

# Ruthenium-106 plaque brachytherapy for the treatment of diffuse choroidal hemangioma in Sturge-Weber syndrome

Ying-Ying Yu<sup>1,2,3,4</sup>, Xiao-Xin Li<sup>1,2,3,4</sup>, Jian-Hong Liang<sup>1,2,3,4</sup>

<sup>1</sup>Department of Ophthalmology & Clinical Center of Optometry, Peking University People's Hospital, Beijing 100044, China

<sup>2</sup>Eye Diseases and Optometry Institute Peking University People's Hospital, Beijing 100044, China

<sup>3</sup>Beijing Key Laboratory of Diagnosis and Therapy of Retinal and Choroid Diseases, Beijing 100044, China

<sup>4</sup>College of Optometry, Peking University Health Science Center, Beijing 100191, China

**Correspondence to:** Jian-Hong Liang. Department of Ophthalmology, Peking University People's Hospital, No.11 Xizhimen South Avenue, Xicheng District, Beijing 100044, China. drliangjianhong@126.com

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## Abstract

• **AIM:** To evaluate the efficacy of ruthenium-106 plaque brachytherapy for the treatment of diffuse choroidal hemangioma (DCH) in Sturge-Weber syndrome (SWS).

• **METHODS:** A total of 8 patients with DCH in SWS managed with plaque brachytherapy were retrospectively included. Patients were treated with ruthenium-106 plaque therapy (median apex dose: 83 Gy) at the thickest tumor region. On follow-up, we recorded the tumor thickness, the best-corrected visual acuity (BCVA), subretinal fluid (SRF) status, and complications following treatment.

• **RESULTS:** At a median follow-up of 43mo, tumor regression was observed in all cases, with a complete resolution of SRF and reduction in tumor-thickness. No radiation complications were recorded during the follow up time.

• **CONCLUSION:** Ruthenium-106 plaque therapy to the thickest portion of the tumor seems to be a useful treatment in patients with DCH in SWS.

• **KEYWORDS:** diffuse choroidal hemangioma; Sturge-Weber syndrome; plaque brachytherapy

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## INTRODUCTION

**D**iffuse choroidal hemangioma (DCH) is frequently located ipsilateral to a facial hemangioma, usually as a component of a variant of Sturge-Weber syndrome (SWS), both congenital and juvenile, which can also include leptomeningeal hemangiomas, seizures, and other manifestations. DCHs in the posterior pole are typically observed as a “tomato catsup fundus”, and are flat to moderately elevated masses with indistinct margins. The majority of patients are susceptible to secondary retinal detachment due to subretinal fluid (SRF) shifts, leading to visual loss<sup>[1]</sup>. DCH management should focus on the best-corrected visual acuity (BVCA) and degree of detachment. For tumors involving juxtapapillary and subfoveal locations, therapy is limited and plaque therapy may be beneficial<sup>[2-6]</sup>. After treatment, the patients showed SRF resolution and a regression of their tumors. This study evaluated the efficacy of ruthenium-106 plaque brachytherapy for DCHs through the measurement of tumor thickness, retinal reattachment, visual acuity, and treatment complications in a large patient cohort.

## SUBJECTS AND METHODS

**Ethical Approval** The study obtained Institutional Review Board approval and adhered to the tenets of the Declaration of Helsinki. All patients signed a statement of informed consent.

This was a retrospective assessment of 8 DCH patients in SWS that were managed with ruthenium-106 plaque radiotherapy at the Department of Ophthalmology in Peking University People's Hospital between July 2009 and September 2014. Diagnoses were made through fluorescein angiographic, ophthalmoscopic characteristics. We recorded the age at diagnosis (years), sex, patient complaints, facial hemangioma, and past-therapies from the patient records. BCVA, quadrant numbers, intraocular pressure (IOP, mm Hg), and hours involving DCH were recorded. We also assessed the quadrant with the thickest hemangioma, SRF and the levels of SRF. B-scan ultrasonography was used to confirm tumor thickness and that was documented with images, ultrasonography, and optical coherence tomography.

