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Review Article

Efficacy and safety of current treatment options for peripheral retinal haemangioblastomas: a systematic review

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ABSTRACT.

Importance: **Approximately twenty per cent of Von Hippel–Lindau patients with retinal haemangioblastomas (RH) suffer from visual impairment. Various treatment options are available for peripheral RH. However, management of peripheral RH is complex due to multifocality and bilaterality.**

Objective: **To summarize published evidence on efficacy and safety of different interventions for peripheral RH and to provide treatment recommendations for specialists.**

Evidence review: **Comprehensive searches were performed using Medline, Embase, Web of Science and Google Scholar database on 4 March 2020. English publications that described outcomes related to efficacy or complications in at least two patients with peripheral RH were included. Efficacy and safety were estimated by complete tumour eradication rate, pretherapeutic and treatment-related complication rate. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to calculate the risk estimate of complications between treatment options.**

Findings: **Twenty-seven articles were included in this review describing nine different treatment options for peripheral RH: laser photocoagulation (n = 230), cryotherapy (n = 50), plaque radiotherapy (n = 27), vitreoretinal surgery (n = 88), photodynamic therapy (PDT; n = 14), transpupillary thermotherapy (TTT; n = 10), external beam radiotherapy (n = 3), systemic treatment (n = 7) and intravitreal anti-VEGF (n = 2). Complete tumour eradication was achieved in 86.7% (95% CI: 83.5–89.9%) of all eyes. For the different treatments, this was after laser photocoagulation 89.9% (86.1–93.7%), cryotherapy 70.2% (57.0–83.4%), plaque radiotherapy 96.3% (89.1–100.0%), vitreoretinal surgery (100.0%), PDT 64.3% (38.3–90.3%) and TTT 80.0% (53.8–100.0%). No complete tumour eradication was achieved after systemic therapy, external beam radiotherapy or intravitreal anti-VEGF. Photodynamic therapy and vitreoretinal surgery showed the highest complication rate after treatment compared to the other treatments (OR 10.5 [95% CI: 2.9–38.4]) and (OR 5.9 [95% CI: 3.4–9.9]), respectively. Cases that had pretherapeutic complications showed a higher treatment-related complication rate (OR 14.8 [95% CI: 7.3–30.0]) than cases without complications before treatment.**

Conclusions and Relevance: **These findings suggest that laser photocoagulation is the safest and most effective treatment method for peripheral RH up to 1.5 mm in diameter. Vitreoretinal surgery has the highest success rate for complete tumour eradication and may be the most suitable treatment option in the presence of pretherapeutic complications and for larger tumours.**

Key words: Benign tumours – haemangioblastoma – retina – von Hippel–Lindau

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Introduction

Retinal haemangioblastomas (RHs) are benign, highly vascularised tumours probably originating from developmentally arrested haemangioblast precursor cells and can be found throughout the peripheral retina or the optic disc. The prevalence of RH has been estimated at 1 in 73.080 individuals (Binderup et al. 2018; Klingler et al. 2020). Peripheral RHs are identified in approximately 85% and juxtapapillary lesions in 15% of patients (Wong et al. 2008). Its development can occur sporadically or as a manifestation of von Hippel–Lindau disease (Singh et al. 2001; Lonser et al. 2003). RH can be asymptomatic in the early stage of development as the majority of tumours is located in the peripheral retina. As RHs grow over time, various progression-related complications, such as vitreoretinal traction and exudation may develop and cause disruption of the integrity of retinal structures, which can lead to retinal detachment, neovascular glaucoma or even phthisis bulbi (Chew 2005).

Challenges in the treatment of RH are multifocality, bilaterality and growth in the juxtapapillary region as well as development of complications related to tumour progression. Therapeutic options for juxtapapillary lesions are limited due to the destructive effect of most treatment modalities to the retina and optic disc. Ablative treatments of lesions adjacent to the macula or optic disc may therefore

cause irreversible vision loss. For peripheral tumours on the other hand, a wide variety of treatment options is available. However, the applicability and efficacy are highly dependent on size of the tumours and associated findings such as the presence of exudation and traction. Applied treatment methods for peripheral RH include laser photocoagulation, cryotherapy, plaque radiotherapy, vitreoretinal surgery, photodynamic therapy (PDT), transpupillary thermotherapy (TTT), external beam radiotherapy, systemic therapies and intravitreal anti-vascular endothelial growth factor (anti-VEGF) (Singh et al. 2002; Haddad et al. 2013; Wiley et al. 2019a). So far, several studies have reported the treatment outcome of different therapeutic approaches for RH, but the approach and outcomes were variable across studies (Singh et al. 2002; Kim et al. 2014). To our knowledge, no study has systematically compared the outcomes and complications of different treatment options. The purpose of this systematic review is to evaluate clinical outcomes of different treatment methods for peripheral RH.

