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## Review Article

# Role of Radiation Therapy for Choroidal Hemangioma: A Brief Review

### Abstract

Choroidal hemangioma is an uncommon benign vascular hamartoma. Depending on the extent of the involved choroid, it can be subtyped into circumscribed form that occurs sporadically as an isolated tumor or a diffuse form that occurs in association with Sturge-Weber syndrome. It appears as an orange-red mass, located commonly posterior to the equator and is mostly asymptomatic. Poor vision is attributed to exudative retinal detachment, cystoid macular edema, foveal distortion and refractive errors. Diagnosis is crucial and is aided by ancillary tests such as ophthalmic ultrasonography, fundus fluorescein angiogram and Indocyanine green angiogram. The aim of treatment is to induce tumor atrophy, resolve the exudates, improve the vision, preserve the overlying retinal function and salvage the globe. Symptomatic tumors are treated by various treatment methods such as laser photocoagulation, transpupillary thermotherapy, photodynamic therapy and radiation therapy. Though external beam radiotherapy is a safe and effective treatment method, radiation induced complications limited its utility. Advanced radiation delivery techniques (such as proton beam therapy, plaque brachytherapy and stereotactic radiosurgery with Gamma Knife Radiosurgery) precisely target the tumor without damaging surrounding ocular tissues. These focal treatment methods enhance both in regressing the tumor, resolve the subretinal fluid/exudates thereby re-attaching retina and preserve or stabilize the visual acuity. The radiation induced ocular side effects are less with these newer radiation delivery methods. Anti-vascular endothelial growth factors and oral  $\beta$ -blockers are newer treatment methods available for treating choroidal hemangiomas.

## Abbreviations

CH: Choroidal Hemangioma; CCH: Circumscribed Choroidal Hemangioma; DCH: Diffuse Choroidal Hemangioma; Gy: Gray; TTT: Transpupillary Thermotherapy; PDT: Photodynamic Therapy; EBRT: External Beam Radiotherapy; PBT: Proton Beam Radiation; PB: Plaque Brachytherapy; GKRS: Gamma Knife Radiosurgery; VEGF: Vascular Endothelial Growth Factor; CGE: Cobalt Gray Equivalent; RD: Retinal Detachment; CME: Cystoid Macular Edema; SRF: Subretinal Fluid; RPE: Retinal Pigment Epithelium; OCT: Optical Coherence Tomography; FFA: Fundus Fluorescein Angiogram; ICG-A: Indocyanine Green Angiogram; AF: Auto Fluorescence; Mw: Milli Watt; J: Joules

## Introduction

Choroidal hemangiomas (CH) are benign vascular hamartomas. They are rare congenital ocular tumors, commonly located in the posterior fundus. Depending on the extent of choroidal involvement, they can be subtyped into circumscribed or diffuse. They are mostly asymptomatic until adulthood and can be diagnosed either on routine examination or when they cause significant visual disturbances [1-4]. They are common in the Caucasian population with no gender preferences. Proper diagnosis is crucial and can be achieved with ancillary tests. Multiple treatment modalities are available for the treatment of CH. This brief review focuses mainly on radiation therapy methods and their effect on choroidal hemangioma.

## Clinical features

Circumscribed choroidal hemangiomas (CCH) are solitary isolated tumors that occur sporadically with no associated systemic