Of the patients, 2/8 received double-therapy. All patients were administered ruthenium-106 plaque therapy at the thickest region of the tumor. To cover the base of the intraocular tumor, eye plaques were sewn onto the episclera and the patients received radiotherapy for a period of 3-7d. Plaques were then

**Table 1 Patient demographic information and DCH characteristics**

Patient	Age/ gender	Presenting symptoms/ duration of symptoms (mo)	Affected eye/ (BCVA)	IOP (mm Hg)	Facial hemangioma	Tumor features at presentation			Previous treatment
						Ultrasonographic thickness (mm)	Total quadrants involved/total clock hours involved/ thickest in quadrant	SRF/extent of SRF	
1	8/F	DV/60	OS (20/1600)	11	Y	5.4	4/12/temporal	Y/4 (extensive RD)	TTT, anti-VEGF therapy
2	35/M	DV/6	OD (20/200)	20	Y	3.5	4/12/temporal	N/0	
3	7/F	DV/1	OD (NLP)	20	Y	3.6	4/12/temporal	Y/4 (bullous RD)	
4	29/M	DV/6	OS (20/60)	17	Y	4.8	4/11/nasal	Y/4 (extensive RD)	
5	9/M	DV/12	OD (20/100)	11	Y	5.1	4/12/temporal	Y/4 (extensive RD)	PDT
6	37/F	DV/18	OS (20/50)	28	Y	6.6	3/7/nasal	Y/3 (little SRF)	Laser
7	10/M	DV/1	OD (HM)	9	Y	5.5	4/12/temporal	Y/4 (extensive RD)	
8	6/F	DV/2	OD (NLP)	35	Y	5.1	4/12/temporal	Y/4 (bullous RD)	

DCH: Diffuse choroidal hemangioma; IOP: Intraocular pressure; OD: Right eye; OS: Left eye; BCVA: Best-corrected visual acuity; NLP: No light perception; HM: Hand movements; DV: Decreased vision; SRF: Subretinal fluid; RD: Retinal detachment; TTT: Transpupillary thermotherapy; PDT: Photodynamic therapy; Y: Yes; N: No.

**Table 2 Results of ruthenium-106 treatment**

Patient	Plaque type	Apex dose (Gy)	Sclera contact dose (Gy)	Treatment duration (d)	Tumor thickness			Visual acuity		Follow up (mo)
					Pretreatment (mm)	Final (mm)	Reduction (%)	Pretreatment	Final	
1 <sup>a</sup>	COB	57	380	5.9	5.4	2.8	46	20/1000	20/500	90
	COB	89	600	4	5.5	Flattening	100			
2 <sup>a</sup>	COB	70	280	5.9	3.5	Flattening	100	20/200	20/200	95
	COB	81	260	6.0	2.8	Flattening	100			
3	COB	101	410	3	3.6	2.4	33	NLP	NLP	41
4	COB	112	650	6.8	4.8	1.7	65	20/60	20/25	48
5	COB	108	480	7.2	5.1	Flattening	100	20/100	20/40	23
6	COB	73	760	5.9	6.6	Flattening	100	20/50	20/25	45
7	COB	91	420	7	5.5	Flattening	100	HM	20/1000	39
8	COB	59	390	7	5.1	2.4	53	NLP	NLP	23
Median		83	415	6.35	5.1	Flattening	100			43

<sup>a</sup>Cases 1 and 2 received plaque treatment twice.

removed. Radiation was targeted to the tumor apex based on the tumor thickness. Dose rate and treatment time were calculated on the basis of the thicknesses of the tumors, the location of the thickest portion of the tumor where the plaques centered on and the amount of retinal detachment. The decision and treatment process was operated by the same experienced radiation oncologist. Follow-up examinations were performed at 1, 3, and every 6mo post-removal of the plaques. At follow-up, we recorded the post-treatment BCVA, the rates of tumor regression by ultrasonography, SRF status and associated complications. At follow-up, visual acuity was compared *via* the comparison of the BCVA before and after treatment. Treatment success was deemed stable, improved (>1 Snellen line increase), or declined (>1 Snellen line decrease).

