High recurrence rate in patients with choroidal hemangioma treated with limited single spot photodynamic therapy during long-term follow-up

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ABSTRACT.

Purpose: To evaluate the long-term follow-up of patients with a circumscribed choroidal hemangioma (CCH) treated with limited single spot photodynamic therapy (PDT) at the Amsterdam University Medical Center, location AMC (AUMC).

Methods: This cross-sectional study included 17 patients, treated between 2001 and 2012. Evaluation included best corrected visual acuity, slitlamp examination, fundoscopy, ophthalmic ultrasonography (USG), fluorescein/indocyanine green angiography (FA/ICG), fundus autofluorescence (FAF) and optical coherence tomography (OCT). Primary outcome: recurrence rate, secondary outcomes: long-term functional and structural changes.

Results: An unexpected high recurrence rate of 35% (n=6) was found with a mean follow-up time between treatment and recurrence of almost 6 years, range 2.8–10.7 years. With a recurrence, the classical CCH pattern was no longer recognizable on FA or ICG. Signs of leakage were best observed with OCT, and the recurrence could be confirmed with USG. Retreatment with PDT of all recurrences was successful. After a successful initial PDT, the achieved visual acuity (VA) showed a small decrease over time, median VA from 0.10 LogMar to 0.15 LogMar (p 0.09) after a mean follow-up of 11.36 years (range 5.1–15.5 years). During follow-up study visit, the OCT revealed a slightly increased thickness of the choroid in 86% of cases at the site of the original tumour, without a clear correlation to the recurrences.

Conclusion: Limited single spot PDT is a safe and effective treatment for CCH preserving a good VA. However, because of the relatively high recurrence rate found in this study, we recommend regular follow-up with OCT every 6 months.

Key words: circumscribed choroidal hemangioma – long-term follow-up – photodynamic therapy – recurrence

Introduction

Circumscribed choroidal hemangioma (CCH) is a relatively rare vascular hamartoma that typically presents in the posterior pole. Although it is a benign tumour, visual acuity can drop as a consequence of a hyperopic shift caused by increasing tumour size within the macula or by leakage, leading to serous retinal detachment and less often intraretinal macular oedema. In the past, when visual acuity dropped, several therapies could be considered such as argon laser treatment, radiation (external beam, photon irradiation, brachytherapy) and hyperthermia (microwave thermo therapy, transpupillary thermotherapy) (Bottoni et al. 1990; Finger et al. 1991; Lanzetta et al. 1995; Schilling et al. 1997; Kamal et al. 2000; Fuchs et al. 2002; Scott et al. 2004; Shields et al. 2004; Berry & Lucas 2017; Papastefanou et al. 2018). All these treatment modalities had a less favourable outcome with regard to maintenance of visual acuity when the lesion involved the fovea because of direct or indirect foveal damage.

In 2000, promising results of photodynamic therapy (PDT) with verteporfin were reported to treat choroidal hemangioma (Barbazetto & Schmidt-Erfurth 2000). Photodynamic therapy (PDT) works through selective photothermal injury to the vascular endothelial cells, while preserving the
neuroretinal structures and seemed more suitable for subfoveal lesions. Photodynamic therapy (PDT) for CCH was performed according to several protocols, differing in dosage of drug, the timing of infusion, timing of laser application, energy level, spot size, single or overlapping spots and single or repeating treatment (Landau et al. 2002; Schmidt-Erfurth et al. 2002; Perrini et al. 2003; Boixadera et al. 2009; Zhagn et al. 2010; Pilotto et al. 2011; Su et al. 2014; Liu et al. 2018; Papastefanou et al. 2018; Susskind et al. 2018; Lee et al. 2019). All with high success rates and rarely unwanted side-effects (Jurklies et al. 2003; Vicuna-Kojchen et al. 2006; Tuncer et al. 2009; Xiao et al. 2013). At the Academic Medical Center, a protocol was developed limiting PDT treatment to a single spot, aimed at the most elevated part of the CCH, with standard verteporfin dosage (6 mg/m² BSA), starting the laser, with standard energy, 5 min following a 1 min infusion of the drug. This limited single spot PDT proved to be an effective treatment resulting in resolution of subretinal fluid and tumour regression with even completely flattening of the tumour (Verbraak et al. 2003). The same treatment was also applied in patients with a relatively good visual acuity and subtle complains in order to prevent permanent loss of visual acuity (Verbraak et al. 2006). In some patients, a second treatment was necessary, because the tumour did not regress below 1 mm, considered to be the limit of a successful treatment. At follow-up of one year, all patients showed no recurrence or other changes. They were considered to be stable without need for further close follow-up, and therefore, after the first year, the patients were dismissed and follow-up was continued by their own ophthalmologist.

