ANALYSIS OF LONG TERM OUTCOMES OF RADIOTHERAPY AND VERTEPORFIN PHOTODYNAMIC THERAPY FOR CIRCUMSCRIBED CHOROIDAL HEMANGIOMA

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PURPOSE

To determine the long-term therapeutic outcome for different treatments of circumscribed choroidal hemangioma (CCH)

DESIGN

Retrospective observational study

SUBJECTS

Patients with newly diagnosed CCH

METHODS/INTERVENTION

Observation, visudyne photodynamic therapy (PDT), lens-sparing external beam radiotherapy (LS-EBRT) or plaque brachytherapy

MAIN OUTCOME MEASURES

Best-corrected visual acuity (BCVA) at baseline and throughout follow-up, tumor dimensions and OCT central thickness (where available) at baseline and throughout follow-up were recorded.

RESULTS

There were 60 treatment-naïve consecutive cases with CCH during the period January 2000 to June 2014; 42 (70%) received treatment. These were LS-EBRT (23/60, 38%, mean follow-up 45.5 months), PDT (16/60, 27%, 38 months), plaque radiotherapy (3/60, 5%, 92 months). Macular location, mottled or orange pigment and absence of drusen were significantly more frequent in the treatment group.

In the LS-EBRT group, median thickness reduction on ultrasound B scan was 1.6 mm (mean, 1.65±1.6 range, -6.5 - +0.7). BCVA gain was 0.22±0.34, with > 3 Snellen lines in 48% of cases. Kaplan-Meier estimates were 80% for any gain and 40% for >3 Snellen lines gain at 5 years.

In the PDT group, median thickness reduction was 0.95mm (1±0.8, -2.5 - +0.2). BCVA gain was at 0.3±0.51, with > 3 Snellen lines in 30% of cases. Kaplan-Meier estimates were 93% for any gain and 68% for >3 Snellen lines at 5 years. Double versus single duration PDT had more favorable outcomes with a greater reduction in tumor thickness (p=0.04), central retinal thickness (p=0.02) and improvement in visual acuity (median 0.33 vs -0.05).

There was no significant difference in tumor thickness reduction or BCVA gain between LS-EBRT and PDT.

With plaque brachytherapy, mean thickness reduction was 2.5mm, but BCVA loss of >2 Snellen lines was noted in all three cases at end of follow up. Radiation complications developed in 10/23 (43.5%) cases from the LS-EBRT group and 2/3 (87%) cases from the plaque brachytherapy group.

CONCLUSION

LS-EBRT is equivalent to PDT in CCH management for post-treatment BCVA and tumor thickness reduction. The risk of LS-EBRT and plaque brachytherapy was late radiation-related complications. Double-duration PDT was more favorable than single duration.

Introduction

Circumscribed choroidal hemangioma (CCH) is a vascular tumor of the choroid composed of endothelium-lined vascular channels occupying the choroid up to its full thickness.[1] It is almost always unifocal and unilateral and develops usually between the second and fourth decade of life. Its pathogenesis is unknown. The tumor is often overlooked on routine eye examination or is misdiagnosed. The differential diagnosis of circumscribed choroidal hemangioma includes highly vascular amelanotic melanoma, early choroidal osteoma, and orange-coloured metastases such as thyroid, renal, and neuroendocrine carcinoma.[2] The presence of an associated detachment needs to be differentiated from central serous retinopathy, exudative age-related macular degeneration and posterior scleritis.[3]

These lesions are often asymptomatic, though symptoms can occur as a direct function of the tumor location or behaviour [1,2]. Subfoveal tumors can induce unilateral hypermetropic shift as a result of anterior displacement of the retina [4]. Juxta- or parafoveal tumors cause vision loss if associated with exudative subretinal fluid or retinoschisis

A variety of modalitites has been used for the treatment of these lesions aiming principally at reduction of leakage and secondly at regression of the lesion. Laser photocoagulation, [5-8] external beam radiation therapy,[9-11] stereotactic radiotherapy,[12-14] proton beam radiotherapy,[15-17] plaque radiotherapy, [11,18-20] transpupillary thermotherapy,[21-23] and more recently photodynamic therapy with verteporfin have been used [24-25] The aim of this retrospective study is to determine the long term therapeutic outcome for different treatments of circumscribed choroidal hemangioma (CCH).

Patients and methods

This was a retrospective observational study of referred CCH cases from January 2000 to June 2014. Institutional Review Board (IRB)/Ethics Committee approval was obtained (SAGM1003s) from Moorfields Eye Hospital and the research adhered to the tenets of the Declaration of Helsinki. Hemangiomas were diagnosed either incidentally or because of

blurred vision. All patients underwent full ophthalmic examination, B-scan ultrasonography (Sequoia, Siemens, Erlangen, Germany), fluorescein and indocyanine green angiography as required. Spectral-domain optical coherence tomography (Spectralis, Heidelberg, Germany and Topcon, Tokyo, Japan) scans were used during the study period, when available and as required. Doppler B-scan ultrasonography was examined where available (Sequoia, Siemens, Erlangen, Germany),

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Data collected included patient demographics (age, sex, presenting symptom), visual acuity (decimal scale and Snellen lines), tumor features (height, maximal diameter, associated clinical findings). B-ultrasonography and Spectral-domain optical coherence tomography. OCT measurements were obtained from the automated software and manual measurements as needed in order to avoid discrepancy because of the different software platforms. Visual acuity was assessed during the study before, throughout treatment and at final follow up. Analysis of vision change was subdivided in to any visual gain, ≥ 2 snellen visual acuity line gain, ≥ 3 snellen visual acuity line gain, any visual acuity loss, ≥ 2 snellen visual acuity lines loss, ≥ 3 snellen visual acuity lines loss.

The indication for treatment was the presence of symptoms, including blurred vision, photopsiae, or hyperopic shift and if there was fluid at the fovea or worsening subretinal fluid threatening the fovea. Patients requiring treatment were offered lens-sparing external beam radiotherapy (LS-EBRT), verteporfin photodynamic therapy (PDT) or plaque radiotherapy. All patients received these as first line treatment. The non-treatment group consisted of patients that did not require treatment during the follow up period.

Studies in the literature were identified by a systematic search using Medline (http://www.ncbi.nlm.nih.gov/pubmed). Terms searched were as follows: “choroidal hemangioma” along with “photodynamic therapy”, “external beam radiotherapy,” and “plaque brachytherapy”. In reports referring to treatment of choroidal hemangiomas with photodynamic therapy published results on protocol settings, lesion thickness and visual

acuity outcomes were collected and analysed. Visual acuity outcomes presented were converted to the decimal scale for analysis purposes.

Lens-sparing external beam radiotherapy (LS-EBRT)

LS-EBRT was provided with the Varian Eclipse 6MV linear accelerator following CT and mapping of the lesion (isodose curves in grays) with the appropriate software (Aria). The axial mid-ocular/lens CT section was chosen for the planning and isodosimetry calculated such that the lens received less than 10% of the prescribed dose. A prescription dose of 40Gy was delivered in 20 fractions (2 GY per fraction) over 28 days.

Photodynamic Therapy with Verteporfin (PDT)

Photodynamic therapy (Activis, Quantel Medical, Cournon d' Auvergne, France) with Verteporfin (Visudyne; Novartis Ophthalmics, Basel, Switzerland) was performed with a single spot covering the lesion using Area Centralis lens or Quadraspheric lens (Volk, Mentor, OH, USA) based on lesion size. Photodynamic therapy-treated cases were subcategorized based on laser application settings. Treatment parameters were for standard 50 J/cm^2 fluence, 600 mW/cm^3 light dose, and single (83 sec) or double (166 sec) duration.

Plaque brachytherapy

Plaque brachytherapy using ruthenium applicators (Bebig, Berlin, Germany) was performed in some patients. A prescription dose of 40-50 Gy at the lesion apex was prescribed and duration varied from 1d 1hr to 4 d 2hrs due to specific activity of the source and height of the tumor.

Efficacy and Safety

Efficacy of different treatment modalities was determined by best corrected visual acuity (BCVA) (decimal scale and conversion to Snellen lines for statistical analysis purposes), height on B-scan (mm) and OCT central retinal thickness change (µm) at the end of follow up period. Radiation retinopathy and other complications of treatment were recorded.

Statistical analysis

Descriptive statistical analysis, with x^2 and non-parametric Mann-Whitney tests, was used to evaluate the findings following prior Kolmogorov-Smirnov tests indicating the presence of non-normal distribution of the results. Kaplan-Meier survival analysis was performed for the endpoints of any visual gain, ≥ 2 snellen visual acuity line gain, ≥ 3 snellen visual acuity line gain, any visual acuity loss, ≥ 2 snellen visual acuity lines loss, ≥ 3 snellen visual acuity lines loss and resolution of fluid at the end of follow-up period. Cumulative probability was recorded and statistical significance of survival curves was assessed with log-rank test. A difference of 0.05 was considered statistically significant.