Methods

Search strategy and study eligibility

The study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al. 2009) (Table S1). Identification of relevant studies was performed with the support of a senior medical librarian (W.B.) through searches of MEDLINE (PubMed), EMBASE (Ovid), Web of Science and Google Scholar for peer-reviewed articles published between 1 January 1980 and 4 March 2020 by use of the following search terms: retinal haemangioblastoma; retinal capillary haemangioma; retinal angioma; von Hippel–Lindau. References from retrieved articles were also reviewed to identify additional related studies. Duplicate publications were eliminated after merging the records from the individual database searches. Single subject case reports were excluded as these represent only experimental treatments. Studies published in another language than English were also excluded. Literature reviews, animal studies, laboratory studies without the assessment of a clinical outcome, correspondence, editorials and conference abstracts were excluded. Only full-text published studies were considered (Document S1). Endnote software version X9 (Thomson Reuters, New York, NY) was used to process the references in this study.

Data extraction and quality assessment

Two authors (AH and OG) independently screened all titles and abstracts and resolved disagreements through discussion. Study characteristics including year of publication, study design, sample size, demographic features, treatment option and follow-up were extracted from the text. The outcomes extracted from the studies contained three aspects: pretherapeutic complications, complete tumour eradication and treatment-related complications. Quality of the included studies was assessed with a modified version of the Newcastle–Ottawa Scale (Lo et al. 2014). A 'star system' was used in which a study is judged on the basis of the following three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest (Table S2).

Outcomes and definitions

The definition of a positive effect of the applied treatments varied considerably among studies. Ablative treatments such as laser photocoagulation and cryotherapy are mainly focused on tumour destruction, whereas the aim of systemic therapy is a reduction in tumour size. The overarching criterion for the treatment outcome to be defined as successful is tumour eradication. The primary outcome was efficacy of the treatment options estimated by the complete tumour eradication rate. The eradication rate was defined by complete regression, complete destruction or complete resection of the tumour. Secondary outcomes consist of the presence of complications related to tumour progression or to previous treatments defined as pretherapeutic complications, and adverse events defined as treatment-related complication rate.

Statistical analyses

The rate of pretherapeutic complications, complete tumour eradication and treatment-related complications between nine treatment options for peripheral RH was summarized and presented in numbers and percentages. Continuous data were estimated as the weighted mean and range. The chi-square test and the Fisher's exact test were applied to calculate the risk estimate of dichotomous data expressed as odds ratio (OR) with corresponding 95% confidence intervals. Data analysis was performed using IBM SPSS Statistic software version 25.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

Results

A total of 1289 unique articles were identified by the search, of which 1217 articles were excluded based on title and/or abstract. We selected the remaining 72 articles for a full-text review (Fig. 1). Of these, 27 studies met the eligibility criteria and were included in this systematic review. The 27 studies comprised a total of 438 cases that were included for analysis (Table 1). Two studies were included that applied systemic therapy as a treatment for peripheral RH. Niemelä et al. described the therapeutic outcomes after application of subcutaneous injections of recombinant human interferon-α-2a at a dose of 3×10^6 IU, 3 times/week for 12 months (Niemela et al. 2001). In the second study, VHL patients with RH were treated with oral propranolol 40 mg, 3 times/day for 12 months (Albinana et al. 2017).

Pretherapeutic complications

The presence of ocular complications before treatment, caused by tumour progression or by previous treatments, plays a major role in formulating a treatment strategy for peripheral RH. The extent of pretherapeutic complications was reported for 173 eyes (49.4%) in 24 studies. In cases that received previous treatment, it could not be deducted from the articles whether complications were caused by previously applied treatment or by tumour progression. The most common pretherapeutic complication was exudation ($n = 126$ cases; 72.8%), followed by retinal detachment ($n = 114$ cases; 65.9%), vitreoretinal traction ($n = 60$ cases; 34.7%), proliferative