conditions [1-3]. The etiology is unknown. They occur at older age (2<sup>nd</sup> to 4<sup>th</sup> decade of life) and are mostly asymptomatic for longer duration. They are commonly located in the posterior pole and appear as orange-red masses. There may be a pigmented rim at the margin of the tumor and can be associated with subretinal fluid (SRF). They are usually less than 6 mm in height but the size can vary along with different basal dimensions. At younger age, they are commonly asymptomatic. After some time, patients can experience symptoms such as diminution of vision, metamorphopsia, photopsia, visual field changes or progressive hyperopia due to exudative retinal detachment (RD), cystoid macular edema (CME), retinal pigment epithelial (RPE) changes and choroidal fibrosis. Progressive enlargement of the tumor with visual deterioration may occur over decades in CCH. Diffuse choroidal hemangiomas (DCH) are usually present at birth in association with Sturge-Weber syndrome (encephalofacial hemangiomatosis). They are usually unilateral and are present ipsilateral to the nevus flammeus (port-wine stain) in most of the cases, but can be bilateral. DCH are generally dark red-orange tumors (tomato-catsup fundus) and can cause diffuse choroidal thickening with less delineating pigmented margins [1-3]. Causes for poor vision in DCH are exudative RD, foveal distortion and refractive errors. Amblyopia induced by progressive hyperopia is the leading cause of vision loss in young children with DCH and subfoveal CCH. Choroidal hemangiomas can be mistaken for amelanotic choroidal melanoma, choroidal metastasis, granuloma, osteomas, posterior scleritis or lymphomas. Histopathologically, depending on the type of abnormal tumor blood vessels, they can be classified into cavernous, capillary or mixed. They are usually non-proliferative

tumors. Progressive venous congestion leads to the increased size of these tumors than the cellular proliferation. Other pathological features noted with CH are pigmentary changes with overlying RPE hyperplasia, overlying retinal degeneration with cystoid edema and overlying orange-pigment due to lipofuscin [1-6].

## Diagnosis

Apart from fundus photographs, ancillary tests such as ultrasonography, optical coherence tomography (OCT), fundus fluorescein angiography (FFA), Indocyanine green angiography (ICG-A) are helpful in differentiating these lesions from other choroidal lesions [3-5]. With indirect ophthalmoscopy using a 20 diopter lens, non-pigmented orange-red lesions can be seen in the posterior pole near the optic disc region. Other associated features seen are retinal detachment (serous or exudative), macular edema, RPE changes, subretinal fibrosis overlying the lesion and occasional orange pigment. On Ultrasonography, CCH are acoustically solid, oval or dome shaped (B-scan) lesions with high internal reflectivity (A-scan). Whereas DCH are flat lesions with diffuse choroidal thickening. There are no visible intrinsic vascular pulsations with choroidal hemangiomas. Early arterial filling phase of fluorescein angiogram shows hyperfluorescent mass with fine network of choroidal blood vessels followed by increasing fluorescence in late phases. FFA does not provide much diagnostic information for choroidal hemangioma. Indocyanine green angiogram is a best non-invasive tool both in diagnosis and treatment follow-up of CH. ICG-A reveals intrinsic vascular pattern in early filling phases (30 seconds) followed by rapid hyperfluorescence in late phases (3-4 minutes) and dye washout in later phases (30-60 minutes). Dye wash out is commonly seen with CCH than DCH [3-5]. OCT is helpful to demonstrate mild or shallow subretinal fluid, cystoid macular edema and epiretinal membrane (ERM). In chronic cases of CH, OCT shows overlying RPE changes and subretinal fibrosis. Enhanced depth Imaging-Spectral Domain (SD) OCT, a newer OCT tool is used to assess the diffuse choroidal thickening both pre and post treatment of CH. SD-OCT is helpful in distinguishing the acute (exudative RD with preserved retinal architecture) from chronic (retinal atrophy) changes in CH. Fundus autofluorescence (AF) detects the disturbances in the RPE-photoreceptor complex. Choroidal hemangiomas reveal less intrinsic AF. Extrinsic hyperautofluorescence of CH indicates overlying orange pigment & fresh subretinal fluid and hypoautofluorescence indicates RPE hypertrophy, atrophy & fibrous metaplasia [6]. Magnetic resonance imaging (MRI) of the brain is done to detect the leptomeningeal lesions in patients with DCH and also in follow-up after treatment.