Collected data from previous studies were analysed with descriptive statistics, ANOVA and t-test. A difference of 0.05 was considered statistically significant. Analysis was done with SPSS v.11 (IBM Corp, NY, USA)

Results

There were 60 consecutive cases of CCH included in the study. The median age at presentation was 61.5 years (mean±SD ,58±15 – range, 18-87) with 51% male and 49% female patients. Tumors were located in the macula in 59% (35/60), juxtapapillary in 25% (15/60) and peripheral (outside the retinal vascular arcades) in 17% (10/60). Patient demographics and tumor features are summarised in **Table 1**.

At baseline, the median tumor height was at 2.6mm (2.7±1, 1-6.6) and median maximal diameter was at 7mm (7.±2.7, 2.5-16.3). Subretinal fluid was present on clinical examination in 46/60 patients (77 %)**.** OCT scan was available in 28 patients and median central retinal subfield thickness was 335µm (418±250, 208-1200). Internal blood flow of tumors at baseline was available in 13 cases. Median internal blood flow was 22cm/s (21.5±9.7, 4-45).

Treatment vs non-treatment group

Out of 60 eyes with CCH, 42 received treatment (70%). The median follow up after treatment was 47 months (49±11, 2-144). The remaining 30% (18/60) consisted of the non-treatment group. Median follow up for the non-treatment group was 27.5 months (42±21, 5-156).

Comparison of tumor dimensions and features between groups are presented in **Table 2**. In our cohort, hemangiomas with macular location (p-0.001, x^2), mottled (p=0.03, x^2) or orange pigment (p=0.008, x^2) and absence of drusen (p=0.003, x^2) were significantly more frequent in the treatment group. In addition, tumor height at baseline was significantly higher in the treatment group at baseline at 2.7 (2.9±1, 1.5-6.6) mm vs non-treatment group at 2.0 (2.2±1, 1-4.7), (p=0.018, Mann-Whitney).

Treatment modalities

There were 38% (23/60) of eyes that were managed with LS-EBRT (20 fractions), 27% (16/60) received PDT (14/16 received one session only, 1/16 with two sessions 84 months apart and 1/16 with three sessions at 8 months and 32 months) and 5% (3/60) patients were treated with plaque brachytherapy. Median follow up for LS-EBRT cases was 30.8 months (mean 45.5±30, range 5-143), for PDT 24 months (mean, 38.6 ±32.6, range 2-93) and for plaque brachytherapy 79 months (mean 92±28, range 72-125).

With regard to tumor location, 66% (10/15) of juxtapapillary tumours were treated with LS-EBRT and the remainder did not receive any treatment. For macular tumors, 40% (14/35) were treated with PDT, 29% (10/35) with LS-EBRT, 8% (3/27) with plaque brachytherapy whereas 23% (8/35) did not require any treatment. For peripheral tumors, 50% (5/10) required treatment, LS-EBRT in 3 cases and PDT in 2 cases.

Tumor dimensions

Thickness

The median reduction in tumor thickness in the LS-EBRT group was 1.6 mm (mean, 1.65±1.6 range, -6.5- +0.7); With photodynamic therapy was -0.95 (mean, 1±0.8 range, -2.5 - +0.2) and for plaque brachytherapy was at 2.7 mm (mean, 2.5±0.8 range, -3,2 - -1.6). There was no significant difference in tumor thickness reduction between LS-EBRT and PDT (p=0.177). In the non-treatment group the tumor thickness reduced by a median of 0.25 mm (mean, 0.01 ± 0.8 range, -1.7-+1.5). In all treatment groups compared to non-treatment, there was a significant reduction in thickness.

Maximal basal diameter (MBD)

On ultrasound B scan measurements, the median MBD reduction in the LS-EBRT group was at -1.8 mm (mean, -2.26±2.5, range -8.1-+1.5); with photodynamic therapy was -0.15 mm (mean, -0.8±2.3, range -5.2 - + 3.7) and with plaque radiotherapy was at -4.3 mm (mean -3.7±2.4, range -5.8 - -1). There was a statistically significant difference in MBD reduction between LS-EBRT and PDT (p=0.044). In the non-treatment group median tumor MBD reduction on was at 0 mm (mean, -0.25±2, range -5.2 - +3) **(Figure 1)**. Compared to the non-treatment group, there was a significant difference in MBD in the LS-EBRT group (p=0.003) and the plaque radiotherapy group (p=0.017), but not in the photodynamic therapy group (p=0.422). **(Figure 2A-D).**

Visual acuity outcomes

Treatment subgroups

At the end of follow up period visual acuity gain was significant in LS-EBRT (p=0.008) and PDT (p=0.014) in comparison to plaque brachytherapy though there was no significant difference between PDT and LS-EBRT (p=0.94, Mann-Whitney). In particular, visual gain >2 Snellen lines was noted in 52% of cases with LS-EBRT and in 50% of cases with PDT (p=0.576, x^2) and visual gain >3 Snellen lines was noted in 47.8% of cases with LS-EBRT vs 25% of cases with PDT (p=0.15, x^2). Loss of >2 Snellen lines was noted in all three cases which underwent plaque brachytherapy with two cases demonstrating considerable visual loss (>3 Snellen lines) (**Table 3**).

Kaplan –Meier analysis

Visual acuity gain **(Figure 3A-C)**

For patients with CCH undergoing LS-EBRT, Kaplan-Meier estimates for visual acuity gain by 12 months were 70% for any gain, 45% for > 2 Snellen line gain and 30% for > 3 Snellen line gain**.** By 5 years the corresponding estimates were 80% for any gain, 45% for > 2 Snellen line gain and 40% for >3 Snellen line gain.

For patients who underwent PDT, Kaplan Meier estimates by 12 months were at 75% for any gain, 57% for >2 Snellen line gain and 30% for >3 Snellen line VA gain. By 5 years the corresponding estimates were 93% for any gain, 65% for >2 Snellen line gain and 68% for >3 Snellen line gain.

Despite these differences no statistical significance was noted between curves for PDT and LS-EBRT (p=0.24 for any gain, 0.3 for >2 Snellen line gain and 0.34 for >3 Snellen line gain, log-rank test)

Comparing the observation group versus treatment with either LS-EBRT or PDT, a significant difference was found for any gain and >2 Snellen line gain. In addition a significant difference was noted between observation group and PDT group for >3 Snellen line gain (p=0.014, log rank test)

Visual acuity loss **(Figure 3D-F)**

For patients with CCH undergoing LS-EBRT Kaplan-Meier estimates for visual acuity loss by 12 months were 17% for any loss and 5% for >2 Snellen line VA loss or >3 Snellen line VA loss. By 5 years the corresponding estimates were 33% for any loss, 17% for >2 Snellen line visual acuity loss but 30% for >3 Snellen line visual acuity loss.

For patients who underwent PDT, Kaplan Meier estimates by 12 months were at 14% for any loss and 9% for >2 or >3 Snellen line loss. By 5 years, the corresponding estimates were at 32% for any loss and 38% for >2 and >3 Snellen line loss.

Despite these differences, no statistical significance was noted between curves for PDT and LS-EBRT in each endpoint (p=0.95 for any loss, 0.32 for >2 Snellen line loss and 0.23 for >3 Snellen line visual loss, log-rank test)

The Kaplan Meier survival curves are presented in **Figure 3(A-F)** and all log-rank values among groups in **Table 4.**

Non treatment group

In this group, a mild visual acuity improvement of 0.08±0.13 was noted by the end of follow up period with the majority of cases 11/18 (61%) not demonstrating any change in visual acuity.

Central Retinal Thickness and Resolution of Fluid on Optical Coherence Tomography

OCT scans of the macula were available in 21 cases (7 in the LS-EBRT group and 14 in the PDT group**).** Median CRT reduction in the LS-EBRT group was -63 µm (mean -233±397, range -1085 – 26) and median CRT reduction in the PDT group was at -87.5µm (mean -99±184, range -391 - +341). Despite these differences there was no significant difference between LS-EBRT and PDT central retinal thickness reduction at the end of follow up (p=0.9)

Resolution of fluid on OCT at the end of follow up period was noted in 4/7 (57.1%) cases in the LS-EBRT group and in 9/14 (64.3%) cases in the PDT group (**Figure 4).** There was no significant difference between groups (p=0.554, x^2).