Recently, however, a patient showed up in the Amsterdam University Medical Center (AUMC) clinic with a definite recurrence, unnoticed by the patient himself, despite a visual acuity drop from 20/16 to 20/400, 3 years following a successful PDT treatment.

Long-term follow-up studies following PDT treatment in CCH patients are scarce, and the purpose of the present study is to evaluate the long-term follow-up of patients with a CCH treated with limited single spot PDT at the AUMC.

Patients and Methods

Between 2001 and 2016, 35 patients with CCH were treated according to the single spot limited PDT protocol in the AUMC. Two patients were excluded because they received radiation or hyperthermia treatment before the PDT treatment. The remaining 33 patients were all invited by letter and phone to participate in the study. This study followed the tenets of the declaration of Helsinki and was approved by the Medical Ethics Committee of Academic Medical Center, Amsterdam. Fourteen patients were willing to participate and were informed about the nature of the study and gave their written informed consent before entering the study. Three additional patients refused to come to the AUMC, but had regular follow-up by their own ophthalmologist and agreed to share their follow-up data. These patients were included into the study with the following data: recurrence yes/no, best corrected visual acuity and if present optical coherence tomography (OCT).

Of the 16 non-participating, six patients were deceased before the start of the study (none of them had a recorded recurrence in there file, but had a relatively short follow-up time). Five patients refused to participate, two because of general health problems and three were not interested (two of them had a recorded recurrence). The five last patients could not be re-traced (one of them had a recorded recurrence).

The baseline characteristics of all 33 patients with PDT treated CCH, participating and non-participating in the present study, are listed in Table 1.

The primary diagnosis of a CCH was based on the classical findings on ophthalmoscopy, colour fundus photography, fluorescein angiography (FA), indocyanine green angiography (ICG) and ophthalmic ultrasonography (USG). Since 2004, the OCT was also part of the standard examinations (see Fig. 1).

All patients between 2001 and 2016 were treated with the limited single spot photodynamic treatment, conducted using a Coherent Opal Photoactivator diode laser, with a laser application time of 83 seconds, and an exposure of 50 J/cm². Verteporfin (Visudyne, Novartis AG, Basel, Switzerland) dosage was 6 mg/m² body surface area and administered intravenously as a 1 min bolus injection. Laser induced photosensitization started 6 min after the start of the infusion. A single laser spot was used with a diameter that covered the most prominent part of the hemangioma, no overlapping laser spots were used, and the optic disc was avoided. The largest possible laser spot was 7500 μm with use of the Volk Super Quad contact lens (enlargement × 1.92), a standard PDT contact lens. Retreatment after 6 weeks was given in case the residual tumour thickness was more than 1 mm, as measured by USG, or there was residual intra or subretinal fluid seen on OCT.

All participants received a complete ophthalmic examination including best corrected visual acuity, slit-lamp examination, slit-lamp biomicroscopy, ophthalmic USG, FA combined with ICG, fundus autofluorescence (FAF) and OCT (HRA + OCT, Heidelberg Engineering, Heidelberg, Germany). In case of signs of a recurrence during the study examination, the patient was informed and treatment with PDT was offered, as described above. The definition of a recurrence in the present study: recurrence or increase of tumour mass seen with slit-lamp biomicroscopy confirmed on USG (Aviso, Quantel Medical, Clermont-Ferrand, France), or signs of leakage of the lesion on OCT confirmed by FA and/or ICG angiography.