## Treatment

The goal of treatment in choroidal hemangiomas is to regress/destroy the tumor vessels which induces tumor atrophy, to prevent fluid leakage which resolves the subretinal fluid and to improve or stabilize the vision loss. Treatment options are observation, laser photocoagulation, transpupillary thermotherapy (TTT), photodynamic therapy (PDT), external beam radiotherapy (EBRT), proton beam therapy (PBT), plaque brachytherapy, stereotactic radiotherapy such as gamma knife radiosurgery (GKRS), anti-vascular endothelial growth factors (VEGF), oral  $\beta$ -blockers and enucleation

[7-36]. The aim of any treatment is also to preserve the overlying retinal function and prevent distortion of foveal architecture along with achieving the above goals.

Observation is usually reserved for solitary circumscribed choroidal hemangiomas located in extra-macular area with no associated RD. Frequent follow-up of asymptomatic patients with Sturge-Weber syndrome and DCH is done to check for exudates, macular edema and increasing tumor thickness [3].

## Laser therapies

Laser photocoagulation (xenon or argon) is rarely used nowadays as there are many advanced treatment methods available for managing choroidal hemangioma. It allows resolution of the sub retinal fluid in 40-60% of cases with improvement in visual acuity in 70% [3,7]. Laser photocoagulation is inappropriate for tumors located in the subfoveal region and it doesn't completely regress the tumor. The disadvantages of laser photocoagulation are retinal pigment epithelial atrophy, recurrence of SRF, retinal hemorrhages, persistent scotomas, vascular occlusions, ERM and choroidal neovascularization [3,7]. Recurrences are common with laser photocoagulation. This technique is not used currently due to advances in treatment modalities for CH.

Transpupillary thermotherapy (infrared diode laser at 810 nm (power range 800-1200 mW) with a large beam diameter (2 or 3 mm) for a longer duration (3-6 minutes)) is considered for extrafoveal, post-equatorial circumscribed choroidal hemangiomas with shallow SRF. TTT causes sclerosis of tumor vessels leading to complete regression of the tumor. It is helpful in total reabsorption of serous retinal detachment thereby re-attaching the retina and improving the visual acuity. The disadvantages of TTT are CME, choroidal atrophy, RPE hypertrophy, pre-retinal fibrosis, focal iris atrophy and retinal vascular occlusions [8,9,33].

Photodynamic therapy (laser wavelengths range of 689-692 nm at an intensity of 600 mW/cm<sup>2</sup> with duration of 83 seconds [50-100 J/cm<sup>2</sup>], one spot or multiple partial overlying spots) with intravenous verteporfin (dose of 6 mg/m<sup>2</sup>) is preferred in patients with isolated symptomatic CCH with localized RD where laser photocoagulation is ineffective [10-13]. PDT causes atrophy of hemangioma vessels that decreases the exudation thereby significantly improving the visual acuity. The response to a single session of PDT is 75-100% in resolving the SRF and stabilizing the vision. PDT is also an effective treatment modality in patients with visual deterioration due to exudates in DCH associated with Sturge-Weber syndrome in young children. The retina re-attaches completely with the resolution of macular edema after PDT. Following PDT, there is no recurrence of exudates for longer durations which preserved the visual acuity in children [12,13]. The advantage of PDT is that it protects the overlying retina without destroying its function and the retinal vessels. The tumor (CCH & DCH) regresses well both in height and basal dimensions following a single spot or overlapping multiple spots of PDT. Multiple sessions of PDT may cause choroidal atrophy and neurosensory retinal degeneration [10,11]. It is not associated with any major systemic or ocular complications and is a safe and effective method to perform in the office without the need for specialized centers/machines unlike radiation.

