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Proton beam radiotherapy (PBR) for the treatment of retinal capillary haemangioblastoma stabilises tumour progression but with poor visual outcomes

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Retinal capillary haemangioblastomas (RCH) may occur sporadically or as part of von Hippel-Lindau disease (VHL), an autosomal dominant condition. Mutations in the VHL gene, a tumour suppressor gene, cause abnormal production of the VHL protein and the subsequent uncontrollable cellular division results in the development of vascular tumours and cysts in the central nervous system and elsewhere. Approximately 2–4% of intraocular haemangioblastomas are juxtapapillary where the risk of visual loss is higher [1] and the destructive effects of laser photocoagulation, cryotherapy and brachytherapy usually lead to severe and permanent visual loss.

We report our experience with proton beam radiotherapy (PBR) of RCH located at the optic disc or unresponsive to other treatments. Four daily fractions were administered, with a total dose of 18 proton Gy.

Eight patients (three male, five female) were treated with mean age 49 years (range, 29–84 yrs). Four patients had a genetic diagnosis of VHL. All patients had juxtapapillary haemangioblastomas and two also had mid peripheral lesions.

Basal tumour diameter at presentation was 3.1–7.2 mm (mean 5.0 mm) with thickness of 1.2–4.2 mm (mean 2.4 mm). Visual acuity ranged from 0.0 logMAR to hand movements (mean 0.9). All patients had exudative changes. Six patients had previous unsuccessful therapy: argon laser photocoagulation ($n = 3$), photodynamic therapy ($n = 4$), intravitreal anti-VEGF injections (bevacizumab or aflibercept) ($n = 4$), ruthenium-106 plaque brachytherapy ($n = 2$) and vitrectomy with endolaser ($n = 1$) (Table 1).

All patients were followed up for 3–7 years. Within three months of treatment, all haemangioblastomas regressed (mean longitudinal measurements 3.2 mm, depth 1.8 mm) with a decrease in tumour volume (decrease 1.6 mm longitudinally and 1.2 mm depth), continuing over 3 years. All lesions demonstrated resolution of subretinal fluid within 3–6 months; however three patients developed radiation-induced maculopathy between 12 and 22 months and were treated with intravitreal bevacizumab. Vision was stabilised in all cases but the majority had very poor vision at baseline and no improvement following therapy (baseline logMAR 0.0-Hand motions; last follow up 0.0-Perception of light; Table 1).

Treatment of juxtapapillary capillary haemangioblastomas is challenging. External beam radiotherapy (EBR) [2] has been successful but increases the risk of secondary central nervous system malignancies [3], as well as the potential development of radiation effects to both the retina and the optic nerve. Proton beam therapy has been described in two small series utilising 20 Gy but 3/8 still developed optic neuropathy or maculopathy [4, 5].

PBR may be considered in patients where other treatment modalities fail to control aggressive disease in patients with juxtapapillary or peri-macular lesions. This may help with control of eye threatening exudative complications. Although the treatment enables control of tumour progression and growth, the high rate of radiation maculopathy despite reduced radiation doses is disappointing. As such this treatment should be considered only as a stabilising strategy as visual acuity does not improve; laser therapy is an alternative strategy, however in the peri-papillary region will certainly result in visual field defects.

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Table 1 Summary of previous treatments, vision and tumour characteristics for each case