The primary outcome of the study was the recurrence rate of a CCH after a first successful treatment with limited single spot PDT. Long-term functional and structural changes following PDT treatment were identified as secondary outcomes. An attempt was made to identify factors which were predictive of a recurrence.

Statistical analysis is performed with paired samples t-test. Survival outcome was calculated according to the Kaplan–Meier method. All statistical analyses were performed using IBM SPSS Statistics, version 25 (IBM Corp., Armonk, New York, USA).

Results

Recurrence rate

In total, 17 patients were included in this study, of whom 14 followed the complete study protocol and three were included after receiving the results of
the ophthalmic examinations by their own ophthalmologist. An unexpected high number of recurrences were found during this study, in total six out of 17 participants. Mean age at first PDT treatment in the patients with a recurrence was 46 years (median 48, range 27–60) versus 53 years old in those without a recurrence (median 50, range 39–76).

Figure 2 shows the Kaplan–Meier curve of recurrence-free probability over the years for all participating patients, and for those with and without a residual tumour mass after the first successful PDT treatment on USG. The mean follow-up time between treatment and recurrence (if multiple, first recurrence) was almost 6 years, range 2.8–10.7 years. The patients with a recurrence are listed in Fig. 3, showing the timeline between PDT treatment of the CCH and its recurrence combined with the visual acuity before and after PDT (re-)treatment. Two patients had multiple recurrences. In three patients, a recurrence was diagnosed during the study. Only one of the three had a drop in visual acuity as a consequence of substantial intra- and subretinal fluid.

Retreatments of a recurrence, using the same single spot limited PDT protocol, were all successful. All tumours regressed and intra- and subretinal fluid disappeared (Fig. 4). Two cases were seen with multiple recurrences (Fig. 3, case 1 and 4), and the visual acuity in one of those cases dropped dramatically after the third recurrence.

**Functional outcome**

**Visual acuity**

After initial PDT, an improvement in visual acuity (VA) was seen (from median 0.4 LogMar to 0.1 LogMar, p < 0.001) in all participants except for two whose VA remained the same. The achieved VA showed in most participants a small decrease over time with a loss of VA from median 0.1 LogMar (range 1.0 to −0.1) to 0.15 LogMar (range 1.7 to −0.1) (p 0.09) after a mean follow-up of 11.36 years (range 5.1–15.5 years). This trend was similar between the patients without (0.1–0.15 LogMar; p 0.24) and with a retreated recurrence (0.075–0.2 LogMar; p 0.27) as shown in Fig. 5.

During the follow-up study visit, five participants proved to have an additional ocular problem with minor influence on their visual acuity. Of them, two participant (one with and one without a recurrence, pt 6 Fig. 3) had an incipient cataract (VA after initial PDT 0.1 and 0.05; during follow-up both 0.2), two participants were treated for glaucoma, and one had amblyopia in the treated eye.

Comparing the VA before initial PDT and at last follow-up, an improvement in VA was found in 13 out of 17 participants irrespective of a recurrence. Two participants had a stable VA as mentioned above. Two other patients showed first an improvement after the initial PDT but had a drop in VA over time. One of them had multiple recurrences of the CCH. The other was known with a symptomatic CCH for at least ten years before PDT and although his VA improved after the initial PDT from 1.7 to 0.7 LogMar, VA dropped again to 1.7 due to retinal atrophy.

In the group of patients with a recurrence, VA changed from a median of 0.5 LogMar (range 1–0.3) before the first episode to a median of 0.075 LogMar.

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**Table 1. Patient characteristics.**