Photodynamic therapy – Subgroup analysis

In the subgroup of patients receiving PDT treatment (n=16), 5/16 received single duration PDT, 9/16 received double duration PDT and 2/16 received both. The latter were excluded from this subgroup analysis. (**Table 5**)

Median visual acuity was reduced by 0.05 in the single duration group and improved by 0.33 in the double duration group, though this difference failed to reach statistical significance (p=1.9, Mann-Whitney). However, any visual acuity gain was noted in 2/5 cases (40%) in the single duration group and in all 9 cases (100%) in the double duration group. Amongst this, visual gain >3 Snellen lines occurred in 1/5 cases (25%) for single duration and in 3/9 cases (33%) of the double duration group.

Tumor thickness was significantly reduced in the double duration subgroup (p=0.042).(Table 5) (**Figure 4**) No significant difference was noted with regards to MBD change at the end of follow up period. Central retinal thickness on OCT was also significantly reduced in the double duration group compared to the single duration group (p=0.018)(**Table 5**).

Complications

Radiation related complications occurred in 10/23 (43.5%) cases in the LS-EBRT group and 2/3 (67%) cases from the plaque brachytherapy (**Table 6)**. Radiation retinopathy changes included localized retinal hemorrhage and exudation, cotton wool spots and even radiation maculopathy requiring intravitreal bevacizumab treatment (**Figure 2E-F**). One case developed persistent lid edema that was treated conservatively. In the LS-EBRT group radiation related complications were manifest at an average of 33.3 months after treatment (95% CI 16.6-49.9). Plaque brachytherapy complications occurred at 13 and 56 months respectively after treatment **(Figure 5).** No complications were noted in the PDT treatment group, notably no severe vision loss, choroidal ischaemia or retinal vascular occlusion.

DISCUSSION

Circumscribed choroidal hemangiomas are benign vascular tumors of the choroid, which are often overlooked, but have characteristic ultrasound and angiographic appearance. Treatment is indicated if a CCH is causing visual symptoms or is imminently at risk of causing vision loss (retinal detachment, scotoma or hyperopic shift). [1-2,4] The optimal treatment has yet to be established. In this report, we retrospectively reviewed the long-term outcomes of consecutive cases in a period spanning 14 years. This included both observation and treatment groups, using lens-sparing external beam radiotherapy (LS-EBRT), photodynamic therapy (PDT) and plaque radiotherapy.

An overall comparison of the clinical features of tumors between the treatment versus no treatment groups yielded some interesting findings. The thickness of hemangiomas requiring treatment was significantly higher at 2.7 mm versus 2.0 mm, despite no difference in the maximal basal diameter. As expected, tumors located in the macular area were more likely to require treatment. Orange or yellow tumor color was not a factor but the presence of mottled or orange pigment on the tumours was significantly higher in tumors requiring treatment. The lack of drusen at presentation was also significantly higher in treated tumors, indicating that these changes imply chronicity.

Lens sparing external beam radiotherapy (LS-EBRT)

LS-EBRT has been used in the past for the treatment of circumscribed choroidal hemangioma [9-11,26] with cumulative dose ranging from 18-30 Gy. The exact mechanism of the radiation effect on circumscribed choroidal hemangioma is unknown as there are no histologic descriptions or systematic studies [10]

LS-EBRT giving 40 Gy in 20 fractions over 28 days, without any other treatment, was used in 23 cases in our study with a median follow up 30.8 months. In our cases, 43% of tumors were juxtafoveal, 43% juxtapapillary and 13% were peripheral. In other studies the treatment parameters varied. Schilling et al.[10] reported the long-term outcomes of 20 Gy in 10 fractions LS-EBRT in 36 eyes with CCH with a median follow up of 4 years. In that series, 64% of tumors were juxtafoveal and the remainder extrafoveal. Adjuvant treatment with laser photocoagulation was administered either before or after EBRT in 9 cases. Ritland et al. [9] gave a cumulative dose of 20 Gy or 24 Gy in 10 or fewer fractions in 9 cases, with follow up from 0.4 to 8.8 years. Madreperla et al [11] treated two patients with a cumulative dose of 18 Gy and 30 Gy respectively in 10 and 20 fractions with a one-year follow up and Eide et al.[27] administered 24Gy in 8 fractions in two cases, with a one and two-year follow up respectively.

In the current study, in the LS-EBRT cases, visual acuity improved in 52%, was unchanged in 13% and 18% had significant vision loss. Survival analysis indicated an 88% probability of any visual gain and a 55% probability of any visual loss in 10 years. Schilling[9] reported visual acuity improvement in 40%, no change in 39% and decrease in 22%. All other series reported favorable visual acuity outcomes [9,11,27]. The higher dose of 40Gy appears to have a greater effect on retaining or improving vision.

Anatomic outcomes after LS-EBRT were also favorable. The mean tumor thickness reduced by 1.65 mm and maximal basal diameter by 2.25 mm and in cases where OCT was available, 60% of cases showed resolution of subretinal fluid. Schilling et al [10] did not find any change in tumor thickness following LS-EBRT, which may account for their lower success rate from using a lower radiation dose. They did however, find complete resolution of subretinal fluid in 63.8% of cases and residual fluid distant to the fovea resolved in36.2% cases. Other series [9, 11, 27] also reported favorable anatomic outcomes

We found mild non-proliferative radiation retinopathy that did not affect overall visual prognosis in 10 eyes at an average of 33 months after treatment. One eye needed intravitreal bevacizumab treatment for radiation macular edema, likely as a result of our higher radiation dose. No side effects were noted in the other publications. [9-11,27]

Photodynamic therapy

Photodynamic therapy with verteporfin is a potent vaso-occlusive treatment, selectively generating intraluminal thrombosis at endothelial membranes within specific vascular beds, while sparing the adjacent retina and RPE-Bruch membrane complex. [28] The selective treatment effect of PDT for vascular neoplasms and choroidal neovascularization was assumed to rely on an increased expression of low-density lipoprotein receptors in the rapidly proliferating vascular endothelial cells within these lesions as the sensitizers are coupled with specific carriers (antibodies, markers).[28] Witschell and Font [29] reported a histopathological study of 71 cases of CCH, which revealed the vasculature of the CCH to be mature, without proliferation of endothelial cells or abnormalities of the endothelial basement membrane in all cases. Although CCH is composed of capillary or cavernous vessels with a normal endothelial lining, it is suggested that the localized effect of PDT on CCH may also be driven by the distinctively slower perfusion characteristics of these tumors. [24] This theory was further supported by fluorescein and indocyanine green angiography testing that showed intensive and persistent occlusion of the collateral choroid circulation after PDT [30].

In the literature so far, there are 38 studies including 12 case reports in which PDT has been used as monotherapy in 267 cases and in combination with other modalities in 30 cases adding up to a total of 297 cases. (Table 7) There is variable follow up in these cases with a median of 14.5 months (mean 23.5 2.1 months, range 0.6-67 months). In our study, PDT sub-group follow up was a median of 24 months.

In publications on PDT, tumour location has been reported for a total of 282 cases: the vast majority of these (94%) were in the macula or close to the optic nerve (subfoveal 97/282; juxtafoveal 39/282; extrafoveal 71/282; and juxtapapillary 57/282). In our study only 2/15 cases treated with PDT were peripherally located. In juxtapapillary lesions optic disc exposure

of the laser can be avoided if the lesion is abutting to the optic disc, as complications can adversely affect the visual outcome [24, 25]

The infusion of the photosensitizer varies in different reports. (Table 7) The standard protocol for CNV treatment administers the infusion over 10 minutes (with an added 5 minutes before laser activation) or as a bolus infusion over 1 minute to reduce washout.[24] We treated the cases reported herein using the 10 minute protocol with 5 added minutes before laser activation.

The number of PDT treatments for CCH has also been variable. (Table 7) The indication for retreatment in prior studies was persistent subretinal exudation or residual tumor prominence seen ophthalmoscopically and documented by ultrasonography 6 weeks after the first treatment[14] with recurrence of symptoms or foveal edema[31] In our study treatment was discontinued when there was no evidence of subretinal fluid. Angiographically, CCH treated with PDT demonstrates areas within the tumor showing non-perfusion, reduced leakage, and finally focal choroidal atrophy.[24] The risk of continuing PDT beyond symptomatic relief is tissue ischemia or destruction.[30, 32] Though PDT can be repeated up to 4 times, judgement needs to be exercised in order to cease treatment when visual gain is maximal. In publications on PDT, 71 % of cases (212/297) were treated with a single session of PDT. In the 15 cases reported in this study, 11 had one PDT session but 4 cases required more than 1 session (maximum 3) at a time interval between 3 months to 7 years.

