Saudi Journal of Ophthalmology (2019) 33, 219–228

Original Article

Circumscribed choroidal hemangioma: Clinical features and outcomes by age category in 458 cases

Lauren A. Dalvin [a,b]; Li-Anne S. Lim [a]; Michael Chang [a]; Sanika Udyaver [a]; Mehdi Mazloumi [a]; Pornpattana Vichitvejpaisal [a,c]; Grace L. Su [a]; Eleni Florakis [a]; Arman Mashayekhi [a]; Jerry A. Shields [a]; Carol L. Shields [a,*,1]

Abstract

Purpose: To investigate features and outcomes of circumscribed choroidal hemangioma by patient age.
Methods: Retrospective review of circumscribed choroidal hemangioma from 3/29/1967–6/4/2018 based on age at presentation (≤20 vs. >20–50 vs. >50 years).
Results: There were 458 circumscribed choroidal hemangiomas diagnosed at mean age (13 vs. 41 vs. 64 years, $p < 0.001$). The youngest age group had worse presenting visual acuity (20/400 vs. 20/150 vs. 20/100, $p < 0.001$), larger tumor basal diameter (13.5 vs. 6.6 vs. 6.2, $p < 0.001$), greater tumor thickness (5.8 vs. 3.1 vs. 2.9, $p < 0.001$), closer distance to foveola (0.5 vs. 1.4 vs. 1.2, $p = 0.03$), and greater extent of subretinal fluid (4 quadrants, 26% vs. 8% vs. 2%, $p < 0.001$). The youngest patients were less likely to be treated with primary observation (39% vs. 39% vs. 56%) or photodynamic therapy (10% vs. 27% vs. 22%) and more likely to be treated with plaque radiotherapy (26% vs. 6% vs. 3%) or external beam radiotherapy (13% vs. 1% vs. 0%) ($p < 0.001$). The youngest patients required greater total number of treatments (mean 4 vs. 2 vs. 1, $p < 0.001$). At mean follow-up (44 vs. 68 vs. 60 months, $p = 0.37$), the youngest patients had worse visual acuity (20/400 vs. 20/200 vs. 20/100, $p = 0.03$), but no difference in visual acuity loss of 3 or more Snellen lines (27% vs. 13% vs. 16%, $p = 0.55$).
Conclusion: Younger patients (≤20 years) with circumscribed choroidal hemangioma present with worse visual acuity and larger, more posterior tumors. Future studies are needed to improve early detection and treatment for this subgroup of patients.

Keywords: Eye, Choroid, Tumor, Hemangioma, Circumscribed, Age

https://doi.org/10.1016/j.sjopt.2019.07.002

Introduction

Choroidal hemangioma is a benign vascular tumor, classified as circumscribed or diffuse depending on visibility of defined tumor margins and extent of choroidal involvement.[1–7] Circumscribed choroidal hemangioma displays well-defined margins, whereas diffuse choroidal hemangioma shows ill-defined margins blending imperceptibly into the peripheral choroid. Circumscribed choroidal hemangioma is usually an isolated condition without systemic association, while diffuse choroidal hemangioma usually occurs in association with Sturge-Weber syndrome or other related

Received 22 February 2019; accepted 8 July 2019; available online 16 July 2019.

[a] Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, 840 Walnut Street, Suite 1440, Philadelphia, PA 19107, United States
[b] Department of Ophthalmology, Mayo Clinic, Rochester, MN 55905, United States
[c] Chulabhorn Hospital, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

* Corresponding author.
e-mail address: carolshields@gmail.com (C.L. Shields).
[1] Carol L. Shields, M.D. has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Peer review under responsibility of Saudi Ophthalmological Society, King Saud University

Production and hosting by Elsevier

Access this article online:
www.saudiophthaljournal.com
www.sciencedirect.com

conditions.[1–7] The diagnosis of circumscribed choroidal hemangioma is established based on clinical features including unilateral presentation, orange-red tumor color, round, well-circumscribed shape, and location in the posterior fundus.[7] Imaging features include hyperfluorescence by fluorescein angiography and rapid early filling and late washout on indocyanine green angiography.[7,8] Ultrasonography classically demonstrates a dome-shaped, echodense choroidal mass near the macular region, confirmed on optical coherence tomography (OCT) with dome-shaped contour and absence of choriocapillaris compression.[1–7] Thus the diagnosis of circumscribed choroidal hemangioma depends on clinical and imaging features.[3–5,7]

Circumscribed choroidal hemangioma is most frequently recognized in adulthood when patients become symptomatic with loss of visual acuity from related subretinal fluid (SRF) or macular edema.[7] In a study of 200 consecutive cases of circumscribed choroidal hemangioma by Shields et al, the mean age at diagnosis was 47 years, but choroidal hemangioma affected patients of all ages, ranging from age 4 to 81 years old in the aforementioned study.[1] We herein investigate the clinical features and outcomes of circumscribed choroidal hemangioma to determine whether tumors have different characteristics or risks of vision loss according to age of presentation.

Methods

Medical and imaging records were reviewed to identify all patients diagnosed with circumscribed choroidal hemangioma on the Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, from March 29, 1967 to June 4, 2018. All patients with circumscribed choroidal hemangioma were included and those with diffuse choroidal hemangioma were excluded. Circumscribed choroidal hemangioma was defined as a localized lesion with crisp margins. Lesions lacking visible margins were excluded. This study was in compliance with the Health Insurance Portability and Accountability Act (HIPAA). Institutional Review Board approval was obtained from Wills Eye Hospital.

All patients underwent a complete ophthalmic examination by an ocular oncologist (JAS, CLS, or AM), including slit lamp biomicroscopy and indirect funduscopic evaluation. Color fundus photography, fundus autofluorescence (FAF) imaging, B scan ultrasonography, fluorescein angiography (FA), indocyanine green angiography (ICG), and optical coherence tomography (OCT) were performed when available and as needed.

Clinical and photographic records were retrospectively reviewed for patient demographics (age, sex, race), systemic syndromes (Sturge-Weber, Klippel-Trenaunay), and systemic hypertension. Clinical features included hemangioma laterality, involved eye, associated anterior segment findings (iris heterochromia, iris neovascularization, angle closure, or neovascular glaucoma), presenting visual acuity, number of tumors per eye, largest tumor basal diameter and thickness, distance to optic nerve margin and foveola, and associated SRF, exudation, hemorrhage, or retinoschisis. Imaging features included FAF (lipofuscin extent and quality), ultrasonography (tumor thickness and echodensity), FA (hyperfluorescence in prearterial, arterial, venous, and late phases), ICG angiography (hypercyanescence in early and mid-phases and hypocyanescent ''wash out'' in the late phase), and OCT (SRF over the tumor and under the foveola, photoreceptor status, cystoid macular edema [CME], and macular atrophy). Treatment features included reason for treatment, primary and secondary treatment modality (observation, argon laser photocoagulation, photodynamic therapy, transpupillary thermotherapy, plaque radiotherapy, external beam radiotherapy, transscleral diathermy, intravitreal triamcinolone or anti-vascular endothelial growth factor [anti-VEGF], or enucleation), and number of treatments.