| Characteristic | Participant n = 17 | Without recurrence n = 11 | With recurrence n = 6 | Non-Participant n = 16 | Without known recurrence n = 13 | With known recurrence n = 3 |
|---------------|-------------------|--------------------------|----------------------|------------------------|-------------------------------|---------------------------|
| Sex (male/female) | 14/3 | 10/1 | 4/2 | 10/6 | 8/5 | 2/1 |
| Age at 1e treatment (mean and range) | 50.3 (27 to 76) | 52.9 (39 to 76) | 45.5 (27 to 60) | 52.2 (34 to 76) | 54 (34 to 76) | 44.3 (37 to 53) |
| OD/OS | 12/5 | 9/2 | 3/3 | 5/11 | 5/8 | 0/3 |
| Months of follow-up (mean, range) | 136.3 (61 to 186) | 141.5 (63 to 186) | 126.5 (61 to 168) | 37.6 (3 to 135) | 34 (5 to 135) | 51 (3 to 127) |
| Location | Macular | 14 | 9 | 5 | 14 | 12 | 2 |
| Out outside vascular arcade | Without* | 2 | 1 | 1 | 1 | 0 | 1 |
| Without* | 1 | 1 | 0 | 0 | 0 | 0 |
| Previous laser treatment | VA logMar at baseline (median, range) | 0.4 (1 to 0.1) | 0.4 (0.9 to 0.1) | 0.5 (1 to 0.3) | 0.7 (2 to −0.1) | 0.7 (2 to −0.1) | 0.1 (0.3 to 0.1) |
| VA logMar after 1e PDT (median, range) | 0.1 (1 to −0.1) | 0.1 (1 to −0.1) | 0.075 (0.6 to 0) | 0.35 (2 to 0) | 0.4 (1.8 to 0) | 0.1 (2 to 0) |
| Height of tumour in mm (median, range) at baseline | 3.0 (2 to 4.5) | 3.0 (2 to 4.5) | 3.1 (3 to 3.3) | 3.5 (1.7 to 4.5) | 3.1 (1.7 to 4.5) | 3.5 (3.5 to 3.6) |
| Width of tumour in mm (median, range) at baseline | 8.7 (6 to 11) | 8.7 (6.4 to 11) | 6 (6 to 8.9) | 8.9 (6.5 to 10.8) | 8.6 (6.5 to 10.8) | 10.5 (8.8 to 10.5) |
| Spot size 1e PDT treatment in micron (median, range) | 5.250 (2.500 to 7.000) | 5000 (2.500 to 7.000) | 5500 (5.000 to 8.500) | 6500 (4.000 to 9.300) | 6500 (4.000 to 9.300) | 7000 (6.000 to 9.300) |
| More than 1 session of PDT at 1e PDT treatment | 3 | 1 | 2 | 6 | 5 | 1 |

OD, oculus dexter; OS, oculus sinister; PDT = photodynamic therapy; VA, visual acuity.

* Foveal inclusion.
after the initial PDT treatment (p 0.01). During the (first) recurrence, the VA had a median of 0.25 LogMar (range 2–0.1) and recovered to a median of 0.15 LogMar (range 0.7–0) after retreatment with PDT.

**Structural outcome**

*Fluorescein angiography and indocyanine green angiography*

Before the first PDT treatment, the FA showed in many patients the classical pattern of early filling of the tumour and diffuse leakage on top of the tumour. In a few patients, there were also widespread retinal pigment epithelium (RPE) changes, with pigment clumping and window defects both at the site of the tumour and inferior of the original tumour, probably due to chronic leakage. On the ICG images, the classic pattern of early filling with in most cases a wash out phenomenon could be seen.

These typical classical patterns were not seen at the follow-up study visit; FA and ICG showed a much more confusing pattern. The FA showed now a more widespread loss and clumping of pigment of the RPE in all patients on top of the location of the original tumour. Even a more pronounced loss and pigment clumping of the RPE in a pattern suggestive for continuous chronic leakage (gravitational tract) was found in six patients who did not have a recurrence. In four patients, this pattern was not seen on the images before treatment and in the other two patients this pattern was less evident at the time of the first treatment, suggesting a possible chronic leakage in the absence of a recurrence (Fig. 1). On ICG, atrophy of the choroidal capillaries and smaller choroidal vessels could be seen in most patients. Three patients were diagnosed with an active recurrence during the follow-up study visit. Due to the widespread changes of both the RPE and the choroidal vessels, an active recurrence could not be recognized by the classical CCH pattern on FA or ICG and the wash out phenomenon was absent (Fig. 4).