**RESULTS**

Table 1 shows the patient demographics. The median age at the start of treatment in this group was 9.5y (range 6-37y). All presenting symptoms were blurred vision, with BCVA

values that ranged from 20/50 to no light perception (NLP). All hemangiomas were unilateral and ipsilateral to the nevus flammeus and tumors were posterior to the equator. The tumor involved four total quadrants in seven patients. Median tumor thicknesses were 5.1 mm (range 3.5-6.6 mm). Of the patients, 7/8 developed exudative retinal detachment. In 6/8 patients, SRF occurred in 4 quadrants. Solid acoustic masses showing diffuse choroidal thickening occurred in all patients and with retinal detachment in 7 patients. Ruthenium-106 plaque brachytherapy was applied for a median duration of 6.35d (3-7.2d) with a median sclera contact dose of 415 Gy (270-760 Gy), resulting in a median apex dose of 83 Gy (57-112 Gy; Table 2). Six cases were treated with plaque brachytherapy only once and two was treated twice. One patient received a second plaque brachytherapy 44d after the first plaque removal. Upon tumor recurrence in a separate patient, the repeat ruthenium-106 plaque dose was 89 Gy for 4d after a follow-up of 65mo.

We performed follow-up for a median of 43mo (23-95mo). Tumor and SRF regression occurred in all patients. The thickness of the tumors declined by 81.4% (median, 100%; range 33%-100%). In a single patient with initial tumor regression and BCVA stabilization following initial therapy, tumor recurrence occurred. She received a second plaque brachytherapy. Five, one and one tumor-associated SRF resolved at the 2-, 4- and 5-month follow-up, respectively. In 5/8 patients, we observed improvements in visual acuity (62.5%), with 2/8 patients showing stable values at NLP following surgery. Another patient experienced an improved visual acuity (from 20/200 to 20/20) and tumor regression although the visual acuity decreased to 20/250 because of macular edema and was stable at 20/200 after bevacizumab intravitreal injection three times and intravitreal triamcinolone injection once. No radiation complications were noted during the follow-up period.

## DISCUSSION

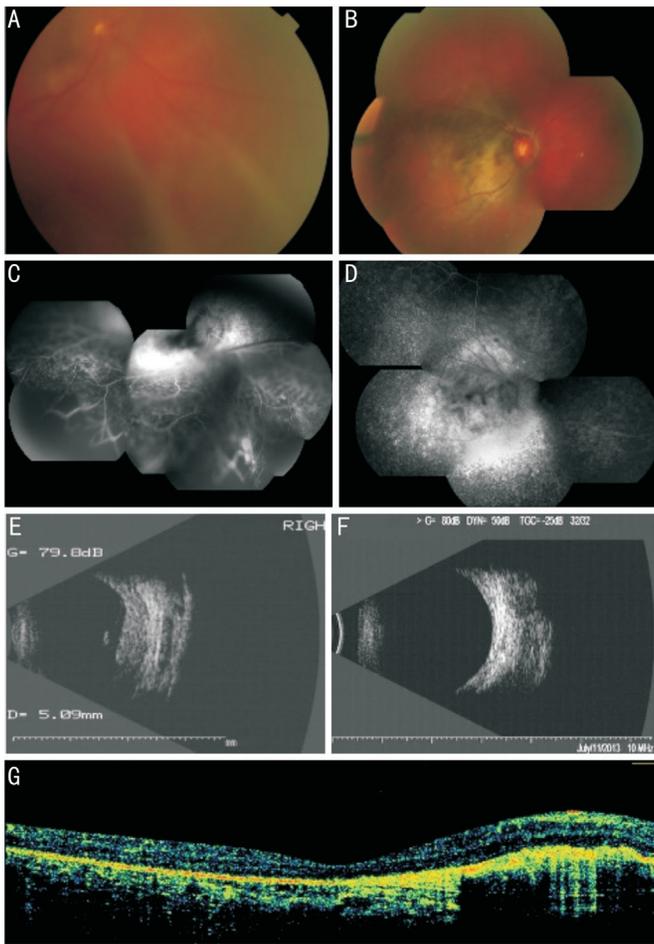
Gass<sup>[1]</sup> first proposed the concept of resorption of the SRF rather than tumor destruction as the main goal of therapy in 1974. External beam radiation therapy (EBRT) is also recommended for exudative DCHs<sup>[7-10]</sup>, however, it usually takes several months to observe the slow absorption of SRF with this therapy<sup>[9]</sup>. A problems with EBRT is the exposure of healthy tissue to radiation, leading to a heightened risk of radiation retinopathy, cataracts papillopathy and optic atrophy<sup>[8-9]</sup>. As a consequence of persisting SRF, degenerative changes in the foveal photoreceptor layer, secondary fibrous metaplasia, atrophy of the pigment epithelium of the retina, and cystoid macular edema led to irreversible functional loss<sup>[10]</sup>. In addition, the exposure to radiation at childhood increases the occurrence of late carcinogenesis<sup>[11]</sup>. Therefore, brachytherapy for benign lesions requires us to weigh the benefits against the risks.