Outcomes included follow-up duration, final visual acuity, visual acuity loss of 3 or more Snellen lines and cause of visual acuity loss, final tumor diameter and thickness, SRF over the tumor and under the macula, cystoid retinal edema over the tumor or CME, retinal hemorrhage, and exudation. Some charts prior to 1990 had incomplete data, and not all study eyes were examined by all imaging modalities. Total numbers of eyes for which each clinical or imaging factor were found are indicated in the tables.

Statistical analysis was performed using SPSS Statistics Software Version 18 (SPSS Inc., Chicago, IL, USA). Demographics, clinical features, image features, treatment features, and outcomes were compared by age of presentation (age $\leq$20 vs. >20–50 vs. >50 years). Categorical variables were compared using Fisher's exact test or Chi-square test, and continuous variables were compared using analysis of variance (ANOVA). Post-hoc analysis for between groups comparison was performed using Bonferroni test. Statistical significance was defined as $p < 0.05$.

Results

There were 458 tumors in 457 eyes of 457 patients with circumscribed choroidal hemangioma managed on the Ocular Oncology Service, Wills Eye Hospital, Philadelphia, PA USA from March 29, 1967 to June 4, 2018. Patient demographics are listed in Table 1. Patient age was $\leq$20 (n = 31 [7%] tumors in 31 eyes), >20–50 (n = 182 [40%] tumors in 181 eyes), or >50 (n = 245 [53%] tumors in 245 eyes) years. Comparison of patients by age category ($\leq$20 vs. >20–50 vs. >50 years) revealed mean patient age at presentation (13 vs. 41 vs. 64 years, $p < 0.001$), with similar percentage of male sex (45% vs. 65% vs. 56%, $p = 0.06$), and the youngest age group demonstrating fewer patients of Caucasian race (71% vs. 87% vs. 87%, $p = 0.03$), and more patients with Sturge-Weber syndrome in youngest age category (48% vs. 2% vs. 1%, $p < 0.001$).

Clinical features are listed in Table 2. A comparison by age category revealed that the youngest age group had lowest mean presenting visual acuity (Snellen equivalent 20/400 vs. 20/150 vs. 20/100, $p < 0.001$), more frequent presence of dilated episcleral vessels (23% vs. 3% vs. 3%, $p < 0.001$), largest tumor basal diameter (13.5 vs. 6.6 vs. 6.2, $p < 0.001$), greatest tumor thickness (5.8 vs. 3.1 vs. 2.9, $p < 0.001$), and closest tumor distance to the foveola (0.5 vs. 1.4 vs. 1.2, $p = 0.03$). The youngest group also presented with greater SRF according to distance from the tumor (>6 mm SRF from the tumor, 48% vs. 27% vs. 13%, $p < 0.001$) and number of quadrants (4 quadrants of SRF, 26% vs. 8% vs. 2%, $p < 0.001$), greater number with submacular fluid (39% vs. 31% vs. 18%, $p < 0.001$) and CME (30% vs. 14% vs. 9%, $p = 0.01$), and less with macular retinal atrophy (0% vs. 2% vs. 4%, $p = 0.01$). On sub-analysis of patients without

Table 1. Circumscribed choroidal hemangioma analysis by age group in 458 cases. Patient demographics.

Demographics	Age ≤ 20 n = 31 tumors in 31 patients (%)	Age > 20–50 n = 182 tumors in 181 patients (%)	Age > 50 n = 245 tumors in 245 patients (%)	*p*-value	Total N = 458 tumors in 457 patients (%)
Age at presentation (years) Mean (median, range)	13 (13, 3–20)	41 (44, 22–50)	64 (63, 51–93)	**<0.001**	51 (52, 3–93)
Sex					
Male	14 (45)	117 (65)	138 (56)	0.06	269 (59)
Female	17 (55)	64 (35)	107 (44)		188 (41)
Race					
Caucasian	22 (71)	158 (87)	213 (87)	**0.03**	393 (86)
African American	1 (3)	3 (2)	8 (3)		12 (3)
Asian	2 (6)	5 (3)	3 (1)		10 (2)
Hispanic	1 (3)	7 (4)	11 (5)		19 (4)
Middle Eastern	1 (3)	1 (1)	0 (0)		2 (<1)
Indian	2 (6)	2 (1)	0 (0)		4 (1)
Other/unknown	2 (6)	5 (3)	10 (4)		17 (4)
Systemic syndrome					
Sturge-Weber Syndrome	15 (48)	3 (2)	2 (1)	**<0.001**	20 (4)
Klippel-Trenaunay Syndrome	0 (0)	0 (0)	0 (0)	NA	0 (0)
Systemic findings					
Facial nevus flammeus	15 (48)	3 (2)	1 (<1)	**<0.001**	19 (42)
Cutaneous hemangioma	1 (3)	2 (1)	1 (<1)	0.46	4 (1)
Mucosal hemangioma	0 (0)	0 (0)	0 (0)	NA	0 (0)
Systemic hypertension	0 (0)	25 (14)	94 (39)	**<0.001**	119 (26)
Laterality					
Unilateral	31 (100)	181 (100)	245 (100)	NA	457 (100)
Bilateral	0 (0)	0 (0)	0 (0)		0 (0)
Study eye					
Right eye	11 (36)	90 (50)	128 (52)	0.21	229 (50)
Left eye	20 (65)	91 (50)	117 (48)		228 (50)

Bold values indicate significant *p*-value.

Sturge-Weber syndrome, differences by age category in presenting visual acuity, tumor basal diameter, and tumor thickness remained significant. Imaging features are listed in Table 3. A comparison by age category revealed no difference in orange pigment or retinal pigment epithelium (RPE) trough by FAF; acoustic density by US; hyperfluorescence or CME by FA; hypercyanescence by ICG angiography; or photoreceptor status, macular SRF, CME, or macular retinal atrophy by OCT. The youngest (≤20 years) and middle age (>20–50 years) patients had greater frequency of SRF by OCT compared to the oldest patients (>50 years) (77% vs. 76% vs. 63%, $p < 0.001$).