*Fundus autofluorescence*

A variety of hyper- and hypofluorescence areas, corresponding to the RPE changes seen on FA, was seen in all patients without a clear difference between the patients with or without a recurrence. No predictive factors were found.
After the first initial PDT, ten of the seventeen participants had a complete disappearance of the tumour on ultrasonography; in the remaining seven patients, the tumour was still detectable. In four of these patients, the tumour height was below 1 mm, and there were no signs of leakage. These patients were considered to be adequately treated. Three patients had a residual tumour thickness of more than 1 mm and received a second PDT treatment 6 weeks after the first PDT treatment. In two of these patients, the residual tumour height was reduced below 1 mm, and in one patient the tumour became undetectable on USG.

Optical coherence tomography
Of the participants seen at the AUMC (n=14), a slight local increase in choroidal thickness was seen on OCT (n=12) and this was not limited to the participants with a recurrence. Seven of the 11 patients without a recurrence showed this slightly increased local thickness of the choroid with a dome shaped elevation of the neuroretina without signs of leakage (Fig. 1G). During the study, in three patients an active recurrence was diagnosed. The OCT images in these patients showed an increase at the site of the original tumour of choroidal thickness with elevation of the neuroretina, a limited neurosensory detachment and intraretinal cysts (Fig. 4). These signs of leakage on OCT were easily detected and, with more difficulty, confirmed on FA and ICG.

Discussion
Through this long-term follow-up study of patients with a CCH successfully treated between 2001 and 2012 with limited single spot PDT, an unexpected high number of recurrences were found. In six out of 17 patients (35%), a recurrence was diagnosed after an average of 6 years (range 2.8–10.7 years) following the initial therapy. Of the 16 patients who did not participate in the study at least an additional three patients had a documented recurrence.

At present, PDT is the preferred first line treatment of CCH. The protocol for PDT treatment differs between studies reported in the literature. Some performed the standard treatment as used in the treatment of exudative age-related macular degeneration (AMD) patients: dosage of the drug 6 mg/m² BSA, infusion of the drug, solved in 30 cc 5% glucose, infusion in 10 min, starting laser treatment 5 min after the infusion, laser time 83 seconds and delivering 50 J/mm² energy. Others shortened the infusion time to a 1 min bolus injection. In some studies, the authors used a spotsize that should cover the whole tumour area, and in case the largest spot was not sufficient, more than one spot was used. Some authors used higher energy levels in case of CCH with a height, measured by USG, of more than 3.5 mm. Other studies prefer a longer application time, based
Fig. 4. A patient with a recurrence (nr 2 of Fig. 3); 2006 first presentation with circumscribed choroidal hemangioma (CCH), colour image (A), ultrasonography (USG) before photodynamic therapy (PDT) (B) and after PDT (C). A recurrence (2016 December) was found during study follow-up: colour (D) and IR image (E). (F) Fundus autofluorescence, visualizing hyper- and hypoautofluorescence areas, (G1) fluorescein angiography (FA) and indocyanine green angiography (ICG) after 1 min, (G2) after 20 min. without the classical wash out phenomenon. (H, I) Optical coherence tomography (OCT) and USG before treatment of the recurrence. (J, K) Optical coherence tomography (OCT) and USG 4 months after treatment.
on the slower blood perfusion through choroidal hemangiomas (Schmidt-Erfurth et al. 2002; Boixadera et al. 2009; Zhang et al. 2010; Pilotto et al. 2011; Su et al. 2014; Liu et al. 2018; Papastefanou et al. 2018; Susskind et al. 2018; Lee et al. 2019). All studies reported a high success rate with PDT treatment. At the AUMC, we started with a higher energy level compared to standard PDT in AMD, and more than one spot in case the largest spot could not cover the whole tumour. Because we observed more than the usual RPE changes following the first patients, we switched to a limited single spot PDT approach. With one spot only covering the most elevated part of the tumour, and 83 seconds laser time, delivering 50 J/mm². With this treatment protocol, 33 patients were treated successfully, leakage disappeared, and the tumour became either undetectable on USG (76%), or a residual tumour was still present, but with a tumour height below 1 mm (24%).