## Radiation therapy methods

Radiation therapy is recommended for choroidal hemangiomas that do not respond to laser photocoagulation, TTT or PDT, symptomatic CCH with extensive serous RD and DCH with exudative RD. CH can be treated with lens sparing low dose EBRT with high energy photons (20-25 Gray (Gy) in 10 fractions for few cases and 30-45 Gy for few cases) [14-18]. EBRT with 6MV photons at a dose range of 16-30 Gy for CCH, reduced the tumor height (95%), allowed total resolution of sub retinal fluid (93%) with re-attachment of retina especially in the macular region and stabilized visual acuity (93%). EBRT absorbed the exudates associated with DCH even at fractionated doses of 20-25 Gy. It improved visual acuity in 80% of the cases [14-16]. There is decrease in the anisometropia as the submacular infiltrated tumors regressed after EBRT [17,18]. Disadvantages of EBRT are slow absorption of SRF, recurrence or persistence of exudative RD. Additional or high doses of EBRT can cause more side-effects such as cataract, ocular surface syndrome, iris neovascularization, radiation papillopathy, maculopathy, retinopathy and secondary glaucoma. EBRT is a very effective treatment method for treating DCH and juxtapapillary CCH.

For patients with failure of response after PDT, *proton beam therapy* is considered as another alternative treatment option. It precisely delivers the radiation to the target tumor tissue by protecting the neighboring ocular structures. Prior to delivering the radiation, surgical placement of tantalum clips is necessary for tumor localization [15,19-22]. Choroidal hemangiomas treated with 20 Cobalt Gray Equivalent (CGE) of proton beam radiation showed 100% resolution of SRF, 90% regression of the tumor and improvement in visual acuity in 55% of cases [19,21]. In Sturge-Weber syndrome children with DCH associated with extensive RD, low dose of proton beam radiation (16-20 Gy in 4 fractions) achieved good success by salvaging the globe and also caused less radiation side effects [20]. Another study delivered PBT with light-field technique without surgical localization of the tumor by using 15-30 CGE in 4 fractions for both CCH and DCH [22]. The outcome results with this technique are comparable to those with a dose of 20 CGE PBT. Even a dose as low as 15 CGE also reduced the tumor height with complete absorption of SRF and significant improvement and stabilization in visual acuity. PBT causes less radiation complications such as cataract, radiation papillopathy or retinopathy than EBRT. Its use is limited due to the need for extra surgery, high cost, and special equipment.

*Plaque brachytherapy* with Ruthenium-106, Cobalt-60, Palladium-103 and Iodine-125 is used in treatment of CCH and DCH with extensive RD where PDT or laser photocoagulation cannot be administered [23-26]. It allows the radiation to reach the target tumor and induces tumor atrophy by regressing the tumor and exudative RD. In Sturge-Weber syndrome patients with DCH, when Ruthenium-106 (31-47 Gy) was used, there was good regression of the tumor with prompt resolution of SRF [23]. Large subfoveal CCH tumors with extensive RD and macular exudates that failed to the other laser therapies when treated with high dose Iodine-125 plaque radiotherapy at a dose of 48 Gy to the tumor apex regressed completely with very few radiation side-effects [24]. Plaque radiotherapy preserves the vision and salvages the globe. Symptomatic CCH treated by Palladium-103 with dose of 29 Gy to the

apex decreased the tumor height by 50% with 100% resolution of SRF and reattachment of the retina [25]. When Cobalt-60 brachytherapy applicators are used for the treatment of CCH involving the macula with large bullous RD, there was a complete re-attachment of the retina with progressive tumor transformation into a flat atrophic scar and improvement in visual acuity even at longer follow-ups of 10 years [26]. Plaque brachytherapy (dose range 25-50 Gy) is an effective and safe radiation delivery method to treat CH except that each patient needs two surgical procedures (plaque application and removal). As plaque may not be able to cover the entire tumor, it may not be ideal for large DCH than CCH. In juxtapapillary CCH treated by plaque brachytherapy, the risk of radiation papillopathy is more due to close proximity of the optic nerve head to the tumor apex that is treated by high target dose (up to 50 Gy).