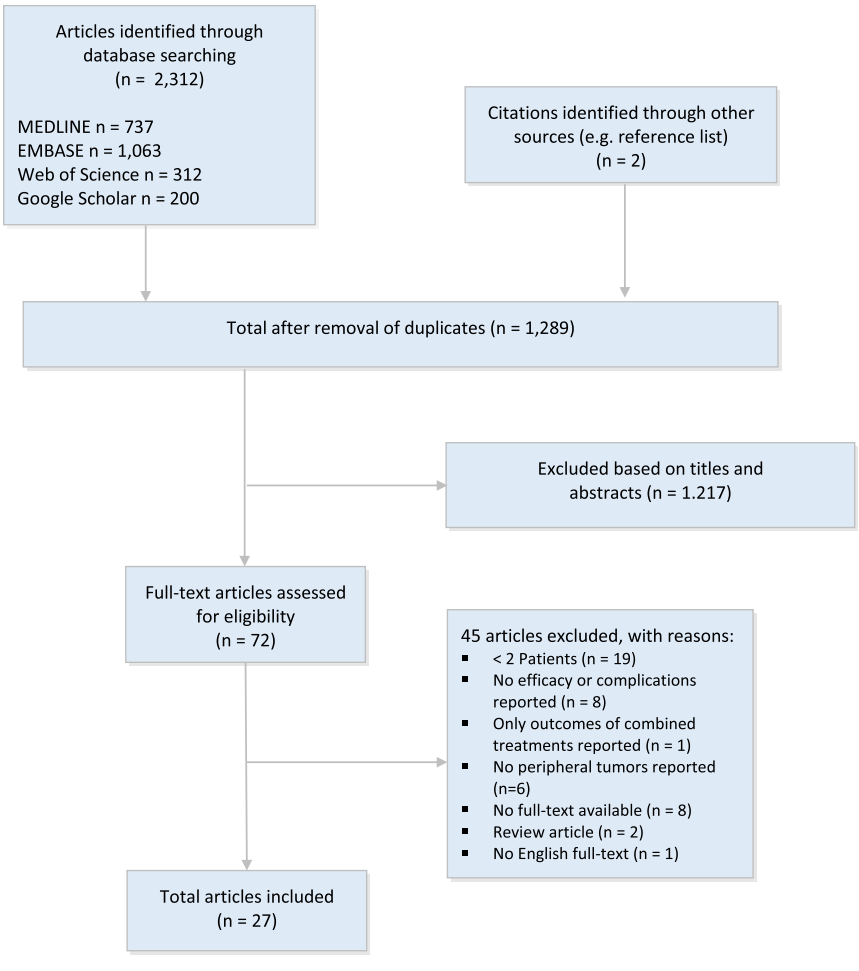

Fig. 1. PRISMA flow diagram showing the selection process for the included publications.

vitreoretinopathy (n = 32 cases; 18.5%), fibrosis (n = 21 cases; 12.1%), haemorrhage (n = 14 cases; 8.1%), macular oedema (n = 10 cases; 5.8%), epiretinal membrane formation (n = 10 cases; 5.8%), subretinal fluid (n = 7 cases; 4.0%) and retinal breaks (n = 4 cases; 2.3%). Thirteen studies mentioned unsuccessful treatment attempts before the studied intervention (Kreusel et al. 1998; Schmidt et al. 2000; Niemelä et al. 2001; Raja et al. 2004; Dahr et al. 2007; Liang et al. 2007; Sachdeva et al. 2010; Gaudric et al. 2011; Krzystolik et al. 2016; Albiñana et al., 2017; Avci et al. 2017; van Overdam et al. 2017; Karacorlu et al. 2018). Schmidt et al. reported eight cases that were treated for RH before receiving laser treatment. Seven cases underwent xenon light coagulation and one case was treated with cryotherapy. The authors did not mention whether the primary treatments were unsuccessful or laser treatment was applied for other lesions (Schmidt et al. 2000). Vitreoretinal surgery was preceded by other treatment methods that failed to destroy the tumours in 44 cases (50.0%). Laser photocoagulation or cryotherapy or a combination of both was applied in 39 of the 44 cases before vitreoretinal surgery (Liang et al. 2007; Gaudric et al. 2011; Krzystolik et al. 2016; Avci et al. 2017; van Overdam et al. 2017; Karacorlu et al. 2018).

The presence of pretherapeutic complications resulted more often in the application of vitreoretinal surgery (OR 178.0 (95% CI: 24.4–1299.9)) and cryotherapy (OR 10.8 (95% CI: 1.4–85.3)), respectively. On the other hand, laser photocoagulation is applied considerably less often if the tumour was accompanied by pretherapeutic complications (OR 0.1 (95% CI: 0.05–0.14)) (Table 2). Cases that had pretherapeutic complications showed a higher treatment-related complication rate (OR 14.8 (95% CI: 7.3–30.0)) than cases without complications before treatment.

Tumour eradication

The overall tumour eradication rate of all interventions for peripheral RH was 86.7% (95%CI, 83.5%-89.9%). The highest eradication rate was achieved after vitreoretinal surgery (100.0%), followed by 96.3% after plaque radiotherapy (95%CI, 89.1%-100.0%), 89.9% after laser photocoagulation (95% CI, 86.1%-93.7%), 80.0% after TTT (95%CI, 53.8%-100.0%), 70.2% after cryotherapy (95% CI, 57.0%-83.4%) and 64.3% after PDT (95% CI, 38.3%-90.3%). No complete tumour eradication was achieved after external beam radiotherapy, systemic treatment or intravitreal anti-VEGF (Table 2). One of the most influential factors in establishing an appropriate treatment strategy is taking the size of the tumour into consideration. An increase in tumour size leads to a decrease in eradication rate, in particular after laser photocoagulation. In six studies, an analysis of the eradication rate after laser photocoagulation was performed based on tumour size. Largest tumour diameter was considered as a measure of the tumour size as this was the most widely used measurement method by the included studies (Lane et al. 1989; Blodi et al. 1990; Schmidt et al. 2000; Singh et al. 2002; Krivosic et al. 2017; Huang et al. 2018). If the tumour size was less or equal to 1.5 mm, the overall eradication rate was 99.5% (427/429 RH). The eradication rate of tumours larger than 1.5 mm was 68.0% (51/75 RH). Although more extensive graduation in tumour size has been described in the analysed studies, the eradication rate could only be distinguished between small (≤1.5 mm) and large tumours (>1.5 mm) due to varying subdivisions. For the other treatment options, it was not possible to distinguish the eradication rate based on tumour size.