In this study, we could evaluate 17 patients who were treated with this limited single spot PDT between 2001 and 2012 for CCH after a mean follow-up time of eleven years and four months (range 5.1–15.5 years). VA improved after PDT treatment, and even after such a long follow-up period, only a minimal decrease in visual acuity over time was seen in these patients, with and without a recurrence, confirming the relative safe aspect of this limited single spot PDT protocol for the neurosensory retina.

In contrast to our initial assumption, that following a successful PDT treatment without any changes after the first year the risk for recurrence was negligible, many patients demonstrated a recurrence later on. In some of them even without new complaints. Based on this study, we now recommend a continued regular follow-up every 6 months, to detect any recurrence in a timely fashion. In this study, we found the OCT to be the best device to detect a recurrence with signs of leakage, showing a neurosensory detachment and intraretinal cysts (Fig. 4). In contrast to the classic presentation, intraretinal cysts was more frequently present during a recurrence, perhaps as a consequence of secondary incompetence of the inner blood-retina barrier (Shields et al. 2004; Liu et al. 2011; Jamison et al. 2018; Lee et al. 2018).

The only possible predictive factor identified in the present study, although not significant, is the presence of a residual tumour following PDT treatment on USG even when the height of this residual tumour was below 1 mm on USG, described as marginal detectable tumour and considered to be an acceptable end-point of treatment. The higher rate of recurrence in these patients makes such an end-point questionable and perhaps the treatment should aim to reach an undetectable tumour on USG. However, there is a risk for tissue ischaemia or destruction when PDT is applied for total regression of the tumour (Schmidt-Erfurth et al. 2005; Papastefanou et al. 2018).

During the follow-up, a slight thickening of the choroid could be seen on the OCT images that was undetectable on USG. This was present in participants with and without a recurrence. It is unknown if this slight elevation was present directly following the initial PDT treatment (data not available). So the slight thickening of the choroid could be a remnant of the treated tumour or an early sign of recurrence, without signs of leakage. In one patient, this thickening of the choroid was scanned with OCT after initial PDT and was stable on the OCT scans in height over 11 years, without any signs of a recurrence. This thickening was as frequently present in the participants with and without a recurrence and its value as a predictive factor remains unclear.

The loss of RPE was much more widespread on FA and FAF than the area of the original tumour in all patients during follow-up, suggesting that an insidious leakage can occur over time even in the absence of a recurrence. The RPE loss in a gravitational tract which had developed over time in a few patients supports this assumption. The presence of signs of chronic leakage was not a predictive factor for a recurrence.

The images of FA, ICG and FAF, and the OCT findings were in a way reminiscent of a chronic serous choroidopathy. This pachychoroid disease is known with recurrence or chronic presence of leakage, resulting in (subclinical) subretinal fluid which
results in areas and traces of RPE loss in gravitational tracts. Very similar images were found in this study. This similarity could be a consequence of a slow flush out of the RPE cells due to an insidious subclinical leakage.

The high recurrence rate found in this study could be the result of an insufficient of the limited single spot PDT protocol, and perhaps other PDT protocols are more effective in that respect. Comparable follow-up studies of CCH are very rare. The follow-up study of Michels et al. had a mean follow-up of 3 years in 15 patients, treated with PDT (Verteporfin 6 mg/m² body surface area, 1 min bolus iv, after 5 min photosensitization with a single light spot of 100 J/cm², irradiance of 600 mW/cm² with a diode laser with a 689 nm wavelength; retreatment if persistent subretinal fluid was seen and a residual tumour prominence was found by ultrasonography after 6 weeks) and found an improved VA after treatment which was stable over 3 years (>80% VA of 20/26). The CCH remained non-detectable on USG, and there were no recurrences during follow-up (Michels et al. 2005). The follow-up study of Blasi et al. included 25 patients, and all treated with PDT (Verteporfin 6 mg/m² body surface area, IV over 10, 5 min after infusion photosensitization with single or overlapping spots of 100 J/cm², irradiance of 600 mW/cm² with a diode laser with a 689 nm wavelength; retreatment when persistent exudation in the macular region, no complete flattening of lesion on USG was necessary). They also reported a good improvement of visual acuity and resolution of (sub-)macular exudation without recurrences over 5 years (Blasi et al. 2010). In contrast with these studies is the study of Beardsley et al. focusing on four patients, all treated with the standard full-fluence treatment, single spot and a 689 nm beam for 83 seconds. Recurrences were noted in the study of Beardsley after 10–38 months, and each patient was retreated multiple times (Beardsley et al. 2013).