In total, 10 cases of recovery following photodynamic therapy have been reported<sup>[12-19]</sup>. One of them were treated with EBRT combined with photodynamic therapy (PDT)<sup>[12]</sup>, and in another two cases<sup>[16-18]</sup>, multiple treatments were needed. Of the remaining seven patients<sup>[13-15,17,19]</sup>, the thickness of the tumor was thinner than that of our patients and the retinal detachment was partial. The degree of SRF, exudative detachment duration, and visual acuity levels prior to operation are the likely causes of the observed variability. Tsipursky *et al*<sup>[15]</sup> reported that the fovea should be avoided to minimize scarring and changes in the retinal pigment epithelium (RPE), though this does not afford a comprehensive visual prognosis. Photodynamic therapy should be avoided for large tumors and cases of severe exudative retinal detachment due to challenges covering the entirety of the tumor in non-overlapping sections.

Plaque brachytherapy can deliver accurate focal radiation with

minimal damage to healthy ocular structures. Only 15 cases of DCHs have been reported to be treated with plaque radiation therapy<sup>[2-6]</sup>. Zografos *et al*<sup>[2]</sup> employed Cobalt-60 in 2 patients, whilst in a single patient, Murthy *et al*<sup>[3]</sup> used a ruthenium-106 plaques for exudative retinal detachment associated with SWS. Kubicka-Trzaska *et al*<sup>[4]</sup> used ruthenium-106 plaques in 2 patients, whilst Arepalli *et al*<sup>[5]</sup> treated 5 DCH patients with iodine-125 plaque radiotherapy. Complete tumor regression, SRF resolution, and improvements in BCVA were reported in all cases. Zografos *et al*<sup>[2]</sup> noted that the use of plaque brachytherapy was limited in patients with DCH because of difficulties in covering the entire tumor with the limited size of the plaque. Subsequently, Arepalli *et al*<sup>[5]</sup> used a custom-designed plaque that surround the tumor and its 2-mm margins in 5 DCH patients. The number of seeds and plaque shape were dictated by the tumor dimensions. In our patients, we used conventional plaques (20 mm diameter for COB, Bebig Isotopen, Germany) and focused on the thickest tumor region. With the intention covering the entire tumor, one of eight patients (case 2) received plaque treatment twice centered on the nodular elevation at the temporal side and the nasal side, respectively. The patient experienced an improved visual acuity (from 20/200 to 20/20) and tumor regression although the visual acuity decreased to 20/250 because of macular edema and was stable at 20/200 after bevacizumab intravitreal injection three times and intravitreal triamcinolone injection once. We found that targeting the thickest tumor region was sufficient. Our six patients were treated with the ruthenium-106 plaques that focused on the thickest tumor region. Using this strategy, we observed complete resolution of the SRF from 2 to 5mo, and a drastic reduction in the size of the choroidal hemangiomas (Figure 1). The results for these patients were similar morphologically to the patient treated with the ruthenium-106 plaque twice. In this study, 4/6 patients showed improved BCVA whilst 2/6 showed no changes due to NLP in preoperative visual acuity, despite the target area of focal radiation involving the foveal region. The visual outcomes of these patients were comparable to those with the thickest tumors at the nasal side.