Treatment modalities are listed in Table 4. A comparison by age category revealed no difference in the most common reasons for treatment, including SRF progression (50% vs. 25% vs. 28%) and SRF at the fovea (39% vs. 71% vs. 63%) ($p = 0.07$). The youngest patients were less likely to be treated with primary observation (39% vs. 39% vs. 56%) or photodynamic therapy (10% vs. 27% vs. 22%) and more likely to be treated with plaque radiotherapy (26% vs. 6% vs. 3%) or external beam radiotherapy (13% vs. 1% vs. 0%) ($p < 0.001$). There was no difference in secondary treatment modality, but the youngest patients required greater total number of treatments (mean 4 vs. 2 vs. 1, $p < 0.001$).

Outcomes are listed in Table 5. A comparison by age category revealed no difference in follow-up (mean 44 vs. 68 vs. 60 months, $p = 0.37$). The youngest patients had worse final visual acuity (mean Snellen equivalent 20/400 vs. 20/200 vs. 20/100, $p = 0.03$) (Fig. 1), but final visual acuity was no longer significantly different after adjustment for presenting visual acuity ($p = 0.90$). There was no difference in visual acuity loss of 3 or more Snellen lines (27% vs. 13% vs. 16%, $p = 0.55$). There was no difference by age category in final status of SRF, cystoid retinal edema, macular SRF, CME, retinal exudation, or retinal hemorrhage. On sub-analysis of patients without Sturge-Weber syndrome, differences by age category in final visual acuity remained significant.

Discussion

Circumscribed choroidal hemangioma is a benign vascular tumor that can cause profound vision loss secondary to chronic SRF and exudation.[1–7] Characteristic clinical features of circumscribed choroidal hemangioma include unilaterality, orange-red color, round, well-circumscribed shape, perimacular location, ultrasonographic echodensity, and ICG-documentation of early hypercyanescence with late washout of hypercyanense.[1–7] A previous large analysis on patients with circumscribed choroidal hemangioma revealed that this tumor typically affects middle-aged patients, at mean age of 47 years, but patients of all ages can be affected.[1] Herein, we specifically investigated, for the first time in the literature, features and outcomes of circumscribed choroidal hemangioma per age category (young (≤20 years), middle-aged (>20–50 years), and older (>50 years)) in a large consecutive case cohort of 458 patients at a single center.

Table 2. Circumscribed choroidal hemangioma analysis by age group in 458 cases. Clinical features at presentation.

Clinical features	Age ≤ 20 n = 31 tumors in 31 patients (%)	Age > 20–50 n = 182 tumors in 181 patients (%)	Age > 50 n = 245 tumors in 245 patients (%)	*p*-value	Total N = 458 tumors in 457 patients (%)
Visual acuity	n = 30	n = 180	n = 245		N = 455
≥20/40	6 (20)	72 (40)	106 (43)		184 (40)
20/50–20/200	14 (47)	66 (37)	89 (36)	0.14	169 (37)
<20/200	10 (33)	42 (23)	50 (20)		102 (22)
Visual acuity (Snellen) Mean (median, range)	20/400 (20/200, 20/20-NLP)	20/150 (20/70, 20/20-NLP)	20/100 (20/50, 20/20-NLP)		20/150 (20/60, 20/20-NLP)
Visual acuity (LogMAR) Mean (median, range)	1.45 (1.00, 0.00–5.00)	0.83 (0.54, 0.00–5.00)	0.67 (0.40, 0.00–5.00)	**<0.001**	0.79 (0.48, 0.00–5.00)
Visual acuity excluding SWS	n = 15	n = 178	n = 242		N = 455
≥20/40	2 (13)	71 (40)	106 (44)		179 (41)
20/50–20/200	9 (60)	66 (37)	88 (37)	0.18	163 (38)
<20/200	4 (27)	41 (23)	48 (20)		93 (21)
Visual acuity (Snellen) Mean (median, range)	20/400 (20/200, 20/20-NLP)	20/150 (20/70, 20/20-NLP)	20/100 (20/50, 20/20-NLP)		20/150 (20/60, 20/20-NLP)
Visual acuity (LogMAR) Mean (median, range)	1.45 (1.00, 0.00–5.00)	0.83 (0.54, 0.00–5.00)	0.67 (0.40, 0–5.00)	**<0.001**	0.79 (0.48, 0.00–5.00)
Related anterior segment findings	n = 31	n = 180	n = 244		N = 455
Conjunctival hemangioma	0 (0)	0 (0)	1 (0.4)	1.0	1 (<1)
Dilated episcleral vessels	7 (23)	5 (3)	6 (3)	**<0.001**	18 (4)
Iris heterochromia	1 (3)	2 (1)	1 (0.4)	0.18	4 (1)
Iris neovascularization	1 (3)	1 (1)	1 (0.4)	0.25	3 (1)
Angle closure	0 (0)	1 (1)	2 (1)	1.0	3 (1)
Neovascular glaucoma	0 (0)	1 (1)	1 (0.4)	1.0	2 (<1)
Number of tumors per eye Mean (median, range)	1 (1, 1–1)	1 (1, 1–2)	1 (1, 1–1)	0.22	1 (1, 1–2)
Tumor dimensions by clinical exam					
Tumor diameter (mm) Mean (median, range)	13.5 (13.5, 4.0–24.0)	6.6 (6.0, 2.0–22.0)	6.2 (6.0, 1.0–12.0)	**<0.001**	6.8 (6.0, 1.0–24.0)
Tumor thickness (mm) Mean (median, range)	5.8 (5.6, 1.8–11.3)	3.1 (3.0, 0.5–7.9)	2.9 (3.0, 0.5–5.9)	**<0.001**	3.2 (3.0, 0.5–11.3)
Tumor dimensions excluding SWS	n = 15	n = 178	n = 242		N = 455
Tumor diameter (mm) Mean (median, range)	12.5 (14.0, 6.0–20.0)	6.5 (6.0, 2.0–22.0)	6.2 (6.0, 1.0–12.0)	**<0.001**	6.5 (6.0, 1.0–22.0)
Tumor thickness (mm) Mean (median, range)	5.9 (6.0, 1.8–11.3)	3.1 (3.0, 0.5–7.9)	2.9 (3.0, 0.5–5.9)	**<0.001**	3.1 (3.0, 0.5–11.3)
Tumor proximity by clinical exam					
Distance to optic nerve (mm) Mean (median, range)	1.2 (0.0, 0.0–7.0)	1.5 (0.0, 0.0–8.0)	1.9 (1, 0.0–18.0)	0.08	1.7 (1.0, 0.0–18.0)
Distance to foveola (mm) Mean (median, range)	0.5 (0.0, 0.0–4.0)	1.4 (1, 0.0–7.0)	1.2 (0.5, 0.0–15.0)	**0.03**	1.2 (0.5, 0.0–15.0)
Tumor location	n = 31	n = 181	n = 241		N = 453
Macula	16 (52)	108 (60)	160 (66)		284 (63)
Inferior	3 (10)	13 (7)	16 (7)		32 (7)
Temporal	8 (26)	17 (9)	22 (9)	0.06	47 (10)
Superior	4 (13)	21(12)	24 (10)		49 (11)
Nasal	0 (0)	22 (12)	19 (8)		41 (9)
Subretinal fluid surrounding tumor	n = 31	n = 179	n = 241		N = 451
None	8 (26)	35 (20)	83 (34)		126 (28)
Subretinal fluid cap	4 (13)	34 (19)	46 (19)		84 (19)
Subretinal fluid < 3 mm from tumor	2 (7)	40 (22)	55 (23)	**<0.001**	97 (22)
Subretinal fluid 3–6 mm from tumor	2 (7)	22 (12)	25 (10)		49 (11)
Subretinal fluid > 6 mm from tumor	15 (48)	48 (27)	32 (13)		95 (21)
Subretinal fluid under macula	n = 31	n = 177	n = 240		N = 448
Submacular fluid	12 (39)	54 (31)	42 (18)	**<0.001**	108 (24)
Other macular features	n = 10	n = 65	n = 118		N = 193
Cystoid macular edema	3 (30)	9 (14)	11 (9)	**0.01**	23 (12)
Retinal atrophy macula	0 (0)	1 (2)	5 (4)	**0.01**	6 (3)