Complications related to treatment

Complications related to interventions for peripheral RH were described in 26 of the 27 included articles. Of the 357 cases from studies that have identified treatment-related complications, 100 cases developed complications related to treatment for peripheral RH (28%). The most common treatment-related complications were retinal detachment

Table 1. Demographic characteristics of the included cases, categorized by treatment options.

Treatment	Studies	Study design	Sample size, no. (% of eyes)	Gender, male/female	Age, mean (range), y	Prior treatment, no.	Follow-up, mean (range), mo	VHL diagnosis, no. (% of patients)
Laser			237 (54.5)	73/104	30.6 (–)	8	58.3 (–)	151 (93.8)
	Blodi et al. (1990)	CA	9	4/5	31.7 (11–63)	0	11.1 (6–16)	8 (88.9)
	Huang et al. (2018)	R, CA	5	–	29.6 (–)	–	51.8 (–)	–
	Krivosic et al. (2017)	R, CO	100	25/49	28.0 (8–62)	0	54.0 (4.8–210)	74 (100.0)
	Kuo et al. (2002)	R, CA	11	6/5	37.3 (19–52)	0	21.8 (2–65)	0
	Lane et al. (1989)	P, CA	15	6/6	24*	0	27.5* (4–136)	–
	Raju et al. (2003)	R, CA	2	1/1	28.0 (25–31)	0	5.5 (5–6)	0
	Schmidt et al. (2000)	P, CO	60	31/38	32.3 (11–75)	Xenon light coagulation (n = 7) Cryotherapy (n = 1)	76.8 (3–180), 8 patients LFU	69 (100.0)
	Singh et al. (2002)†	R, CA	35	–	–	0	–	–
Cryotherapy			50 (14.3)	6/4	28.2 (10–59)	0	11.4 (2–24)	2 (20%)
	Raju et al. (2003)	R, CA	8	5/3	32.1 (21–59)	0	11.2 (2–24), 2 patients LFU	0
	Singh et al. (2002)†	R, CA	39	–	–	0	–	–
	Slim et al. (2014)	R, CA	3	1/1	12.5 (10–15)	0	12	2 (100.0)
Plaque Radiotherapy			27 (6.2)	8/16	25.3 (6–55)	3	30.1 (3–92)	15 (63.0)
	Kreusel et al. (1998)	R, CA	25	8/16	25.3 (6–55)	Laser/cryotherapy (n = 3)	30.1 (3–92)	15 (63.0)
	Singh et al. (2002)†	R, CA	2	–	–	0	–	–
Vitreoretinal Surgery			88 (20.2)	35/46	29.9 (8–64)	44	39.8 (2–168)	69 (83.1)
	Avci et al. (2017)	R, CA	12	5/7	36.2 (21–58)	Laser (n = 4)	30.2 (18–48)	12 (100.0)
	Gaudric et al. (2011)	R, CA	23	9/12	27* (12–47)	Laser+ cryotherapy (n = 10) Laser (n = 6) Cryotherapy (n = 3) Scleral buckling (n = 2) Bevacizumab (n = 1)	68.2 (13–168	19 (95.0) One patient was not tested
	Karacorlu et al. (2018)	R, CA	13	7/5	32.5 (8–64)	Laser (n = 8) Anti-VEGF (n = 1)	50.5 (6–144)	9 (75.0%)
	Krzystolik et al. (2016)	R, CA	24	10/13	27.6 (11–44)	Laser/cryotherapy (n = 7)	24	23 (100.0)
	Liang et al. (2007)	CA	4	2/2	22.8 (17–35)	Laser (n = 1)	4.7 (2–8)	3 (75.0)
	Nicholson et al. (1986)	CA	3	0/3	22.0 (18–27)	0	11.0 (9–12)	1 (33.3)
	van Overdam et al. (2017)	R, CA	4	0/4	27.3 (19–32)	scTCA (n = 1)	51.0 (50–53)	2 (50.0)
	Raju et al. (2003)	R, CA	2	2/0	27.5 (25–30)	0	7.0 (2–12)	0
	Schlesinger et al. (2007)	R, CA	3	–	35.3 (16–46)	0	–	0
PDT			14 (3.2)	5/4	20.5 (–)	1	31.5 (–)	3 (33.3)
	Aaberg et al. (2005)	CA	3	1/2	18.3 (10–29)	0	19.7 (15–24)	0
	Huang et al. (2018)		5	–	16.8 (–)	–	57.0 (–)	–
	Hussain et al. (2015)	P, CA	2	2/0	40.0 (37–43)	0	10.5 (3–18)	0
	Sachdeva et al. (2010)	R, CA	4	2/2	17.0 (8–34)	Bevacizumab (n = 1)	18.8 (8–32)	3 (75.0)
TTT			10 (2.3)	3/4	27.3 (10–53)	0	92.1 (5–216)	3 (42.9)
	Mochizuki et al. (2004)	CA	2	0/2	37.5 (29–46)	0	7.5 (5–10)	0
	Pochop et al. (2018)	P, CA	8	3/2	23.2 (10–53)	0	126.0 (6–216)	3 (60.0)