PDT laser settings reported in the literature have varied considerably with respect to laser power, fluence and duration, with the commonest settings the same as for choroidal neovascularisation in age-related macular degeneration. The standard settings of 50 J/cm power, 600 mW/cm^2 fluence and 83 seconds duration were used in 60% of cases in the literature (177/297 patients).[8,31,33-57] The duration of laser activation has been variable in the literature, with treatments lasting 63 [32] , 113 [58] , 125 [31, 57] and 166 seconds [25, 45, 48, 54, 59, 60]. Of note there have been cases treated for 166 seconds that have received bolus infusion [25, 48] whereas all other reports used standard infusion time of 10 minutes. [45, 54, 59, 60] Double laser power of 100 J/cm with full fluence (600 mW/cm^2) has been also used [54, 59-61]. This was found to be efficient for a re-treatment regimen for PDT for AMD and also selected because of

increased thickness of the lesion. In another report the PDT parameters varied according to the location, with standard AMD settings for foveal or juxtafoveal lesions, increased to 75 J/cm for extrafoveal lesions with duration of 125 seconds.[31]

In our study, using standard infusion and laser parameters, treatment was administered over either 83 seconds or 166 seconds (double duration). Both time durations have been previously used albeit double duration with greater power. [44, 54, 59, 60] The rationale for double duration treatment is based on the slower blood perfusion through choroidal hemangiomas as previously discussed [24, 28] We chose not to increase the power to avoid extensive choroidal atrophy or ischemia.

In 267 previously published cases treated with PDT monotherapy the mean visual acuity was 0.3 ± 0.03 before treatment and 0.479 ± 0.04 after treatment leading to an estimated improvement in visual acuity by 0.186 ± 0.027. Comparative analysis for treatment settings has demonstrated no significant difference in visual acuity difference for different settings (ANOVA, p=0.266). In those reports, standard PDT with double duration was not assessed. In our study there was no significant difference in comparison of the literature to single duration standard PDT but the difference was considerable with an improvement of visual acuity of 0.33 with double duration standard PDT. An important note is that all conclusions from subgroup analysis are restricted from the small sample size.

All different PDT protocols reported show a favorable decrease in tumour thickness, namely -2.1 ± 0.1 mm in 260 cases. Comparing the effect of different settings there were 25 cases in the literature with bolus infusion and double duration that had a mean thickness decrease of -3.2 ± 0.2 mm and 48 cases with power 100 J and double duration presented with a mean thickness decrease of -2.1 ±0.2 when compared with 177 cases with standard PDT with AMD settings at -1.9 ± 0.1; a statistically significant result (ANOVA, $p<0.001$). In our series this trend was also confirmed with a mean reduction in thickness at -1.3 ± 0.7 for double duration PDT vs -0.35 ± 0.57 for standard PDT (t-test, p=0.042). Similarly, OCT reduction in central retinal thickness by -184 ± 131 um vs 138 ±181 um was also significant (t-test, p= 0.018) Double duration PDT therefore has a more favorable anatomic, as well as visual outcome to the thickness of the lesion and the central retinal thickness.

No complications were found in our series, including rare complications following PDT such as retinal neovascularization on the tumour surface,[3, 45] or polypoidal choroidal vasculopathy [53]

Plaque radiotherapy

Cobalt-60, [18] iodine-125, ruthenium-106, [11] iodine-125, [19] and palladium-103 [20] have all been used for treating circumscribed choroidal hemangiomas. Cobalt-60 applicators with apex dose of 40-60 Gy and base dose of 90-240 Gy in 38 patients with macula involving secondary exudative retinal detachments had a favorable response but 3 developed retinal vascular complications.[18] Functional outcomes were worse in patients with subfoveal tumours. Madreperla et al. [11] used plaque brachytherapy with 50 Gy to the tumour apex in 8 patients with CCH (2 with iodine-125 and six with ruthenium-106), showing that at 1 year 5/8 patients had an improved visual acuity of more than three lines. Complications were not reported in one-year follow up. López-Caballero et al [19] used iodine-125 plaque brachtytherapy in 8 patients with a mean apical dose of 46.9 Gy. Despite favorable anatomic response of the tumor and retinal detachment, there was a reduction in mean visual acuity due to radiation retinopathy, glaucoma or cataract by 30 months follow up. Aizman et al [20] used Palladium-103 plaque radiotherapy in 5 cases with a mean apical dose of 29Gy. By two years' visual acuity had improved, resorption of subretinal fluid was noted but one patient developed radiation retinopathy.

In our series, three patients received ruthenium-106 plaque brachytherapy with an apical dose of 40-50 Gy with a mean follow up of 92 months. All cases demonstrated at least >2 Snellen line visual loss with two cases demonstrating >3 Snellen line visual acuity loss. Tumour thickness was improved in all cases. In one eye visual acuity loss was attributed to atrophic changes in the macular area whereas two cases developed radiation retinopathy at 13 and 56 months post treatment. Hence plaque brachytherapy has an initial favorable anatomic and functional outcome but is associated with late radiation retinopathy in 2/3 cases in keeping with other reports. Plaque brachytherapy should be reserved for cases resilient to other treatment options with poor visual prognosis.

In this study we have presented our results of a retrospective series of circumscribed choroidal hemangiomas with long-term follow up from a single centre, including a non-treatment group, and compared the outcomes of different treatment modalities particularly PDT and LS-EBRT with the literature.

We conclude that hemangiomas requiring treatment were significantly more elevated in comparison to hemangiomas that require observation, were located in the macular area and had mottled or orange pigment in their surface more frequently with lack of drusen. There was no significant difference between PDT and LS-EBRT either for visual acuity gain or for the 5-year probability of visual acuity gain. Similar outcomes were noted for visual acuity loss.

There was no significant difference between PDT and LS-EBRT in reduction of thickness of either the lesion itself or central retinal thickness or in resolution of fluid. LS-EBRT significantly reduced maximal basal diameter. Double duration PDT was significantly more successful in lesion thickness reduction in comparison to single duration, confirmed by the collective analysis of previously published cases treated with double duration protocols versus standard PDT settings.

LS-EBRT with a cumulative dose of 40Gy is associated with favorable visual outcomes. There was an increased risk of long-term radiation related retinal complications which in the majority were not vision threatening. In our small number treated with ruthenium plaque radiotherapy, non-proliferative radiation retinopathy developed contributing to significant visual loss.

Based on the above, PDT, especially double duration has favorable anatomic and functional outcomes for symptomatic circumscribed choroidal hemangiomas and LS-EBRT with a cumulative dose of 40Gy has comparable long-term outcomes despite minor radiation-related complications. Plaque brachytherapy is associated with long term radiation related complications and hence can be reserved for hemangiomas that do not involve the posterior pole.

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Figures

Figure 1. Superonasally located circumscribed choroidal hemangioma placed under observation at baseline [A] and at 10 months follow up [B] – SD-OCT indicating the presence of overlying intraretinal fluid. [C]. No change noted in dimensions of the lesion during the follow up period.