Table 2 (*continued*)

Clinical features	Age ≤ 20 n = 31 tumors in 31 patients (%)	Age > 20–50 n = 182 tumors in 181 patients (%)	Age > 50 n = 245 tumors in 245 patients (%)	*p*-value	Total N = 458 tumors in 457 patients (%)
Subretinal fluid quadrants	n = 31	n = 177	n = 240		N = 448
None	17 (55)	118 (67)	193 (80)		328 (73)
1 quadrant	0 (0)	19 (11)	26 (11)		45 (10)
2 quadrants	3 (10)	24 (14)	13 (5)	**<0.001**	40 (9)
3 quadrants	3 (10)	2 (1)	4 (2)		9 (2)
4 quadrants	8 (26)	14 (8)	4 (2)		26 (6)
Related retinal findings	n = 31	n = 181	n = 243		N = 455
Retinal exudation	1 (3)	13 (7)	11 (5)	0.54	25 (6)
Retinal hemorrhage	0 (0)	4 (2)	4 (2)	0.84	8 (2)
Retinal arterial dilation	2 (6)	0 (0)	0 (0)	**0.01**	2 (<1)
Retinal venous dilation	1 (3)	3 (2)	0 (0)	**0.04**	4 (1)
Retinoschisis	0 (0)	12 (7)	10 (4)	0.25	22 (5)

Bold values indicate significant *p*-value.

Abbreviations: SWS = Sturge-Weber syndrome.

Post Hoc analysis (Bonferroni test): Tumor diameter - significant difference between group 1 and group 2 ($p < 0.001$) and between group 1 and 3 ($p < 0.001$). But not between group 2 and group 3 ($p = 0.99$). Tumor thickness - significant difference between group 1 and group 2 ($p < 0.001$) and between group 1 and 3 ($p < 0.001$) but not between group 2 and group 3 ($p = 0.42$). LogMAR visual acuity - significant difference between group 1 and group 2 ($p = 0.002$) and group 1 and group 3 ($p < 0.001$) but not between group 2 and group 3 ($p = 0.25$).

Table 3. Circumscribed choroidal hemangioma analysis by age group in 458 cases. Imaging features at presentation.

Imaging features	Age ≤ 20 n = 31 tumors in 31 patients (%)	Age > 20–50 n = 182 tumors in 181 patients (%)	Age > 50 n = 245 tumors in 245 patients (%)	*p*-value	Total N = 458 tumors in 457 patients (%)
Autofluorescence	n = 12	n = 62	n = 119		N = 193
Orange pigment extent on tumor surface					
0%	9 (75)	37 (60)	68 (57)		114 (59)
<25%	0 (0)	12 (19)	25 (21)		37 (19)
25–50%	3 (25)	9 (15)	16 (13)	0.36	28 (15)
50–75%	0 (0)	4 (6)	4 (3)		8 (4)
>75%	0 (0)	0 (0)	6 (5)		6 (3)
Orange pigment quality					
Geographic	3 (25)	22 (35)	45 (38)		70 (36)
Clumped	0 (0)	1 (2)	5 (4)	0.77	6 (3)
Diffuse	0 (0)	2 (3)	1 (1)		3 (2)
Retinal pigment epithelium trough	1 (8)	6 (10)	12 (10)	0.99	19 (10)
Ultrasonography	n = 28	n = 168	n = 221		N = 417
B-scan acoustic quality					
Solid	27 (96)	163 (97)	218 (99)	0.32	9 (2)
Hollow	1 (4)	5 (3)	3 (1)		408 (98)
Fluorescein angiography (FA)	n = 23	n = 136	n = 178		N = 337
Prearterial phase hyperfluorescence	20 (87)	127 (93)	167 (94)	0.46	314 (93)
Arterial phase hyperfluorescence	21 (91)	134 (99)	171 (96)	0.42	326 (97)
Venous phase hyperfluorescence	20 (87)	134 (99)	175 (42)	0.16	329 (98)
Late phase hyperfluorescence	19 (82)	129 (95)	168 (94)	0.98	316 (94)
Cystoid macular edema	2 (9)	8 (6)	3 (18)	0.06	13 (4)
Indocyanine green angiography (ICGA)	n = 4	n = 69	n = 126		N = 199
Early tumor hypercyanescence (1 min)	4(100)	67 (97)	119 (94)	0.82	190 (95)
Mid tumor hypercyanescence (8 min)	4(100)	67 (97)	122 (97)	0.30	193 (97)
Late tumor hypocyanescence (20 min)	4(100)	44 (64)	58 (46)	0.56	106 (53)
Optical coherence tomography	n = 13	n = 67	n = 120		N = 200
Subretinal fluid	10 (77)	51 (76)	76 (63)	**<0.001**	137 (69)
Photoreceptor status					
Shaggy	8 (80)	46 (90)	72 (95)		126 (28)
Retracted	0 (0)	3 (6)	3 (4)	0.11	6 (3)
Absent	2 (20)	2 (4)	1 (1)		5 (3)
Macular status					
Macular subretinal fluid	6 (46)	35 (52)	39 (32)	0.82	80 (40)
Cystoid macular edema	3 (23)	9 (13)	11 (9)	0.92	23 (12)
Macular atrophy	0 (0)	1 (1)	5 (4)	0.22	6 (3)

Bold values indicate significant *p*-value.