Table 1 (Continued)

Treatment	Studies	Study design	Sample size, no. (% of eyes)	Gender, male/female	Age, mean (range), y	Prior treatment, no.	Follow-up, mean (range), mo	VHL diagnosis, no. (% of patients)
EBR			3 (0.7)	0/3	31.7 (23–47)	2	29.7 (6–51)	3 (100.0)
	Raja et al. (2004)	R, CA	3	0/3	31.7 (23–47)	Cryotherapy (n = 1) Plaque radiotherapy (n = 1)	29.7 (6–51)	3 (100.0)
Systemic Treatment			7 (2.0)	3/2	36.8 (15–62)	4	19.2 (12–30)	7 (100.0)
	Albiñana et al. (2017)	NR, CT	5	3/0	24.3 (15–36)	Laser (n = 2)	12.0	5 (100.0)
	Niemelä et al. (2001)	P, CA	2	0/2	55.5 (49–62)	Laser (n = 2)	30.0	2 (100.0)
Intravitreal anti-VEGF			2 (0.6)	0/2	27.0 (22–32)	2	3.5 (2.7–4.2)	2 (100.0)
	Dahr et al. (2007)	P, CA	2	0/2	27.0 (22–32)	Laser+cryotherapy+PPV (n = 2)	3.5 (2.7–4.2)	2 (100.0)

Anti-VEGF = anti-Vascular Endothelial Growth Factor; CA = case series; CO = cohort study; CT = clinical trial; EBR = external beam radiotherapy; LFU = lost to follow-up; NR = nonrandomized; P = prospective; PDT = photodynamic therapy; R = retrospective; scTCA = subconjunctival triamcinolone acetonide; TTT = transpupillary thermotherapy PPV = pars plana vitrectomy.
* The median was the only variable mentioned in this article and was not included in the analysis of the weighted mean.
† Demographic data of study participants was described as an overall mean regardless of treatment

(43%), epiretinal membrane (ERM) formation (25%), exudation (24%), proliferative vitreoretinopathy (PVR) (17%), preretinal fibrosis (14%), subretinal fluid (14%), pre- or intra-retinal haemorrhage (13%), vitreoretinal traction (11%), cataract (11%), preretinal neovascularization (10%), cystoid macular oedema (5%), retinal break (5%), posterior capsular opacification (3%) and radiation retinopathy (1%). PDT showed the highest treatment-related complication rate, compared to the other treatments (OR 10.46 [95% CI, 2.9–38.4]). Vitreoretinal surgery was also detrimental in terms of complication ratio with an OR of 5.9 (95% CI: 3.4–9.9) in comparison with other treatments. Laser treatment showed a large benefit over other treatment modalities concerning treatment-related complications (OR 0.1 [95% CI 0.1–0.2]) (Table 2). Different treatment methods each have various mechanisms to destroy or regress the tumours, and these methods may cause several complications. We analysed the included studies for treatment-specific complications to investigate which complications are most likely to occur after a particular treatment for peripheral RH. Complications after laser photocoagulation occurred in 23 eyes. Haemorrhages occurred significantly more after laser treatment compared to other treatments (8 (34.8%) versus 5 (6.5%), $p < 0.001$, Chi-square test), as well as subretinal fluid accumulation (10 (43.5% versus 4 (5.2%), $p < 0.001$, Fisher's exact test). Vitreoretinal surgery had the most treatment-specific complications: exudation (17 (35.4%) versus 7 (13.5%), $p = 0.001$, Chi-square test), PVR (14 (29.2%) versus 3 (5.8%), $p = 0.003$, Fisher's exact test), ERM (19 (39.6%) versus 6 (11.5%), $p = 0.001$, Chi-square test), cataract (10 (20.8%) versus 1 (1.9%), $p = 0.003$, Fisher's exact test), preretinal neovascularization (8 (16.7%) versus 2 (3.8%), $p = 0.045$, Fisher's exact test) and preretinal fibrosis (13 (27.1%) versus 1 (1.9%), $p < 0.001$, Fisher's exact test) were significantly more observed after surgical treatment compared to other treatment options. Retinal detachments occurred in four of the five eyes after plaque radiotherapy, this was, however, not significantly different from other treatment options ($p = 0.162$). Eyes treated with PDT had ERM formation in five of the 11

Table 2. Outcome table with prevalence of pretherapeutic and treatment-related complications