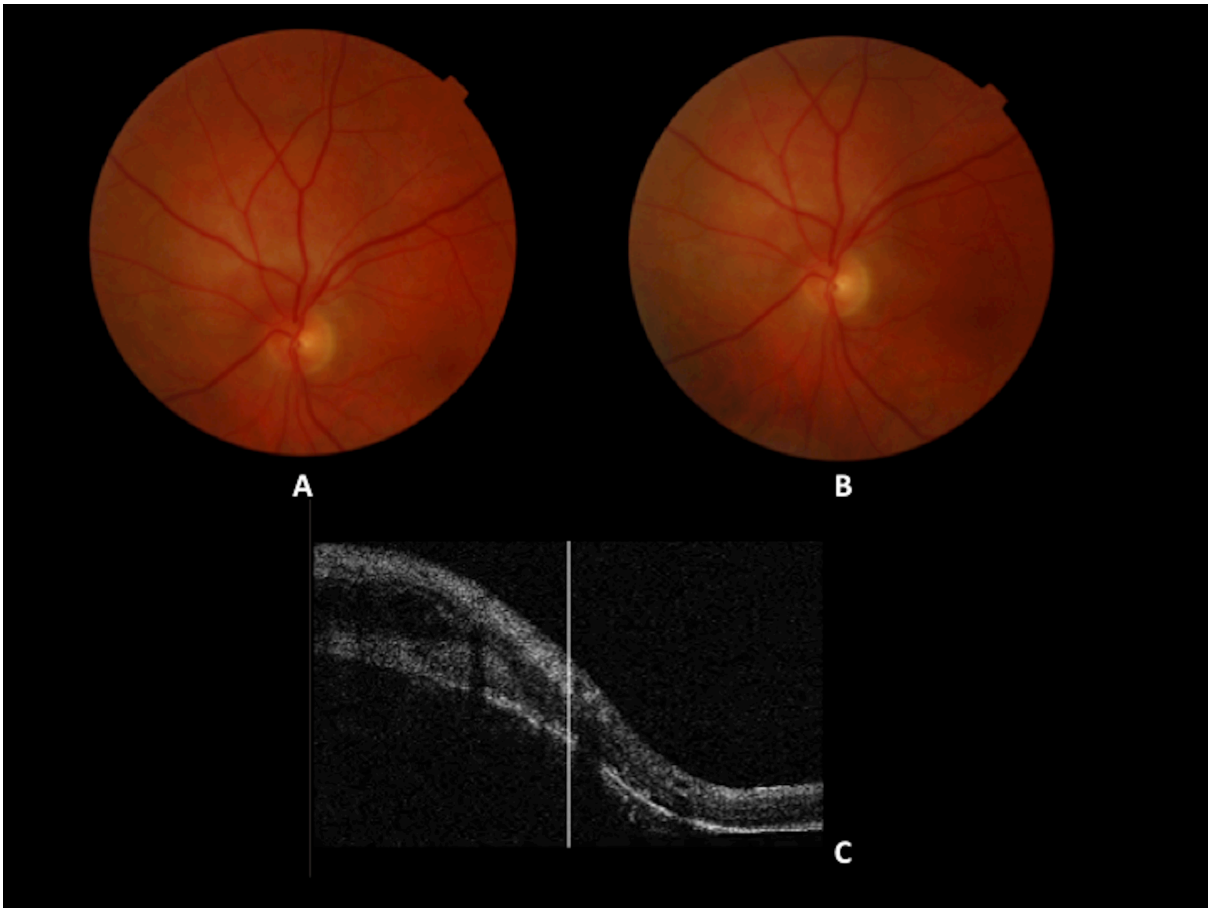
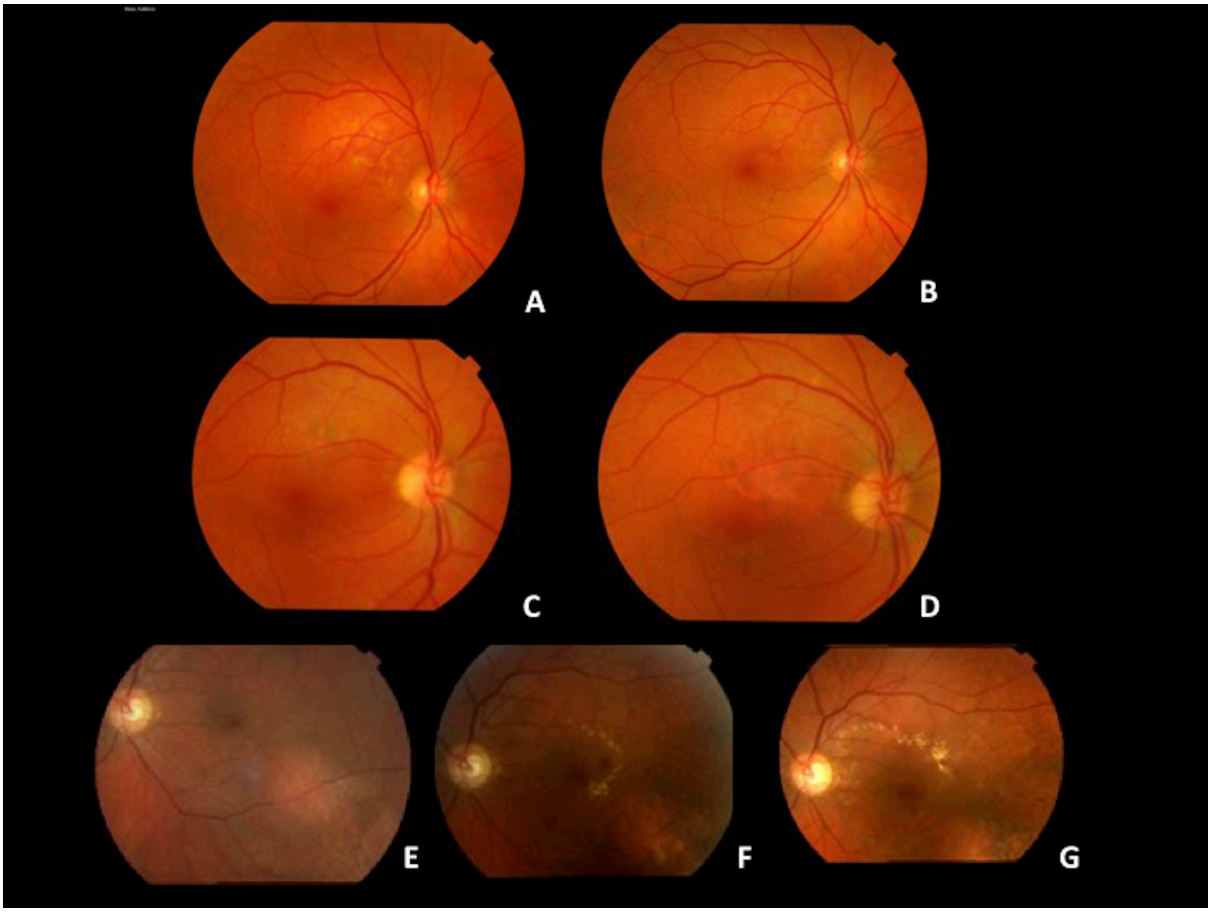


Figure 2– Circumscribed choroidal hemangioma treated with lens-sparing external beam radiotherapy. Top panel: (A) pre-treatment (B) at 15 months follow up - loss of overyling orange pigment, absoprtion of overlying subretinal fluid and visual acuity improvement from 6/9 at baseline to 6/6 at end of follow up. Middle panel: (C) pre-treatment (D) Four years after treatment hemangioma was atrophic. Visual acuity improved from 6/12 to 6/6. Bottom panel: (E) Circumscribed choroidal hemangioma 12 months after LS-EBRT treatment – Lesion is flat and visual acuity was at 6/9 (F,G) 20 and 24 months after (E) radiation maculopathy developed and visual acuity reduced to 6/36



764 Figure 3. Kaplan-Meier survival analysis curves with regards to any visual acuity gain or loss
765 (A,D), significant visual acuity gain or loss (B,E) and very significant visual acuity gain or loss
766 (C,F) in patients with choroidal hemangioma either under observation or receiving treatment
767 with lens-sparing external beam radiotherapy (LS-EBRT) or photodynamic therapy (PDT).
768

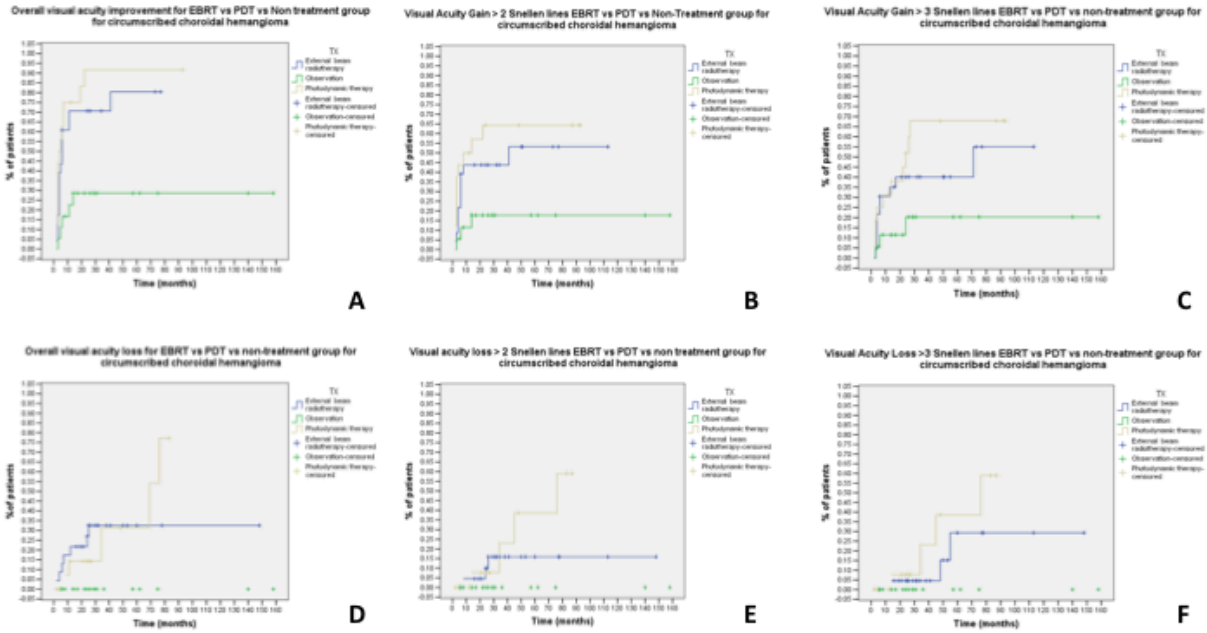


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Figure 4 – Juxtafoveal circumscribed choroidal hemangioma treated with standard single duration PDT before (A) and 5 years after treatment (B). No change noted in the diameter of the lesion. Visual acuity improved from 6/12 to 6/9. Fundus photographs and SD-OCT of macular choroidal hemangioma pre treatment (C,D,E) and 6 months after treatment (F,G,H) with double duration PDT. Lesion thickness reduced to undetectable and macular anatomy was restored.