Table 4. Circumscribed choroidal hemangioma analysis by age group in 458 cases. Treatment features.

Treatment features	Age ≤ 20 n = 31 tumors in 31 patients (%)	Age > 20–50 n = 182 tumors in 181 patients (%)	Age > 50 n = 245 tumors in 245 patients (%)	*p*-value	Total N = 458 tumors in 457 patients (%)
Reason for treatment*	n = 18	n = 105	n = 102		N = 225
Subretinal fluid progression	9 (50)	26 (25)	28 (28)	0.07	63 (28)
Subretinal fluid at fovea	7 (39)	74 (71)	64 (63)		145 (64)
Exudation	0 (0)	2 (2)	2 (2)		4 (2)
Hemorrhage	0 (0)	0 (0)	0 (0)		0 (0)
Macular edema	2 (11)	2 (2)	8 (8)		12 (1)
Choroidal neovascular membrane	0 (0)	0 (0)	0 (0)		0 (0)
Blind painful eye	0 (0)	1 (1)	0 (0)		1 (<1)
Primary treatment modality	n = 31	n = 175	N = 241		N = 447
Observation	12 (39)	68 (39)	135 (56)	**<0.001**	215 (48)
Argon laser photocoagulation	3 (10)	45 (26)	43 (18)		91 (20)
PDT	3 (10)	47 (27)	52 (22)		102 (23)
Transpupillary thermotherapy	0 (0)	1 (1)	0 (0)		1 (0.2)
Plaque radiotherapy	8 (26)	11 (6)	8 (3)		27 (6)
External beam radiotherapy	4 (13)	2 (1)	0 (0)		6 (1)
Transcleral diathermy	0 (0)	0 (0)	0 (0)		0 (0)
Sub-Tenon's triamcinolone	0 (0)	0 (0)	0 (0)		0 (0)
Intravitreal triamcinolone	0 (0)	0 (0)	0 (0)		0 (0)
Intravitreal anti-VEGF	0 (0)	0 (0)	2 (1)		2 (<1)
Enucleation	1(3)	1 (1)	1 (<1)		3 (1)
Secondary treatment modality	n = 23	n = 127	n = 168		N = 318
Observation	15 (65)	95 (75)	136 (81)	0.06	246 (77)
Argon laser photocoagulation	3 (13)	14 (11)	8 (5)		25 (8)
PDT	1 (4)	6 (5)	16 (10)		23 (7)
Transpupillary thermotherapy	0 (0)	0 (0)	2 (1)		2 (1)
Plaque radiotherapy	3 (13)	7 (6)	2 (1)		12 (4)
External beam radiotherapy	1 (4)	1 (1)	0 (0)		2 (1)
Transcleral diathermy	0 (0)	1 (1)	1 (1)		2 (1)
Sub-Tenon's triamcinolone	0 (0)	0 (0)	0 (0)		0 (0)
Intravitreal triamcinolone	0 (0)	0 (0)	1 (1)		1 (<1)
Intravitreal anti-VEGF	0 (0)	2 (2)	2 (1)		4 (1)
Enucleation	0 (0)	1 (1)	0 (0)		1 (<1)
Number of treatments Mean (median, range)					
Total	4 (2, 1–19)	2 (1, 0–12)	1 (1, 0–4)	**<0.001**	2 (1, 0–19)
PDT	2 (2, 0–7)	1 (1, 0–6)	1 (1, 0–7)	0.30	1 (1, 0–7)
Argon laser photocoagulation/ Transpupillary thermotherapy	1 (1, 0–2)	1 (1, 0–4)	1 (1, 0–3)	0.13	1 (1, 0–4)

Abbreviations: PDT = photodynamic therapy, VEGF = vascular endothelial growth factor, TTT = transpupillary thermotherapy.
Bold values indicate significant *p*-value.
Post Hoc analysis (Bonferroni test): Total number of treatments - significant difference between group 1 and group 2 ($p < 0.001$) and between group 1 and 3 ($p < 0.001$) but not between group 2 and group 3 ($p = 0.59$).
* Reason for treatment not available for patients (n = 7) who received primary treatment elsewhere.

The youngest patient category presenting with circumscribed choroidal hemangioma at age ≤20 years demonstrated greater frequency of Sturge-Weber syndrome, despite having a circumscribed and not a diffuse hemangioma. Additionally the young category showed worse presenting visual acuity, larger tumor basal diameter and thickness, more posterior tumor location, and greater extent of SRF. The youngest patients were less likely to be managed with observation as their disease more often demonstrated activity and visual loss, and they were less likely to be managed with primary photodynamic therapy (PDT) as patient cooperation for laser delivery is critical with this method. This young category was more likely to receive treatment with radiation (plaque radiotherapy or external beam radiotherapy). Final visual acuity was poorest in the youngest patients, but after adjustment for presenting visual acuity, this was no longer significant. There was no difference between age groups in visual acuity loss of 3 or more Snellen lines, final status of SRF, cystoid retinal edema, macular SRF, CME, retinal exudation, or retinal hemorrhage.

The poorer visual acuity in young patients could be a reflection of larger tumor size and greater amount of SRF or possibly related to underlying GNAQ R183Q mutation found in some of the choroidal vessels in a single published case of Sturge Weber syndrome.[9] However, differences in visual acuity and tumor size by age category remained significant even after exclusion of Sturge-Weber patients on subanalysis, indicating that younger patients with circumscribed choroidal hemangioma have worse visual prognosis even in the absence of an associated systemic syndrome. Thus, younger patients were more likely to be managed with radiotherapy for more extensive disease, often with persistent poor visual acuity after treatment. While children might not be able to cooperate for office laser procedures, treatment with PDT at an earlier point, especially in children, could potentially improve visual outcomes.

Table 5. Circumscribed choroidal hemangioma analysis by age group in 458 cases. Outcomes.