	Age	Gender	VHL-1 gene mutation	Previous treatment	Presenting vision (logMAR)	Number of lesions	Location of lesions	Macular oedema	Largest tumour diameter (mm)	Tumour height (mm)	Post treatment diameter (mm)	Post treatment height (mm)	Post treatment OCT changes	Notes	Latest vision (logMAR)
1	29	F	Y	PDT	CF	1	Juxtapapillary	Yes	3.2	1.8	2.4	1.0	Resolution of oedema but persisting exudates		CF
2	55	F	Y	Contralateral eye enucleation (rubeotic glaucoma)	1.0	3	1 Juxtapapillary, 2 along arcades	Yes	3.9	1.4	2.7	1.1	Resolution of oedema but persisting exudates and destruction retinal architecture	Widespread exudates	1.0
3	34	M	Y	Laser photocoagulation Intravitreal bevacizumab PDT Plaque brachytherapy to periphery	HM	Multiple	Juxtapapillary and mid peripheral	Yes	4.3	1.4	2.5	0.9	Resolution of subretinal fluid.	Developed radiation maculopathy and refused further treatment	PL
4	28	F	Y	Laser photocoagulation Cryotherapy PDT Intravitreal bevacizumab, aflibercept, triamcinolone Plaque brachytherapy to periphery Multiple vitrectomy with endolaser, delamination and membrane peeling, retinectomy and silicone oil tamponade Cataract surgery	CF	2	Juxtapapillary	Yes	5.1	1.3	3.8	2.6	Improved oedema	Developed further lesions, required further vitrectomy for tractional retinal detachment	CF
5	62	M	N	Nil	0.0	1	Juxtapapillary	Yes	4.88	3.66	1.9	1.1	Minimal persistent fluid nasal to disc		0.0
6	71	F	PDT	Nil	0.5	1	Juxtapapillary	Yes	5.2	4.2	4.3	3.2	Resolution of oedema	Developed radiation maculopathy requiring further intravitreal injections	0.5
7	29	M	N	Nil	0.4	1	Juxtapapillary	Yes	6.2	1.2	3.9	0.8	Resolution of oedema	Developed radiation maculopathy requiring further intravitreal injections	0.4 (amblyopic)
8	84	F	N	PDT Intravitreal bevacizumab	1.0	1	Juxtapapillary	Yes	7.2	4.2	2.1	2.8	Reduced but persistent subretinal fluid		1.0

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Comment on: Clinical outcomes in Caucasian patients with polypoidal choroidal vasculopathy

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We have read the recent article from Agorogiannis et al. [1] reporting real world data from the treatment of polypoidal choroidal vasculopathy (PCV) in a Caucasian cohort with great interest. As described, there is a paucity of data from Caucasian individuals to inform the management of PCV, and so we aim to augment their informative dataset with longer follow-up and a greater representation of verteporfin photodynamic therapy (PDT) (Table 1).

Mean (SD) gain in ETDRS letters at one, two, three and four years was 0.8 (17.2), −1.6 (21.7), −1.6 (24.1) and −8.5 (29.7), respectively. Central foveal thickness (CFT) also improved at those timepoints by 68.0 µm (204.9), 96.7 µm (124.9), 83.5 µm (153.2) and 128.6 µm (142.6). Although the mean acuity gained from PDT monotherapy was greater than from the combination of PDT and anti-vascular endothelial growth factor (anti-VEGF) treatment at

Table 1 Demographics and descriptors of 29 eyes from Caucasian patients undergoing treatment for polypoidal choroidal vasculopathy who were subsequently followed up for 6 months or more

Gender	Female (%)	18 (62.1)
	Male (%)	11 (37.9)
Laterality	Left (%)	15 (51.7)
	Right (%)	14 (48.3)
Location	Macular (%)	4 (13.8)
	Peripapillary (%)	22 (75.9)
	Peripheral (%)	3 (10.3)
Follow-up from treatment initiation (months)	% at 1 year	86.2
	% at 2 years	72.4
	% at 3 years	51.7
	% at 4 years	31
Final follow-up status	Under follow-up (%)	21 (72.4)
	Discharged (%)	6 (20.7)
	Lost to follow-up (%)	1 (3.4)
	Deceased (%)	1 (3.4)
Treatment received	Anti-VEGF IVIs (%)	3 (10.3)
	PDT (%)	12 (41.4)
	Both (%)	14 (48.3)
Initial visual acuity	Mean ETDRS letters (SD)	66.7 (14.3)
Initial central foveal thickness	Mean µm (SD)	332.3 (68)

SD standard deviation, VEGF vascular endothelial growth factor, PDT photodynamic therapy, IVI intravitreal injection.

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