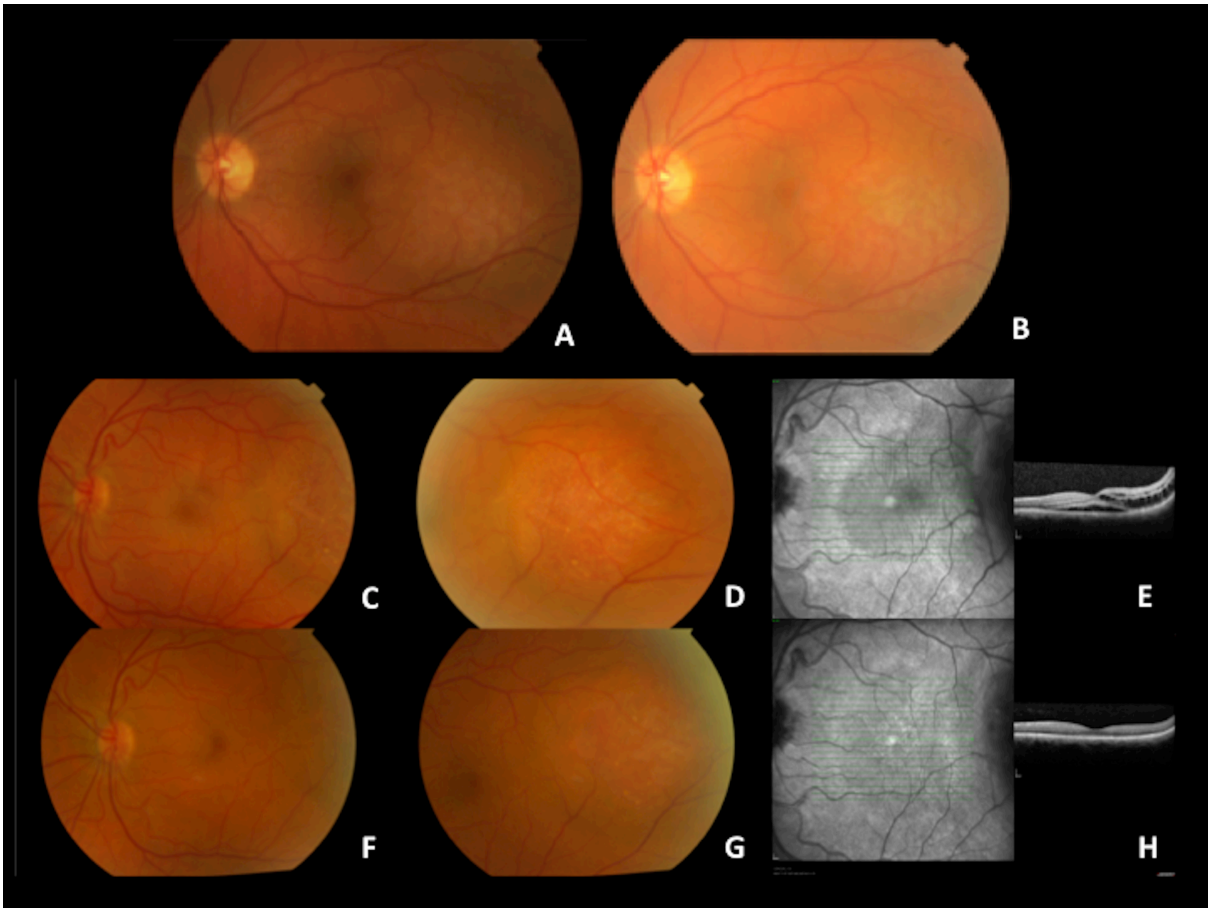
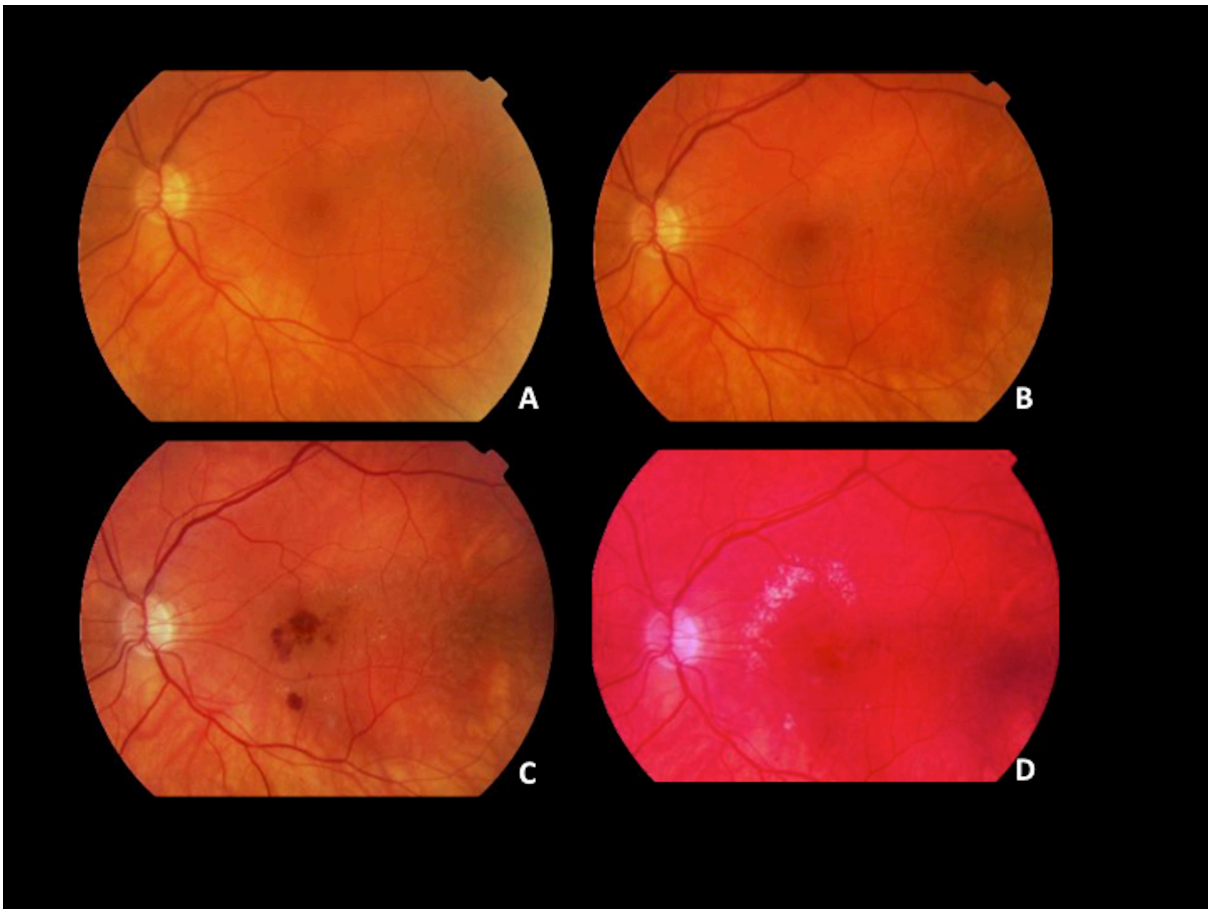


Figure 5. Juxtafoveal circumcribed choroidal hemangioma treated with plaque brachytherapy at baseline (A), at 18 months after treatment with sparse atrophic areas in the periphery (B), at 56 months after treatment with hemorrhage, exudation at the foveal area (radiation maculopathy) and expansion of the atrophic areas) (C) and at 72 months with considerable thinning and exudation (D). Visual acuity had reduced from 6/12 pre treatment to CF at the end of follow up period.