Outcomes	Age ≤ 20 n = 31 tumors in 31 patients (%)	Age > 20–50 n = 182 tumors in 181 patients (%)	Age > 50 n = 245 tumors in 245 patients (%)	*p*-value	Total N = 458 tumors in 457 patients (%)
No follow-up	9 (29)	63 (35)	76 (31)	0.65	148 (33)
Follow-up duration (months) (n = 457 patients) Mean (median, range)	44 (35, 1–272)	68 (35, 0–409)	60 (28, 0–355)	0.37	62 (32, 0–409)
Visual acuity	n = 19	n = 116	n = 168		N = 303
≥20/40	4 (21)	52 (45)	78 (46)		134 (44)
20/50–20/200	4 (21)	28 (24)	53 (32)	**0.01**	85 (28)
<20/200	11 (58)	36 (31)	37 (22)		84 (28)
Visual acuity (Snellen) Mean (median, range)	20/400 (20/400, 20/20-NLP)	20/200 (20/60, 20/20-NLP)	20/100 (20/50, 20/20-NLP)		20/150 (20/60, 20/20-NLP)
Visual acuity (LogMAR) Mean (median, range)	1.50 (1.30, 0.00–5.00)	0.96 (0.48, 0.00–5.00)	0.77 (0.40, 0.00–5.00)	**0.03**[a]	0.89 (0.48, 0.00–5.00)
Visual acuity	n = 8	n = 115	n = 167		N = 290
≥20/40	2 (25)	52 (45)	78 (47)		132 (46)
20/50–20/200	1 (13)	27 (24)	53 (32)	**0.05**	81 (28)
<20/200	5 (63)	36 (31)	36 (22)		77 (27)
Visual acuity (Snellen) Mean (median, range)	20/400 (CF, 20/20-NLP)	20/200 (20/60, 20/20-NLP)	20/100 (20/50, 20/20-NLP)		20/150 (20/60, 20/20-NLP)
Visual acuity (LogMAR) Mean (median, range)	1.60 (1.70, 0.00–5.00)	0.97 (0.48, 0.00–5.00)	0.74 (0.40, 0.00–5.00)	**0.03**	0.86 (0.40, 0.00–5.00)
If visual acuity ≥ 20/40 at presentation (n = 131 eyes), final visual acuity	n = 4	n = 48	n = 78		N = 130
≥20/40	2 (50)	31 (65)	57 (73)		90 (69)
20/50–20/200	2 (50)	12 (25)	17 (22)	0.50	31 (24)
<20/200	0 (0)	5 (10)	4 (5)		9 (7)
If visual acuity 20/50–20/200 at presentation (n = 114 eyes), final visual acuity	n = 7	n = 47	n = 60		N = 114
≥20/40	1 (14)	20 (43)	20 (33)		41 (36)
20/50–20/200	0 (0)	14 (30)	27 (45)	**0.004**	41 (36)
<20/200	6 (86)	13 (28)	13 (22)		32 (28)
If visual acuity < 20/200 at presentation (n = 57 eyes), final visual acuity	n = 8	n = 21	n = 28		N = 57
≥20/40	1 (12)	1 (5)	1 (4)		3 (5)
20/50–20/200	2 (25)	2 (10)	8 (29)	0.44	12 (21)
<20/200	5 (63)	18 (86)	19 (68)		42 (74)
Visual acuity loss ≥ 3 lines	n = 22	n = 120	n = 167		N = 309
	6 (27)	15 (13)	27 (16)	0.55	48 (16)
Visual acuity loss ≥ 3 lines excluding SWS	n = 8	n = 115	n = 167		N = 290
	1 (10)	21 (18)	25 (15)	0.76	47 (16)
Total visual acuity lines lost Mean (median, range)	2 (2, 0–8)	3 (2, 0–14)	3 (2, 0–11)	0.57	3 (2, 0–14)
Reason for visual acuity loss ≥ 3 lines	n = 6	n = 15	n = 27		N = 48
Cataract	0 (0)	0 (0)	3 (11)	0.95	3 (6)
Epiretinal membrane	0 (0)	0 (0)	1 (4)		1 (2)
Cystoid macular edema	0 (0)	2 (1)	2 (7)		4 (8)
Subretinal fluid	2 (33)	4 (5)	9 (33)		15 (42)
Foveal outer retinal atrophy	0 (0)	3 (1)	1 (4)		4 (8)
Subfoveal orange pigment	0 (0)	0 (0)	0 (0)		0 (0)
Choroidal neovascular membrane	0 (0)	0 (0)	1 (4)		1 (2)
Retinal pigment epithelium atrophy	0 (0)	1 (1)	2 (7)		3 (6)
Radiation maculopathy	0 (0)	1 (1)	1 (4)		2 (4)
Radiation papillopathy	0 (0)	0 (0)	0 (0)		0 (0)
Unknown	4 (67)	4 (20)	7 (26)		15 (21)

(continued on next page)

Table 5 (*continued*)

Outcomes	Age ≤ 20 n = 31 tumors in 31 patients (%)	Age > 20–50 n = 182 tumors in 181 patients (%)	Age > 50 n = 245 tumors in 245 patients (%)	*p*-value	Total N = 458 tumors in 457 patients (%)
Tumor dimensions by clinical exam					
Tumor diameter (mm) Mean (median, range)	10.4 (10.0, 7.0–16.0)	6.1 (6.0, 1.0–12.0)	6.1 (6.0, 2.0–12.0)	**<0.001**	6.3 (6.0, 1.0–16.0)
Tumor thickness (mm) Mean (median, range)	3.4 (3.0, 2.0–7.0)	2.7 (2.5, 1.0–5.0)	2.6 (2.7, 0.0–6.0)	**0.004**	2.7 (2.6, 0.0–7.0)
Tumor dimensions excluding SWS	n = 8	n = 115	n = 167		N = 290
Tumor diameter (mm) Mean (median, range)	10.4 (10.0, 7.0–16.0)	6.1 (6.0, 1.0–12.0)	6.1 (6.0, 2.0–12.0)	**<0.001**	6.3 (6.0, 1.0–16.0)
Tumor thickness (mm) Mean (median, range)	3.4 (3.0, 2.0–7.0)	2.7 (2.5, 1.0–5.0)	2.6 (2.7, 0.0–6.0)	**0.004**	2.7 (2.6, 0.0–7.0)
Tumor related features by optical coherence tomography	n = 10	n = 62	n = 95		N = 167
Subretinal fluid (SRF)					
SRF resolved completely	8 (80)	38 (61)	51 (54)	0.23	97 (58)
SRF resolved partially	2 (20)	9 (15)	11 (12)		22 (13)
SRF unchanged	0 (0)	2 (3)	1 (1)		3 (2)
SRF increased	0 (0)	5 (8)	4 (4)		9 (5)
New SRF	0 (0)	0 (0)	2 (2)		2 (1)
Never SRF	0 (0)	8 (13)	26 (27)		34 (20)
Cystoid retinal edema	n = 10	n = 56	n = 86		N = 152
Cystoid edema resolved completely	2 (20)	6 (11)	6 (7)	0.33	14 (9)
Cystoid edema resolved partially	2 (20)	7 (13)	6 (7)		15 (10)
Cystoid edema worse	0 (0)	1 (2)	1 (1)		2 (1)
New cystoid edema	0 (0)	6 (11)	5 (6)		11 (7)
Never cystoid edema	6 (60)	36 (64)	68 (79)		110 (72)
Macula status by optical coherence tomography	n = 10	n = 56	n = 94		N = 160
Subretinal fluid (SRF)					
SRF resolved completely	8 (80)	37 (66)	58 (62)	0.91	103 (64)
SRF resolved partially	1 (10)	5 (9)	9 (10)		15 (9)
SRF increased	0 (0)	3 (5)	2 (2)		5 (3)
New SRF	0 (0)	1 (2)	3 (3)		4 (3)
Never SRF	1 (10)	10 (18)	22 (23)		33 (21)
Cystoid macular edema (CME)	n = 10	n = 56	n = 93		N = 159
CME resolved completely	4 (40)	13 (23)	7 (8)	0.06	24 (15)
CME resolved partially	1 (10)	3 (5)	7 (8)		11 (7)
CME worse	0 (0)	3 (5)	2 (2)		5 (3)
New CME	0 (0)	2 (4)	5 (5)		7 (4)
Never CME	5 (50)	35 (63)	72 (77)		112 (7)
Related retinal findings	n = 22	n = 119	n = 167		N = 308
Retinal exudation	1 (5)	8 (7)	3 (2)	0.58	12 (4)
Retinal hemorrhage	0 (0)	4 (3)	1 (1)	0.56	5 (2)

