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Analysis of Long-term Outcomes of Radiotherapy and Verteporfin Photodynamic Therapy for Circumscribed Choroidal Hemangioma

Vasilios P. Papastefanou, MD, PhD,[1] P. Nicholas Plowman, FRCR,[2] Ehud Reich, MD,[1] Efthymia Pavlidou, MD,[1] Marie Restori, PhD,[3] John L. Hungerford, FRCOphth,[1] Amit K. Arora, MBBS, FRCOphth,[1] Victoria M.L. Cohen, MB, BChir, FRCOphth,[1] Mandeep S. Sagoo, MB, PhD, FRCS (Ed)[1,4]

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: Observation, verteporfin (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 between January 2000 and June 2014; 42 (70%) received treatment. These were LS-EBRT (23/60 [38%]; mean follow-up, 45.5 months), PDT (16/60 [27%]; mean follow-up, 38 months), and plaque radiotherapy (3/60 [5%]; mean follow-up, 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 ± standard deviation, 1.65±1.6; range, −6.5 to +0.7). The mean ± standard deviation 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, the median decrease in thickness was 0.95 mm (mean ± standard deviation, 1.0±0.8; range, −2.5 to +0.2). The mean ± standard deviation 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 difference in decrease in tumor thickness or BCVA gain between the LS-EBRT and PDT groups. With plaque brachytherapy, the mean decrease in thickness was 2.5 mm, but BCVA loss of >2 Snellen lines was noted in all 3 cases at the end of follow-up. Radiation complications developed in 10 of 23 cases (43.5%) from the LS-EBRT group and 2 of 3 cases (67%) from the plaque brachytherapy group.

Conclusions: 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. *Ophthalmology Retina 2017;■:1−16 © 2017 by the American Academy of Ophthalmology*

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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 decades of life. Its pathogenesis is unknown. The tumor is often overlooked on routine eye examination or is misdiagnosed. The differential diagnosis of CCH includes highly vascular amelanotic melanoma, early choroidal osteoma, and orange-colored 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, although symptoms can occur as a direct function of the tumor location or behavior.[1,2] Subfoveal tumors can induce unilateral hypermetropic shift as a result of anterior displacement of the

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retina.[4] Juxtafoveal or parafoveal tumors cause vision loss if associated with exudative subretinal fluid or retinoschisis.

A variety of modalities 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 (PDT) 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 CCH.

Patients and Methods

This retrospective, observational study included referred CCH cases from January 2000 to June 2014. Institutional Review Board and 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), and fluorescein and indocyanine green angiography as required. Spectral-domain OCT (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).

Data collected included patient demographics (age, sex, presenting symptom), visual acuity (decimal scale and Snellen lines) and tumor features (height, maximal diameter, associated clinical findings). B-ultrasonography and spectral-domain OCT measurements were obtained from the automated software and manual measurements as needed to avoid discrepancy because of the different software platforms. Visual acuity was assessed during the study—before treatment, 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, and ≥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 PDT, or plaque radiotherapy. All patients received these as first-line treatment. The nontreatment group consisted of patients who did not require treatment during the follow-up period.

Studies in the literature were identified by a systematic search using Medline. Terms searched were as follows: "choroidal hemangioma" along with "photodynamic therapy," "external beam radiotherapy," and "plaque brachytherapy." In reports referring to the treatment of choroidal hemangiomas with PDT, published results on protocol settings, lesion thickness, and visual acuity outcomes were collected and analyzed. Visual acuity outcomes presented were converted to the decimal scale for analysis purposes.

Lens-sparing External Beam Radiotherapy

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

PDT with Verteporfin

PDT (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) based on lesion size. The PDT-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 s) or double (166 s) duration.

Plaque Brachytherapy

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

Efficacy and Safety

The efficacy of different treatment modalities was determined by best-corrected visual acuity (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 the follow-up period. Radiation retinopathy and other complications of treatment were recorded.

Statistical Analysis

Descriptive statistical analysis, with the χ^2 and nonparametric Mann–Whitney tests, was used to evaluate the findings after prior Kolmogorov-Smirnov tests indicating the presence of nonnormal 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 the 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 significant.

Collected data from previous studies were analyzed with descriptive statistics, analysis of variance, and the *t* test. A difference of 0.05 was considered statistically significant. Analysis was done with SPSS v.11 (IBM Corp, Armonk, NY).

Results

There were 60 consecutive cases of CCH included in the study. The median age at presentation was 61.5 years (mean ± standard deviation [SD], 58±15 years; range, 18–87 years) 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 summarized in Table 1.

At baseline, the median tumor height was at 2.6 mm (mean ± SD, 2.7±1.0 mm; range, 1.0–6.6 mm) and the median maximal diameter was 7 mm (mean ± SD, 7.0±2.7 mm; range, 2.5–16.3 mm). Subretinal fluid was present on clinical examination in 46 of 60 patients (77%). An OCT scan was available for 28 patients and the median central retinal subfield thickness was