792 **Table 1. Retrospective analysis of 60 patients with circumscribed**
793 **choroidal hemangiomas from 2000-2014. Patient demographics and**
794 **features of circumscribed choroidal hemangiomas at baseline**
795 ***[1]median(mean±SD)(range)***
796 ***[2]location of tumor epicentre, Quadrantic location in location to fovea (macular),***
797 ***optic disc (juxtapapillary) and location outside the vascular arcades (peripheral)***
798 ***[3]Detected clinically and on OCT***
799

Number of patients	***60***
Age	***61.5(58**±15)(18-87)[1]***
Male	***31/60 (51%)***
Female	***29/60 (49%)***
Follow up(months)	***31(47**±39)(2-173)[1]***
Location of hemangioma[2]	
Macular	***35/60 (58.5%)***
Superior	6/35 (17%)
Inferior	3/35 (8.6%)
Temporal	25/35 (69.7%)
Nasal	1/35 (2.9%)
Juxtapapillary	***15/60 (25%)***
Superior	7/15 (46.7%)
Inferior	1/15 (6.7%)
Temporal	3/15 (20%)
Nasal	4/15 (26.7%)
Peripheral	***10/60 (16.6%)***
Superior	3/10 (30%)
Inferior	3/10 (30%)
Temporal	2/10 (20%)
Nasal	2/10 (20%)
Distance to fovea	***1.5 (1.92**±1.6)(0-5.5)[1]***
Distance to optic disc	***1.7 (2.5**±2.1)(0.1-8.5)[1]***
Color	

Orange	***36/60 (60%)***
Yellow	***24/60(40%)***
RPE	
Mottled pigment	***22/60 (36.7%)***
Orange pigment	***13/60 (21.7%)***
Fibrous metaplasia	***7/60 (11.7%)***
Osseous metaplasia	***1/60 (1.7%)***
No RPE changes	***17/60 (28.3%)***
Exudation	
Yes	***2/60(3.3%)***
No	***58/60(96.7%)***
Drusen	
Yes	***14/60(23.3%)***
No	***46/60(76.7%)***
Intraretinal or Subretinal fluid[3]	
Yes	***46/60 (77%)***
No	***14/60 (23%)***
Haemorrhage	
Yes	***1/60 (1.6%)***
No	***59/60 (96.7%)***

802 **Table 2**
803 ***Retrospective analysis of 60 patients with circumscribed choroidal***
804 ***hemangiomas from 2000-2014. Treatment vs no treatment group***
805 ***features at baseline***
806 *[1]p value was determined by x[2]or Mann-Whitney (see text)*
807 *[2]Median (mean±SD, range)*
808

	Treatment group	**Non-treatment group**	**P value[1]**
Number of patients	42/60 (70%)	18/60 (30%)	
Male	21/60 (67.7%)	10/60(32.3%)	
Female	21/60 (72.4%)	8/60 (27.6%)	
Location			
Juxtapapillary	10/15 (66%)	5/15 (34%)	0.197
Macular	27/35 (77%)	8/35 (23%)	0.001
Peripheral	5/10 (50%)	5/10 (50%)	1
Height at baseline	2.7 (2.9±1, 1.5-6.6)[2]	2(2.2±1, 1-4.7)	0.018 (mw)
Diameter at baseline	7.6(7.2±2.8, 2.5-16.3)	6.9(6.7±2.3, 3.5-11.2)	0.61
Color			0.571
Orange	25/36 (69.5%)	11/36(30.5%)	
Yellow	17/24 (70%)	7/24(30%)	
RPE changes			
Mottled pigment	16/22 (73%)	6/22 (27%)	0.03
Orange pigment	12/13 (92.3%)	1/13(7.7%)	0.008
Fibrous metaplasia	3/7 (42.9%)	4/7(57.1%)	0.7
Osseous metaplasia	1/1(100%)	0/1(0%)	

No RPE changes	10/17 (58.8%)	7/17(41.2%)	0.467
Exudation present	0/2 (0%)	2/2 (100%)	
Drusen present	9/14 (64.3%)	5/14(35.7%)	0.285
Drusen absent	33/46 (71.7%)	13/46 (28.3%)	0.003
Hemorrhage present	1/1 (100%)	0/1 (0%)	

Table 3

Retrospective analysis of 60 patients with circumscribed choroidal hemangiomas from 2000-2014 Visual acuity outcomes at the end of follow up period.

Treatment Groups	**VA preTx**	**VApostTx**	**VAdiff**	**GAIN >3 SNELLEN LINES**	**GAIN >2 SNELLEN LINES**	**ANY GAIN**	**ANY LOSS**	**LOSS >2 SNELLEN LINES**	**LOSS >3 SNELLEN LINES**	**NO CHANGE**
Observation	0.66±0.45	0.74±0.45	**0.08±0.23**	2/18 (11.1%)	3/18 (16.7%)	6/18 (33%)	1/18 (5.6%)	1/18 (5.6%)	1/18 (5.6%)	11/18 (61%)
LS-EBRT	0.45±0.23	0.68±0.4	**0.22±0.34**	11/23 (47.8%)	12/23 (52.2%)	14/23 (61%)	6/23 (26%)	4/23 (17.4%)	2/23 (8.7%)	3/23 (13%)
PDT	0.46±0.17	0.67±0.4	**0.3±0.51**	4/16 (25%)	8/16 (50%)	13/16 (81%)	3/16 (6.3%)	2/16 (18.75%)	2/16 (12.5%)	0/16 (0%)
PLAQUE	0.35±0.13	0.1±0.17	**-0.2±0.3**	0/3 (0%)	0/3 (0%)	0/3 (0%)	3/3 (100%)	3/3 (100%)	2/3 (66.7%)	0/3 (0%)

Table 4

Retrospective analysis of 60 patients with circumscribed choroidal hemangiomas from 2000-2014 . Log rank test results for observation, LS-EBRT and PDT groups following Kaplan-Meier analysis.

Visual acuity	Groups	Observation	LS-EBRT
Any gain	Observation		
	LS-EBRT	0.003	
	PDT	<0.001	0.24
Gain >2 Snellen lines	Observation		
	LS-EBRT	0.049	
	PDT	0.006	0.29
Gain >3 Snellen lines	Observation		
	LS-EBRT	0.098	
	PDT	0.014	0.339
Any loss	Observation		
	LS-EBRT	0.02	
	PDT	0.02	0.948
Loss> 2 Snellen lines	Observation		
	LS-EBRT	0.157	
	PDT	0.052	0.32
Loss > 3 Snellen lines	Observation		
	LS-EBRT	0.151	
	PDT	0.052	0.23

824 ***Table 5***

825 ***Retrospective analysis of 14 patients with circumscribed choroidal hemangiomas treated with photodynamic therapy***
826 ***(PDT) (standard settings vs double duration). Visual acuity results, Hemangioma Thickness / Maximal Diameter***
827 ***difference and OCT CRT difference***

828

Parameter	**PDT settings**	**FU**	**N**	**Median (mean±SD, range)**	**GAIN >3 LINES**	**GAIN >2 LINES**	**ANY GAIN**	**ANY LOSS**	**LOSS >2 LINES**	**LOSS >3 LINES**
Visual acuity change	Standard settings	58±40	5	-0.05 (0.06±0.46, -0.05-0.7)	1/5 (25%)	2/5 (40%)	2/5 (40%)	3/5 (60%)	2/5 (40%)	2/5 (40%)
(p=1.9)	Double duration	19±10	9	0.33 (0.47±0.53, -0.1-1.7)	3/9 (33%)	6/9 (66%)	9/9 (100%)	0/9 (0%)	0/9 (0%)	0/9 (0%)
Height change (mm)	Standard settings		5	-0.1 (-0.36±0.57, -1.2 - 0.2)						
(p=0.042)	Double duration		9	-1 (-1.3±0.77, -2.5 - -0.3)						
Max diam change (mm)	Standard settings		5	1.5 (0.58±2.8, -3.8 – 3.7)						
(p=0.147)	Double duration		9	-0.2 (-1.4±2, -5.2 – 0.2)						
OCT CRT change (µm)	Standard settings		3	82 (138±181, -8 - 341)						
(p=0.018)	Double duration		9	-202 (-184±131, -391-0)						

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Table 6.