Bold values indicate significant *p*-value.

Abbreviations: SWS = Sturge-Weber syndrome.

Post Hoc analysis (Bonferroni test): Tumor base - significant difference between group 1 and group 2 ($p < 0.001$) and between group 1 and 3 ($p < 0.001$) but not between group 2 and group 3 ($p = 0.99$). Tumor thickness - significant difference between group 1 and group 2 ($p = 0.009$) and between group 1 and 3 ($p = 0.003$) but not between group 2 and group 3 ($p = 0.99$). Visual acuity (LogMAR) - significant difference between group 1 and group 3 ($p = 0.036$) but not between group 1 and group 2 ($p = 0.23$) or between group 2 and group 3 ($p = 0.46$).

[a] Using linear regression, after adjusting for visual acuity (LogMAR) at presentation the association between age and final visual acuity (LogMAR) was not significant (p = 0.90).

We recently investigated treatment outcomes for circumscribed choroidal hemangioma in 458 cases in the PDT and pre-PDT eras, demonstrating that patients treated in the PDT era regained better visual acuity outcomes with mean LogMAR visual acuity of 0.51 (Snellen equivalent 20/60) versus 1.28 (Snellen equivalent 20/400) in the pre-PDT era ($p < 0.001$).[10] Further comparison (PDT era vs. pre-PDT era) demonstrated that patients with better entering visual acuity ≥20/40 maintained better final visual acuity ≥20/40 in the PDT era (75% vs. 60%, $p < 0.001$) and those with mediocre entering visual acuity of 20/50–20/200 better regained ≥ 20/40 in the PDT era (47% vs. 25%, $p < 0.001$).[10] Other small series have found similarly improved visual outcomes with PDT.[11,12] In a small cohort comparison (PDT vs. laser photocoagulation) (5 vs. 23 cases), Scott et al found complete resolution of SRF (100% vs. 57%) and stable or improved visual acuity (100% vs. 83%).[11] In a comparison of radiotherapy (external beam radiotherapy (n = 23), plaque radiotherapy (n = 3)) vs. PDT (n = 16), Papastefanou et al found no difference in visual acuity improvement between groups but noted radiation complications in 10/23 (44%) eyes treated with external beam radio-