In conclusion, CCH can be successfully treated with PDT. The limited single spot PDT protocol is a safe treatment preserving the VA even after a long follow-up time. With the relatively high recurrence rate found in this study, we recommend regular follow-up with OCT every 6 months, especially in the patients with a marginal detectable tumour on USG following PDT treatment.

References

Barbaretz J & Schmidt-Erfurth U (2000): Photodynamic therapy of choroidal hemangioma: two case reports. Graefes Arch Clin Exp Ophthalmol 238: 214–221.

Beardsley RM, McCannel CA & McCannel TA (2013): Recurrent leakage after Visudyne photodynamic therapy for the treatment of circumscribed choroidal hemangioma. Ophthalmic Surg Lasers Imaging Retina 44: 248–251.

Berry M & Lucas LJ (2017): Circumscribed choroidal hemangioma: a case report and literature review. J Ophthalmol 10: 79–83.

Blasi MA, Tiberi AS, Scupola A, Balestrazzi A, Colangelo E, Valente P & Balestrazzi E (2010): Photodynamic therapy with verteporfin for symptomatic circumscribed choroidal hemangioma: five-year outcomes. Ophthalmology 117: 1630–1637.

Boxadra A, Garcia-Arumi J, Martinez-Castillo V, Encinas JL, Elizalde J, Blanco-Mates G & Oluo JL (2009): Prospective clinical study evaluating the efficacy of photodynamic therapy for symptomatic circumscribed choroidal hemangioma. Ophthalmology 116: 100–105.e101.

Bottoni F, Terverati DC & Deutman AF (1990): Fluorescein angiographic findings and results of laser therapy with verteporfin for symptomatic circumscribed choroidal hemangioma. Int Ophthalmol 14: 239–265.

Finger PT, Paglione RW & Packer S (1991): Microwave thermotherapy for choroidal hemangioma. Am J Ophthalmol 111: 240–241.

Fuchs AV, Mueller AJ, Grueterich M & Ulbig MW (2002): Transpupillary thermotherapy (TTT) in circumscribed choroidal hemangioma. Graefes Arch Clin Exp Ophthalmol 240: 7–11.

Jamison A, Cauchi P & Gilmour DF (2018): Photodynamic therapy for circumscribed choroidal hemangioma in a scottish cohort. Ocul Oncol Pathol 4: 322–330.

Jurkles B, Anastassios G, Ortmanns S, Schuler A, Schilling H, Schmidt-Erfurth U & Bornfeld N (2003): Photodynamic therapy using verteporfin in circumscribed choroidal hemangioma. Br J Ophthalmol 87: 84–89.

Kamal A, Watts AR & Rennie IG (2000): Indocyanine green enhanced transpupillary thermotherapy of circumscribed choroidal hemangioma. Eye (Lond) 14(Pt 5): 701–705.

Lamdua IM, Strein B & Seregard S (2002): Photodynamic therapy for circumscribed choroidal haemangioma. Acta Ophthalmol Scand 80: 531–536.

Lanzetta P, Virgili G, Ferrari E & Mencini U (1995): Diode laser photocoagulation of choroidal hemangioma. Int Ophthalmol 19: 239–247.

Lee J, Lee CS, Kim M & Lee SC (2018): Retinal fluid changes and therapeutic effects in symptomatic circumscribed choroidal hemangioma patients: a long-term follow up study. BMC Ophthalmol 18: 321.

Lee JH, Lee CS & Lee SC (2019): Retinal fluid changes and therapeutic effects in symptomatic circumscribed choroidal hemangioma patients: a long-term follow up study. Photodiagnosis Photodyn Ther 24: 372–376.