Retrospective analysis of 60 patients with circumscribed choroidal hemangiomas from 2000-2014 Radiation-related complications

Treatment modality	Time point after treatment (mo.)	Complication	Treatment required
LS-EBRT	76	Hemorrhage	N
LS-EBRT	26	Hemorrhage	N
LS-EBRT	47	Hemorrhage, exudate	N
LS-EBRT	33	Hemorrhage, exudate	N
LS-EBRT	12	Hemorrhage	N
LS-EBRT	12	Lid edema	Conservative
LS-EBRT	68	Hemorrhage, exudate	N
LS-EBRT	9	Macular edema	Avastin
LS-EBRT	25	Cotton wool spots	N
LS-EBRT	25	Cotton wool spots	N
Plaque brachytherapy	13	Cotton wool spots, hemorrhage	N
Plaque brachytherapy	56	Hemorrhage, exudate	N

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837 ***Table 7.: Representative case series and case reports of patients with circumscribed choroidal hemangioma treated with***
838 ***photodynamic therapy***
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Publication	**Type**	**N**	**CCH location**	**Follow up (mo)**	**PDT settings**	**Prior Tx**	**Post Tx**	**Sessions of PDT**	**Visual acuity outcomes (1)**	**CCH thickness outcomes (mm)**
Chan, 2014	Case report	1	Juxtapapillary	14	Standard PDT 63 sec	antiVEGF		1	+0.4	-2.0
Bazin, 2012	Case report	1	N/A	9	Standard PDT	Dexamethasone intravitreal implant		1	+0.2	0.0
Bhatt, 2011	Case report	1	N/A	6	Standard PDT			1	+0.2	N/A
Elizalde, 2012	Case series	13	Subfoveal (n=4) Juxtafoveal (n=3) Extrafoveal (n=2) Juxtapapillary (n=4)	7-67	Standard PDT		EBRT (n=1)	54% (n=7) 1 38% (n=5) 2 7.7% (n=1) 5	+0.1- +0.5 (n=11) 0.0 (n=2)	3.4 to 2.5 mm (2)
Hsu, 2011	Case report	1	Juxtafoveal	12	Standard PDT 113 sec		antiVEGF	1	+0.05	-1.4
Pilotto, 2011	Case series	20	Subfoveal (n=2) Extrafoveal (n=13) Juxtapapillary (n=5)	58	Standard PDT (n=10) Bolus infusion 166 sec duration (n=10)	TTT (n=2)		1	0.0 (n=10) +0.1 (n=4) +0.2 (n=5) -0.3 (n=1)	-2.4
Andonegui, 2010	Case series	2	Extrafoveal (n=1) Juxtapapillary (n=1)	9 and 15	Standard PDT			1	+0.1 and +0.3	0.0 and -1.5
Liu, 2011	Case series	14	Subfoveal (n=10) Extrafoveal (n=1) Juxtapapillary (n=3)	12-42	Standard PDT (one case at 125 seconds)			1	+0.1	-1.8 (4)

Zhang, 2010	Case series	25	Subfoveal (n=18) Perifoveal (n=7)	35±15	Standard PDT for subfoveal 75 J/cm2 and 125 sec for perifoveal			1 2 (n=2)	+0.21[4]	3.2 to -1.3 [4]
Blasi, 2010	Case series	25	Subfoveal (n=2) Juxtrafoveal (n=9) Extrafoveal (n=14)	60+	Standard PDT for three cases and double power 100 J/cm2 and duration for the remainder			1 (n=22)	+0.04 to +0.15	-2.31 [4]
Chalam, 2009	Case report	1	Juxtafoveal	1	Standard PDT			1	0.23	N/A
Wachtlin, 2009	Case series	13	Subfoveal (n=7) Juxtapapillary (n=6)	26	75J PDT 125 sec / paint brush application			1	0.25	-1.7 to -1.8
Sagong, 2009	Case series	2	Extrafoveal (n=1) Juxtapapillary (n=1)	6 and 9	Standard PDT	antiVEGF (n=1)	antiVEGF (n=2)	1	+0.2 to +0.4	-2.3 [4]
Huang, 2009	Case series	14	Subfoveal (n=7)	6-36	Standard PDT		IVTA (n=4)	1 (n=8) 2 (n=6)	+0.1	-2.2[4]
Tuncer, 2009	Case report	1	juxtapapillary	36	Standard PDT			1	0	-2.7
Boixadera et al Ophthalmology 2008	Case series	31	Subfoveal (n=3) Juxtafoveal (n=7) Extrafoveal (n=10) Juxtapapillary (n=9)	12	Standard PDT	TTT (n=2) laser (n=2) TTT and laser (n=2)		1-3	+0.2	-2.3
Lopez-Quero et al	Case report	1	Subfoveal	17	Standard PDT			4	0	-3.4

Arch Soc Esp Sep 2008										
Vicuna - Kojchen et al Ophthalmologica 2006	Case series	9	Subfoveal (n=2) Juxtafoveal (n=1) Extrafoveal (n=2) Juxtapapillary (n=1) Peripheral (n=3)	2-24	Standard PDT			1-3	+0.15	-1.7
Kubicka-Trzaska et al Klin Oczna 2006	Case series	4	Subfoveal (n=2) Extrafoveal (n=2)	3-14	Standard PDT			1 (n=3) 4 (n=1)	N/A	N/A
Leys A et al Retina Jul Aug 2006	Case series	3	Subfoveal (n=1) Juxtafoveal (n=2)	12	Standard PDT (n=2) 100J PDT 166sec (n=1)		IVTA	1,2,4	+0.1	-2.7
Verbraak et al Graefes Sep 2003	Case series	13	Subfoveal (n=4) Juxtafoveal (n=1) Extrafoveal (n=3) Juxtapapillary (n=5)	3-22	Standard PDT (n=10) 100J PDT 166sec (n=3)	Laser and EBRT (n=1) EBRT (N=1)		1-2	+0.2	-3.0
Hussain N et al Ophth Surg Lasers Imaging Jan 2006	Case report	1	Extrafoveal	16	Standard PDT			2	0	-1.3
Michels et al Retina Sep 2005	Case series	15	Subfoveal (n=3) Extrafoveal (n=12)	36.6	Bolus infusion, double fluence, 166 sec.			2.3	+0.2	-3.8

Shields CL et al Ophth Surg Lasers Imaging May-Jun 2005	Case report	1	Juxtapapillary	1	Standard PDT			1	+0.7	-1.8
Bosch et al Klin Monbl Augenheik d Mar 2005	Case report	1	Subfoveal	2	Standard PDT			2	+0.15	-3.3
Singh AD et al BJO Nov 2004	Case series	10	Subfoveal (n=7) Extrafoveal (n=1) Juxtapapillary (n=2)	1-13	Standard PDT		TTT (n=2) EBRT	1-2	+0.01	-2.6
Scott IU et al Ophth Surg Lasers Imaging Jul-Aug 2004	Case series	5	Subfoveal (n=3) Juxtafoveal (n=1) Juxtapapillary (n=1)	3-12	Standard PDT			1-2	+0.2	-1.1
Soucek et al Neuro Endocrinol Feb-Apr 2004	Case series	9	N/A	8	Standard PDT			1	+0.45	-2.3
Gupta M et al Eye Feb 2004	Case series	2	N/A	0.5-2	Standard PDT			1-2	+0.3	-2.4

Nicolo et al EJO Aug-Sep 2003	Case report	1	Subfoveal	12	Standard PDT			1	+0.65	-1.0
Porrini et al Ophthalmology Apr 2003	Case series	10	Subfoveal (n=4) Extrafoveal (n=3) Juxtapapillary (n=2)	7-16	100J 186sec (larger than 2mm) 75J 125sec (n=1)(smaller than 2mm)			1-3	+0.25	-1.3
Jurklies BJO Jan 2003	Case series	19	Subfoveal (n=9) Juxtafoveal (n=2) Peripheral (n=7)	10.6	100J 166sec		EBRT (n=1) Laser (n=1) EBRT+laser (n=1)	1-5	+0.2	-1.4
Landau IM et al Acta Ophthalmol Scand Oct 2002	Case series	8	Juxtafoveal (n=2) Juxtapapillary (n=6)	3-15	Standard PDT		Plaque (n=3) Laser (n=1)	1	+0.3	+2.7
Sheidow et al CJO Aug 2002	Case report	1	Subfoveal	5	Standard PDT			2	+0.3	-3.8
Robertson DM Arch Ophthalmol Sep 2002	Case series	3	Juxtapapillary (n=3)	11-14	Standard PDT			1	+0.5	-3.0
Madreperla et al Arch	Case series	3	Juxtafoveal (n=1) Subfoveal (n=1)	3-9	Standard PDT		Laser (n=1)	1	+0.4	-2.0

Ophthalmol Nov 2001			Extrafoveal (n=1)							

[1] Converted to decimal from original papers for homogeneity of results
[2] Median value
[3] The only case treated with 125 seconds had a better outcome of +0.5
[4] Mean value