4	50	38.5	32.5
Radiation-related complication, *n* (%)				
Retinopathy	2 (8)	0	5 (23.8)	0
Papillopathy	0	0	1 (4.8)	0
Mean tumor height, mm				
Baseline	3.99	4.8	3.87	5.0
Last visit	0.84	2.1	0.7	Not reported
GLD, mm, mean				
Baseline	9.36	10.6	10.0	12.7
Last visit	7.40	Not reported	8.33	Not reported
BCVA, mean				
Baseline	≈20/200	20/80	20/80	Not reported
Last visit	≈20/160	20/30	20/50	Not reported
Visual acuity improvement, %	Two or more lines, 52	Three or more lines, 63	Two or more lines, 57	Not reported
Follow-up period, mo, mean	28.0	25.0	38.6	Not reported

CCH: Circumscribed choroidal hemangioma; BCVA: Best-corrected visual acuity; GLD: The greatest linear diameter.

A major difference in patient characteristics was the variation in hemangioma location, more frequently (92%) located in the extra-foveal area in this study compared to previous ones[8,13]. Hemangioma dimension also became significantly downsized to an extent similar to or greater than those in previous reports[4,8,16,18-19,21-22]. An additional benefit of high-dose ^{106}Ru plaque brachytherapy was achievement of complete SRF resolution in the great majority (96%) of patients.

Major safety concern is radiation-induced retinopathy in the scenario of high-dose therapy. Within a follow-up duration of at least 1y and up to 9y, only a small portion (2/25, 4%) of patients developed radiation-induced retinopathy within the first year of ^{106}Ru plaque therapy, significantly lower than that reported by Naseripour *et al*[9]; Schemia and hypoxia are still recognized as one of the important causes of radiation retinopathy, so intravitreal anti-VEGF medication is the treatment regimen of choice for radiation-induced retinopathy.

There were some limitations in our study. First, the present work was not in a randomized or controlled design due to rarity of symptomatic CCH. Second, the sample size was relatively small but comparable to those of previous proof-of-concept studies. Third, the efficacy outcomes might be biased by confounding factors, including patient's characteristics, operator's expertise and follow-up procedure, which were controlled in the study design, such as operation by a single ophthalmologist.

In conclusion, the present work demonstrated that ^{106}Ru plaque radiotherapy at a dose (>50 Gy) higher than recommended (29-50 Gy) was effective for treatment of symptomatic CCH in Chinese patients. The clinical benefits included significant improvement in visual acuity and marked hemangioma regression similar to or greater than those in previous studies. Radiation-induced retinopathy occurred at a relatively low frequency but remained manageable and responsive to medical intervention. A randomized, dose-controlled study powered with a sufficient sample size is yet to be done for validation of the long-term efficacy and safety of high-dose ^{106}Ru plaque radiotherapy for treating symptomatic CCH.

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