	Pretherapeutic complications (%)	OR (95% CI)*	Complete eradication (%)	Treatment-related complications (%)	OR (95% CI)
Laser (n = 237)	50/197 (25.4)	0.08 (0.05–0.14)	213/237 (89.9)	23/202 (11.4)	0.13 (0.08–0.22)
Cryotherapy (n = 50)	10/11 (90.9)	10.80 (1.37–85.28)	33/47 (70.2)	3/11 (27.3)	0.96 (0.25–3.70)
VR surgery (n = 88)	87/88 (98.9)	178.05 (24.39–1299.89)	88 (100.0)	48/83 (57.8)	5.86 (3.45–9.95)
Plaque radiotherapy (n = 27)	11/25 (44.0)	0.79 (0.35–1.74)	26/27 (96.3)	5/25 (20.0)	0.62 (0.23–1.71)
Systemic treatment (n = 7)	2/7 (28.6)	0.40 (0.08–2.10)	0/7 (0.0)	2/7 (28.6)	0.40 (0.08–2.10)
TTT (n = 10)	2/10 (20.0)	0.25 (0.05–1.18)	8/10 (80.0)	3/10 (30.0)	1.11 (0.28–4.36)
PDT (n = 14)	9 (100.0)	–	9/14 (64.3)	11/14 (78.6)	10.46 (2.85–38.37)
EBR (n = 3)	2/3 (66.7)	2.06 (0.19–22.91)	0/3 (0.0)	3 (100.0)	–
Intravitreal anti-VEGF (n = 2)	–	–	0/2 (0.0)	2 (100.0)	–
Overall	173/350 (49.4)		377/435 (86.7)	100/357 (28.0)	

CI = confidence interval; EBR = external beam radiotherapy; OR = odds ratio; PDT = photodynamic therapy; VR surgery = vitreoretinal surgery.
* Odds ratios are in comparison to other treatment methods.

Table 3. Indications of treatment modalities based on expert opinion reviews.

Treatment	Classification tumour	Indication	Contra-Indication
Laser	• Up to 1 DD • 1 DD – 3 DD	• Smaller tumours without pretherapeutic complications	• Involvement of ora serrata • Presence of exudation, epiretinal fibrosis, vitreous haemorrhage
Cryotherapy	• 1 DD– 3 DD	• Lesions peripheral to the equator • Secondary treatment after ineffective laser therapy	• Presence of exudation
Plaque Radiotherapy	• 1 DD – 4 DD	• Unsuccessful laser or cryotherapy	• Pre-operative exudative RD • Larger than 4 DD
Vitreoretinal Surgery	• All sizes	• Presence of rhegmatogenous or tractional retinal detachment • Presence of epiretinal or vascular proliferation • Vitreous haemorrhage	• Risk of PVR in eyes with exudation, epiretinal or vascular proliferation
PDT with Verteporfin infusion	• Up to 3 DD	• Juxtapapillary location • Tumour growth control • Presence of exudates or exudative retinal detachment	• Presence of traction

cases (45.5%) compared to 20 of the 89 cases (22.5%) that received other treatment options (p = 0.097).

Discussion

To date, peripheral RHs are managed based on ophthalmologist expert opinions and preferences. No guideline has yet been published on how this ocular disease should be approached. Expert opinions and reviews of the current literature provide some guidance on how to manage RH (Table 3) (Wiley et al. 2019b).

This systematic review confirms that current treatment options can successfully eradicate peripheral RH in most eyes. The included studies reported an overall complete eradication rate of 86.7%. A large benefit was found for laser photocoagulation over other treatment options (eradication rate 89.9%; OR treatment-related complication 0.1 [95% CI 0.1–0.2]). Haemorrhages and subretinal fluid accumulation are the complications associated with laser treatment for peripheral RH. Laser photocoagulation seems to be the safest treatment option with consistent results in both cohort studies and case series. However, the tumour size should be taken into consideration as the efficacy of laser photocoagulation decreases in tumours larger than 1.5 mm (Lane et al. 1989; Blodi et al. 1990; Singh et al. 2002; Krivosic et al. 2017). Measurement of tumour size was either expressed in disc diameter or millimetres in these studies. We used the estimation of one vertical optic disc diameter as 1.5 mm to compare the results between the studies (Crowston et al. 2004). The best tumour eradication rates are reported for vitreoretinal surgery with a 100% eradication rate in nine studies, independent of the surgical techniques used.

Cryotherapy is considered a standard treatment option for mid-sized tumours based on the convenient, relative non-invasive applicability. Our findings demonstrate that the eradication rate of cryotherapy is lower than other standard treatments such as laser photocoagulation, vitreoretinal surgery and plaque radiotherapy (70.2% versus 89.9, 100.0, 96.3%, respectively). Raju et al. reported an incomplete regression after cryotherapy in the presence of pretherapeutic exudation or exudative retinal detachment (Raju et al. 2003). Cryotherapy is known to be less effective as a treatment for RH associated with vitreoretinal neovascularization,