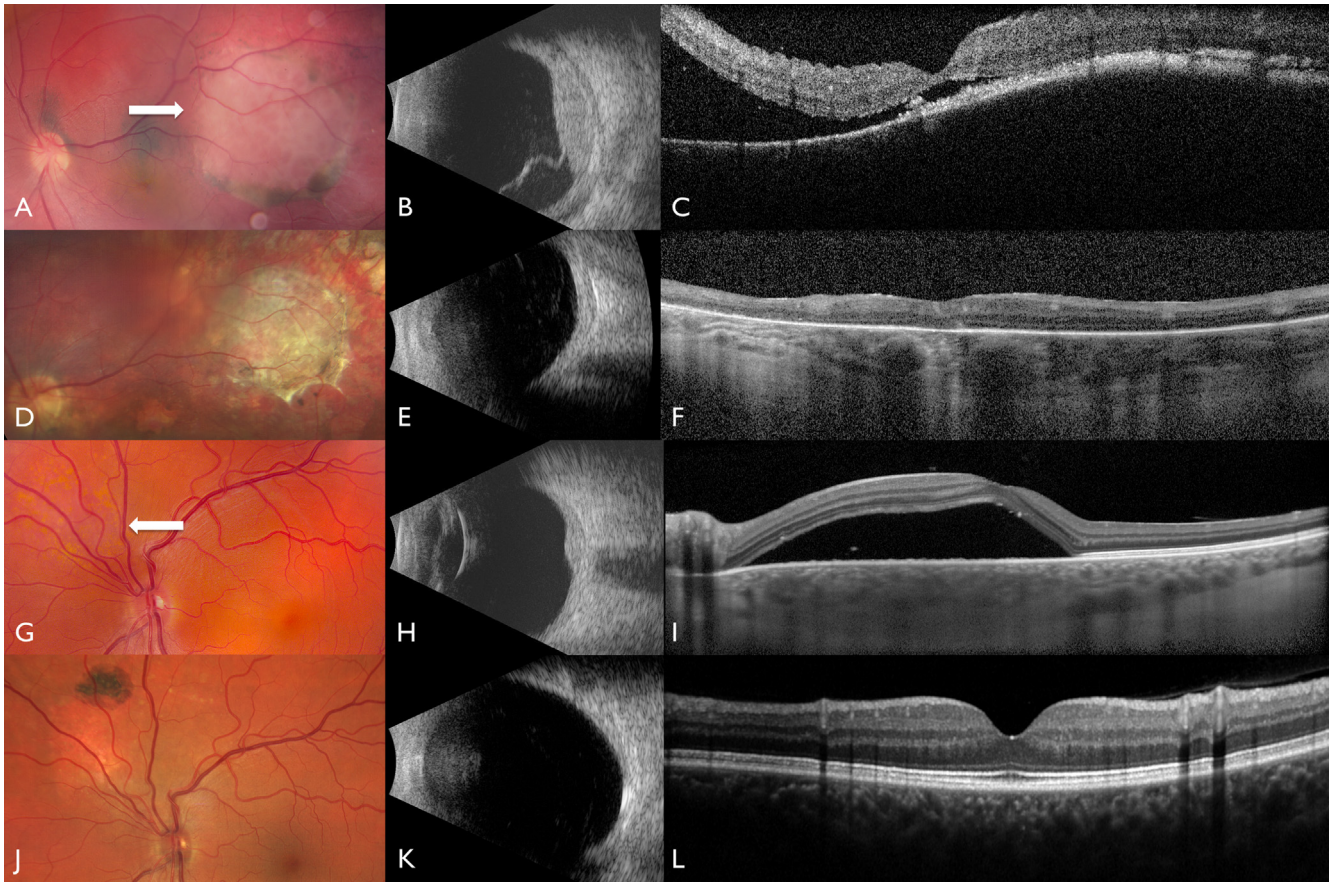

Fig. 1. Circumscribed choroidal hemangioma presenting features and outcomes in young (≤20 years) versus middle (>20–50 years) and older (>50 years) patients. (A) An 11-year-old white male presented with poor visual acuity of 20/200 in his left eye secondary to a macular-involving circumscribed choroidal hemangioma (arrow) of 16 mm in largest basal diameter and (B) 5.3 mm in thickness by ultrasonography with associated (C) submacular subretinal fluid by optical coherence tomography (OCT). (D) Following plaque radiotherapy, the tumor regressed to (E) 1.9 mm in thickness by ultrasonography with (F) resolution of subretinal fluid by OCT and final visual acuity of 20/400 secondary to outer retinal atrophy. (G) A 44-year-old white male presented with decreased visual acuity to 20/70 in his left eye secondary to a circumscribed choroidal hemangioma (arrow) located superonasal to the optic disc measuring 6 mm in largest basal diameter and (H) 2.6 mm in thickness by ultrasonography with (I) associated subretinal fluid tracking into the macula by OCT. (J) Following treatment with photodynamic therapy the tumor regressed to (K) 1.9 mm in thickness by ultrasonography with (L) resolution of subretinal fluid by OCT and improvement in visual acuity to 20/20.

therapy and 2/3 (67%) eyes treated with plaque, which could have long-term adverse effects on visual acuity.[12] These side effects could be particularly detrimental in younger patients who might experience gradual loss of visual acuity over many years and could require ongoing anti-VEGF therapy. Future studies should investigate whether PDT can improve outcomes in this group of patients.

Limitations of this study include its retrospective design and non-standardized treatment regimens, with evolution in management of choroidal hemangioma over the 50-year time period. Each imaging modality was not performed in each patient, with increased availability of OCT in more recent years, allowing for improved detection of SRF. These developmental changes affected all age groups. We also acknowledge that patients with circumscribed choroidal hemangioma in the setting of Sturge-Weber syndrome were included. Some of these patients could have been previously classified as diffuse choroidal hemangioma due to the systemic association. However, only localized lesions with crisp margins were included in this study. Moreover, differences in tumor size and visual acuity between age categories remained significant on sub-analysis with exclusion of those with Sturge-Weber syndrome. Study strengths include the large number of subjects managed at a single center with follow-up over several years to decades for most patients. To our knowledge, prior large series have not specifically examined choroidal hemangioma features and outcomes based on age at presentation.

Conclusion

In summary, in this study of circumscribed choroidal hemangioma, the youngest patients (≤20 years) had poorest presenting visual acuity, larger tumor basal diameter and thickness, more posterior tumor location, greater extent of SRF, more frequent management with radiotherapy, and worse final visual acuity. Future studies should promote early detection and investigate improved treatment modalities for these patients.

Conflict of interest

The authors declared that there is no conflict of interest.

Acknowledgements

Support provided in part by the Eye Tumor Research Foundation, Philadelphia, PA (CLS). The funders had no role in the design and conduct of the study, in the collection, analysis and interpretation of the data, and in the preparation, review or approval of the manuscript.

References

1. Shields CL, Honavar SG, Shields JA, et al. Circumscribed choroidal hemangioma: Clinical manifestations and factors predictive of visual outcome in 200 consecutive cases. *Ophthalmology* 2001;**108**(12):2237–48.
2. Karimi S, Nourinia R, Mashayekhi A. Circumscribed choroidal hemangioma. *J Ophthalmic Vis Res* 2015;**10**(3):320–8.
3. Mashayekhi A, Shields CL. Circumscribed choroidal hemangioma. *Curr Opin Ophthalmol* 2003;**14**(3):142–9.
4. Krohn J, Rishi P, Froystein T, Singh AD. Circumscribed choroidal haemangioma: Clinical and topographical features. *Br J Ophthalmol* 2019.
5. Shields JA, Shields CL, Materin MA, et al. Changing concepts in management of circumscribed choroidal hemangioma: the 2003 J. Howard Stokes Lecture, Part 1. *Ophthalmic Surg Lasers Imaging* 2004;**35**(5):383–94.
6. Anand R, Augsburger JJ, Shields JA. Circumscribed choroidal hemangiomas. *Arch Ophthalmol* 1989;**107**(9):1338–42.
7. Shields JA, Shields CL. *Intraocular tumors. An atlas and textbook*. 3rd ed. Lippincott Wolters Kluwer; 2016. p. 247–63.
8. Arevalo JF, Shields CL, Shields JA, et al. Circumscribed choroidal hemangioma: characteristic features with indocyanine green videoangiography. *Ophthalmology* 2000;**107**(2):344–50.
9. Bichsel CA, Goss J, Alomari M, et al. Association of somatic GNAQ mutation with capillary malformations in a case of choroidal hemangioma. *JAMA Ophthalmol* 2018.
10. Shields CL, Dalvin LA, Lim LS, et al. Circumscribed choroidal hemangioma: visual outcome in the pre-photodynamic therapy (PDT) vs PDT eras in 458 cases; 2019 in press.
11. Scott IU, Gorscak J, Gass JD, et al. Anatomic and visual acuity outcomes following thermal laser photocoagulation or photodynamic therapy for symptomatic circumscribed choroidal hemangioma with associated serous retinal detachment. *Ophthalmic Surg Lasers Imaging* 2004;**35**(4):281–91.
12. Papastefanou VP, Plowman PN, Reich E, et al. Analysis of long-term outcomes of radiotherapy and verteporfin photodynamic therapy for circumscribed choroidal hemangioma. *Ophthalmology Retina* 2018;**2**(8):842–57.