Michels S, Michels R, Sinader C & Schmidt-Erfurth U (2005): Verteporfin therapy for choroidal hemangioma: a long-term follow-up. Retina 25: 697–703.

Papastefanos V, Schuman PN, Reich E, Pavlidou E, Restorini M, Hungerford JL & Sagoo MS (2018): Analysis of long-term outcomes of radiotherapy and verteporfin photodynamic therapy for circumscribed choroidal hemangioma. Ophthalmic Surg Lasers Imaging Retina 2: 342–357.

Pilotto E, Urban F, Parrozzi R & Midena E (2011): Standard versus bolus photodynamic therapy in circumscribed choroidal hemangioma: functional outcomes. Eur J Ophthalmol 21: 452–458.

Porini G, Giovannini A, Amato G, Ioni A & Pantanetti M (2003): Photodynamic therapy of circumscribed choroidal hemangioma. Ophthalmology 110: 674–680.

Schilling H, Sauerwein W, Lommatzsch A, Friedlisch W, Bryska S, Bornfeld N & Wessing A (1997): Long-term results after low dose ocular irradiation for choroidal haemangiomas. Br J Ophthalmol 81: 267–273.

Schmidt-Erfurth UM, Michels S, Kuserow C, Jurbles B & Augustin AJ (2002): Photodynamic therapy for symptomatic choroidal hemangioma: visual and anatomic results. Ophthalmology 109: 2284–2294.

Schmidt-Erfurth U, Niemeyer M, Meitzeuwer W & Michels S (2005): Time course and morphology of vascular effects associated with photodynamic therapy. Ophthalmology 112: 2061–2069.

Scott IU, Gorseck J, Gass JD, Feuer WJ & Murray TG (2004): Anatomic and visual acuity outcomes following thermal laser photoocoagulation or photodynamic therapy for symptomatic choroidal hemangioma with associated serous retinal detachment. Ophthalmic Surg Lasers Imaging 35: 281–291.

Shields JA, Shields CL, Materin MA, Marr BP, Demirci H & Mashayekhi A (2004): Changing concepts in management of circumscribed choroidal hemangioma: the 2003 J. Howard Stokes Lecture, Part 1. Ophthalmic Surg Lasers Imaging 35: 383–394.

Zhou DA, Tang XJ, Zhang LX & Su XH (2014): Comparison of outcomes between overlapping-spot and single-spot photodynamic therapy for circumscribed choroidal hemangioma. Int J Ophthalmol 7: 66–70.

Suskind D, Joffenh W, Gelink F & Volker M (2018): Photodynamic therapy with double duration for circumscribed choroidal hemangioma: functional and anatomic results based on internal parameters. Clin Exp Ophthalmol 46: 495–501.

Tancer S, Demirci H, Shields CL & Shields JA (2009): Polypoidal choroidal vasculopathy following photodynamic therapy for choroidal hemangioma. Eur J Ophthalmol 19: 159–162.

Verbraak FD, Schlingemann RO, Keuneen JF & de Smet MD (2003): Longstanding symptomatic choroidal hemangioma managed with limited PDT as initial or salvage therapy. Graefes Arch Clin Exp Ophthalmol 241: 891–898.

Verbraak FD, Schlingemann RO, de Smet MD & Keuneen JF (2006): Single spot PDT in patients with circumscribed choroidal haemangioma and near normal visual acuity. Graefes Arch Clin Exp Ophthalmol 244: 118–1192.

Vicuna-Koehn J, Banin E, Averbukh E, Barzel I, Shulman M, Hemo I & Chowers I (2006): Application of the standard photodynamic treatment protocol for symptomatic circumscribed choroidal hemangioma. Ophthalmologica 220: 351–355.

Xiao Y, Guo X & Ouyang P (2013): Branch retinal artery occlusion associated with photodynamic therapy in a circumscribed choroidal hemangioma. Photodiagnostics Photodyn Ther 10: 644–646.

Zhang Y, Liu W, Fang Y, Qian J, Xu G, Wang W & Gao Q (2010): Photodynamic therapy for symptomatic circumscribed macular choroidal hemangioma in Chinese patients. Am J Ophthalmol 150: 710–715.e711.

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