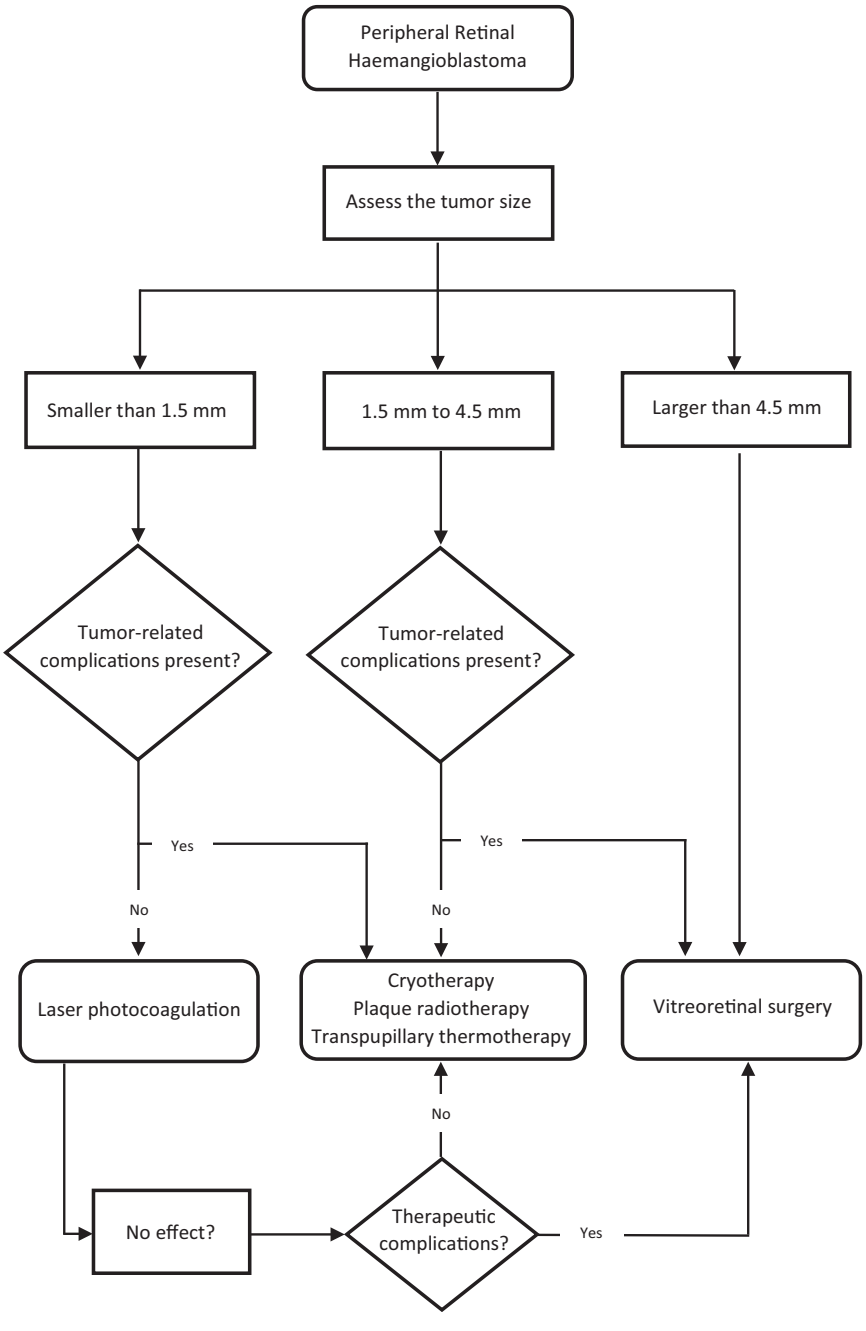

Fig. 2. Flowchart showing the management of peripheral retinal haemangioblastomas.

preretinal fibrosis, exudative or tractional retinal detachment (Gaudric et al. 2011).

Plaque radiotherapy seems to be an effective and safe treatment option for larger tumours with an eradication rate of 96.3% and treatment-related complication rate of 20.0%. Kreusel et al. reported an unfavourable outcome, defined as deterioration of visual acuity or persisting exudative retinal detachment or recurrent tractional detachment, in tumours with a mean size of 5.4 mm (range 3.2–7.8 mm). Retinal detachment was present in 80% of the cases that developed complications after plaque radiotherapy. However, the number of cases with complications after plaque radiotherapy is small and the difference in occurrence of retinal detachments after plaque radiotherapy and other treatment options is not significant. Retinal detachment can therefore not be considered a treatment-specific complication associated with plaque radiotherapy. The authors conclude that plaque radiotherapy is an effective treatment for peripheral RH up to 2.5 DD and without pretherapeutic exudative retinal detachment (Kreusel et al. 1998). The two tumours that received plaque radiotherapy reported by Singh et al. were eradicated successfully and were between 1.6 and 6.0 mm in size. However, the authors did not report any treatment-related complications (Singh et al. 2002).