Choroidal hemangiomas are rare vascular hamartomas which histological examination shows a vascular pattern, dominated by cavernous portions, but capillary tumors and mixed patterns are also observed<sup>[20]</sup>. Shields *et al*<sup>[21]</sup> pointed out choroidal hemangioma rarely demonstrated clinical evidence of growth and the tumor enlargement was due to venous congestion in the tumor and not to cell multiplication. In our patients, we used the conventional applicators (20 mm diameter for COB, Bebig Isotopen, Germany) which could only encompass part as opposed to the entirety of the tumor. Therefore, in design, we used high theoretical apex irradiation doses of about 100 Gy, which



**Figure 1** Follow-up of a 9-year old boy with DCH during SWS A: Fundus images demonstrating DCH with extensive exudative retinal detachment at initial presentation; B: 18mo post-brachytherapy, post-treatment fundus images showing tumor regression and a lack of SRF; C: Fluorescein angiogram highlighting regions of degeneration in the retinal pigment epithelium and DCH leakage; D: Fluorescein angiogram 23mo after plaque radiotherapy shows hyperfluorescence in the treatment area; E: B-scan ultrasonography showing the elevated nodular component of a DCH with extensive exudative retinal detachment and the thickest portion at the temporal side before treatment; F: B-scan ultrasonography illustrating regression of the nodular component 23mo after treatment; G: OCT of the right macula imaged at 11mo post-treatment showing regular foveal contours and SRF resolution.

is much more than reported earlier<sup>[2-6]</sup>, to destroy the thickest region of diffuse tumors. We adjusted the actual irradiation dose in consideration of the thickness of the tumors targeted by the plaques. The levels of retinal detachment and radiation complications during the operation were recorded. The patients developed different degrees of retinal detachment including five advanced patients with bullous retinal detachment with a great deal of SRF. Compared to other patients with same sized tumor without retinal detachment, the distances between the retina and the applicator in these patients with bullous retinal detachment were much longer, resulting in much less

irradiation dose in the retina. The risk for radiation retinopathy would be decreased accordingly. The irradiation doses in the corresponding retina were only 20-40 Gy though the median apex dose in our patients was 83 Gy. Both the distance to the fovea and the volume of the tumors were identified as important risk factors for radiation maculopathy by Tagliaferri *et al*<sup>[22]</sup>. The juxtapapillary location, apical height, and dose administered to the fovea showed a strong correlation with the visual acuity outcome<sup>[23]</sup>. Radiation maculopathy occurs within a mean of 31mo in 25% of patients following plaque treatment<sup>[24]</sup>. In this patient cohort, the median follow-up period was 43mo (ranging from 23-95mo) and no radiation-associated complications were observed. In a single patient, tumor recurrence occurred. The safety of these irradiation doses now require assessment for the management of DCH in larger sample sizes using longer follow-up periods.

In conclusion, these findings indicate that plaque therapy at the thickest tumor region as opposed to targeting the entire tumor can reduce tumor size, eliminate SRF, and improve visual acuity in patients with DCH associated with SWS. Further studies to optimize the irradiation doses are now required to achieve optimal treatment outcomes for DCH associated with SWS.

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**Conflicts of Interest:** Yu YY, None; Li XX, None; Liang JH, None.

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