Currently stereotactic radiation delivery technique, gamma knife radiosurgery (GKRS) is being widely used to treat various head and neck tumors including ocular tumors such as choroidal melanoma, choroidal hemangioma, orbital tumors and choroidal neovascularization [27-30]. Where TTT, PDT or laser photocoagulation is not a feasible option for treating the large CCH, GKRS is a good alternative treatment modality. It causes less damage to the surrounding ocular tissues especially the lens, optic nerve and macula. Single session of GKRS with a dose of 10 Gy for the treatment of choroidal hemangiomas revealed good outcomes without causing major adverse radiation effects [28,29]. Even for diffuse CH associated with Sturge-Weber syndrome, GKRS is a safe and effective method to reduce the tumor height at a marginal dose of 10 Gy in one session. When few authors used 26 Gy marginal dose with GKRS in diffuse CCH, RD resolved in all cases [30]. GKRS is an extremely precise non-invasive treatment method with no reported major ocular side-effects.

## Newer treatment modalities

Intravitreal anti-VEGF agents (bevacizumab, ranibizumab, pegaptanib) is an alternate treatment choice in CH patients who develop visual complications with laser photocoagulation or TTT [31-34]. They can be used either as a primary treatment option or along with PDT and plaque brachytherapy. Pan-VEGF inhibitors (bevacizumab, Avastin) cause regression of abnormal vessels and decrease the leakage of fluid from them. Visual disturbances in CH are mainly due to intra/subretinal fluid accumulation in the macular region. Anti-VEGF agents alone enable the absorption of SRF located in the subfoveal region thereby improving the visual acuity. When used for the extra-foveal CH, by reducing the height of the tumor they enhance the laser uptake (either with TTT or PDT) by the tumor. In patients who are resistant to EBRT with persistent exudative RD, anti-VEGF agents are found to be helpful in resolving the SRF [32]. Intravitreal ranibizumab (Lucentis) is effective in resolving the choroidal neovascularization associated with CCH [34]. Intravitreal VEGF inhibitors by stopping the leakage of the fluid from the tumor vessels sustain the visual acuity for a significant amount of time (up to a year) and is reasonably effective treatment option for CCH and DCH. So far, there were no major complications with no tumor recurrence reported with anti-VEGF agents for treating CH. Very recently, pilot studies using oral propranolol for treating

the juxtapapillary CCH are being done by few authors. Propranolol decreased the tumor height partially and is considered in patients with DCH with extensive exudative RD or juxtapapillary CCH patients who cannot afford the other treatment modalities such as TTT/PDT or radiation therapy. Though it decreased the exudates and stabilized the visual acuity for short term, final results are not that promising so far [35,36]. Enucleation is performed in symptomatic patients with painful blind eye due to secondary glaucoma and considered as a last option after failure of above treatment methods.

## Conclusion

Choroidal hemangioma, a rare benign asymptomatic tumor is usually observed for many years without any intervention. Treatment is considered when it becomes symptomatic with SRF or exudative retinal detachment that compromises the vision. Treatment is challenging despite advanced knowledge and availability of multiple therapeutic modalities. PDT has replaced laser photocoagulation and TTT due to its safety and efficacy. EBRT is a better treatment option for CCH after failed laser photocoagulation with poor vision and pain due to secondary glaucoma and lens-sparing EBRT is very effective for DCH. However, when the juxtapapillary and foveal tumors are treated by RT, ophthalmic complications such as radiation papillopathy and maculopathy are significantly noticeable. Proton beam therapy is a valid therapeutic alternative for complicated CCH especially in young children. Precise, focal radiation with plaque brachytherapy is an effective alternative method to treat symptomatic CCH as it causes less damage to the local ocular tissues. Stereotactic radiosurgery with gamma knife is a newer alternative method to treat CH that is difficult to treat with other therapeutic methods. It causes less radiation induced complications by preserving the visual acuity. Newer treatment modalities such as anti-VEGF agents and oral propranolol are being used either alone or in combination with other therapeutic modalities. In conclusion, different types of radiation delivery methods are effective for treating the choroidal hemangiomas when other treatments are ineffective. The outcomes with various radiation methods are good both in regressing the tumor, resolving the subretinal fluid/exudates, stabilizing or improving the visual acuity and preserving the globe. Novel radiation therapeutic methods cause minimal ocular complications.

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