Vitreoretinal surgery is mainly applied in advanced cases with failed prior treatment methods. Larger tumours are more difficult to treat effectively with approaches such as laser photocoagulation and cryotherapy. Incomplete tumour eradication may lead to partial reperfusion and risk of subsequent haemorrhages and exudative retinal detachment (Karacorlu et al. 2018). A higher complication rate was reported for the approach with tumour endoresection and retinectomy. Although, the cases in this study already had more pretherapeutic complications (Gaudric et al. 2011). Outcomes of endoresection are more favourable in the more recent studies (Avci et al. 2017; van Overdam et al. 2017). The good outcomes in these studies were associated with removal of subretinal exudates, complete removal of all proliferative membranes and vitreous, including vitreoschisis-induced vitreous cortex remnants across the retinal surface (van Overdam 2020). As confirmed in the current study, the presence of pretherapeutic complications is the most important factor in developing treatment-related complications (OR 14.8 [95% CI 7.3–30.0]). This might be explained by the complexity of advanced cases of peripheral RH and the persistence of pretherapeutic complications. Complications such as exudation, PVR, ERM, cataract, preretinal neovascularization and preretinal fibrosis occur more often after vitreoretinal surgery than after other treatment options. The surgical strategy should therefore be focused on reducing the risk of complications. Effective closure of the feeder vessels plays an important role to prevent per- and postoperative haemorrhages and possibly subsequently the risk of proliferative vitreoretinopathy (van Overdam et al. 2017).

PDT has been frequently applied for juxtapapillary lesions (Golshevsky & O'Day 2005; Sachdeva et al. 2010; Mitropoulos et al. 2014). The efficacy of this treatment for peripheral

tumours is suboptimal as the eradication rate is 64.3%. Furthermore, the iatrogenic fibrosis caused by the application of PDT led in many cases to intrinsic retinal contraction causing epiretinal membrane formation in three cases (21.4%) and tractional retinal detachment in one case (Aaberg et al., 2005; Sachdeva et al. 2010). The efficacy of TTT has been questionable for peripheral RH due to insufficient ability to completely eradicate the tumour. A decrease in blood flow of tumours is observed, but no significant changes in tumour size or colour have been reported for TTT with a power of 350 mW (Mochizuki et al. 2004). Interestingly, Pochop et al. used a higher power TTT, up to 1200 mW, that showed a higher efficacy to destroy RHs. Though, their sample size was very small ($n = 8$), making it difficult to compare the outcome with other studies that used a lower power to treat the tumours (Pochop et al. 2018). Raja et al. described a decrease in tumour volume after external beam radiotherapy in the treatment of three cases with peripheral RH (Raja et al. 2004). The convenient location of these tumours makes them more accessible for more aggressive treatments for completely destruction of the tumours. No other case series or higher level of evidence is available for treatment with external beam radiotherapy. Too few evidence has been published to consider this treatment effective for peripheral RH. The same lack of evidence applies for systemic treatments and intravitreal anti-VEGF (Niemelä et al. 2001; Dahr et al. 2007; Albiñana et al., 2017).

This is the first systematic review on the efficacy and safety of treatment options for peripheral RH. This review confirms the complexity of management of these rare but potentially dangerous sight-threatening tumours. The therapeutic strategy depends on the ocular phenotype, including multifocal tumours and bilateral occurrence of RH. To effectuate an evidence-based guideline for the management of RH remains difficult as the studies examining the interventions for RH are methodologically limited by insufficient power resulting from small sample sizes, absence of secondary outcomes or structured follow-up. Some limitations of the present study need to be addressed. First, our search and selection process did not yield any randomized controlled trials comparing different interventions for peripheral RH, merely observational cohort studies, a nonrandomized clinical trial and case series were included. Second, most studies included a small number of cases resulting in large confidence intervals within each study. Third, variation in the analysis of cases made it difficult to estimate the actual effect of treatment as in some studies the analyses were based on the eye and in other studies on the tumour. We merely focused on the analyses at eye level to evaluate the complications that may affect the entire eye and not solely the tumour site. Fourth, statistical analyses adjusted for age, gender and other covariates were not possible due to missing data in certain included studies. And last, some patients received multiple types of treatment. This can cause a bias in determining the efficacy of the treatment outcome. Previous treatments might have led to iatrogenic damage and complications that could make subsequent treatments less effective. In addition, it is difficult and prone to bias to determine the efficacy of a single therapeutic option when more treatment options are applied.

Conclusions

This systematic review contributes to an evidence-based treatment strategy for peripheral RH. RH can be multifocal and bilateral, which should be taken into account in determining a treatment approach. Laser photocoagulation appears to be the safest and most proven treatment option for peripheral RH smaller than 1.5 mm without pretherapeutic complications. Cryotherapy and plaque radiotherapy seem to be relatively safe and effective treatment options for tumours between 1.5 and 4.5 mm. Both options have a worse outcome if exudation is present regardless of tumour size. We suggest that vitreoretinal surgery is inevitable in cases with pretherapeutic complications such as exudation and retinal detachment and in cases with tumours larger than 4.5 mm with an excellent tumour eradication rate but a higher rate of treatment-related complications. Based on the findings of the current systematic review, we propose this flowchart as a tool to determine a treatment strategy for peripheral RH (Fig. 2). The largest tumour, or the tumour accompanied by pretherapeutic complications, should determine the treatment strategy to follow per involved eye in bilateral cases or whenever multifocal tumours are present. Future research should focus on prevention of treatment-related complications and prospective randomized controlled trials should be designed to improve the treatment strategy for peripheral RH.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. PRISMA 2009 Checklist.
Table S2. Quality assessment of included studies with the modified Newcastle-Ottawa Scale.
Document S1. Search Strategy.