Low-Dose Proton Beam Therapy for Circumscribed Choroidal Hemangiomas

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Objective: To evaluate the efficacy and safety of proton beam therapy for complicated circumscribed choroidal hemangiomas.

Methods: The study was a retrospective nonrandomized investigation. Seventeen consecutive patients, referred to the Institut Gustave-Roussy, Villejuif, France, for circumscribed choroidal hemangioma associated with serous retinal detachment were studied. Each eye received a total dose of 20 cobalt gray equivalents (CGEs) delivered in 15-second fractions of 5 CGEs over 4 days. Functional tests included the initial and final best-corrected visual acuity, slitlamp examination, intraocular pressure, fundus examination, fluorescein angiography, and indocyanine green angiography. Tumor thickness was determined on B-scan ultrasonography.

Results: The macula was involved in 7 eyes and the lesion was juxtapapillary in 2 eyes. The mean (SD) tumor thickness was 3.06 (9.0) mm. The mean initial tumor diameter was 6.82 mm (range, 3.2-12.1 mm). The right eye was involved in 7 cases and the left eye in 10 cases. The mean (SD) follow-up period was 52 (58) months (range, 36-90 months). Retinal reattachment was obtained in all cases after a mean period of 2 months (range, 1-12 months; median, 1 month). Tumor regression was obtained in all cases. One recurrence occurred 1 year after the initial treatment in an undertreated area. After re-treatment, however, resolution of the retinal detachment occurred, and flattening of the choroidal lesion was obtained. Final visual acuity improved to 2 Snellen lines or more in 16 eyes (94%), was stable in 1 eye, and attained 20/40 or more in 12 eyes (70.6%). No radiation therapy complications occurred during follow-up.

Conclusions: Proton beam therapy for choroidal hemangiomas seems to be an effective and safe alternative option. A total dose of 20 CGEs delivered in 4 daily 15-second fractions of 5 CGEs seems adequate for local control of both the tumor and serous retinal detachment.

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Circumscribed choroidal hemangiomas are rare, discrete vascular hamartomas that develop in isolated form or are a part of Sturge-Weber syndrome. They are frequently located at the posterior pole and characterized by a red-orange dome with distinct, regular borders.1,2 These lesions are thought to be congenital but only become symptomatic when nodular thickening of a critical size develops causing serous retinal detachment.3,4 The median age at detection and diagnosis of circumscribed choroidal hemangiomas in most large series is in the fourth to fifth decades of life. Choroidal hemangiomas are benign and do not transform into malignant tumors: no treatment is required as long as they remain asymptomatic. However, hemangiomas can cause diminished visual acuity via various mechanisms such as secondary exudative retinal detachment, cystoid macular edema, alteration of the pigment epithelium of the macular region, subretinal fibrosis, areolar macular atrophy, and neovascular glaucoma, a rare complication.5-6 Any treatment for choroidal hemangiomas should ideally achieve complete resolution of the subretinal fluid and tumor regression with minimal collateral damage.

The advantage of proton beam irradiation is that a homogeneous dose can be delivered to the target while sparing the healthy tissue surrounding the tumor.7,8 While radiotherapy may destroy the hemangiomas, late complications of proton beam therapy including radiation maculopathy and optic neuropathy may limit the therapeutic benefit.

We present the results of proton therapy (20 cobalt gray equivalents CGEs delivered in 15-second fractions of 5 CGEs over 4 days) in 17 consecutive patients with circumscribed choroidal hemangiomas who had a minimum follow-up of 3 years.
Our series is composed of 17 eyes in 17 consecutive patients (8 women and 9 men) with isolated circumscribed choroidal hemangiomas who were referred to the Institut Gustave-Roussy, Villejuif, France, between January 1, 1995, and June 30, 2000, and treated with proton beam irradiation. The mean age was 44.7 years (age range, 34-61 years). Inclusion criterion for proton beam irradiation was a circumscribed choroidal hemangioma complicated by retinal detachment or macular edema causing alteration of visual acuity. Patients with Sturge-Weber syndrome were excluded from this study.

The diagnosis of choroidal hemangioma was based on the following criteria: a posteriorly located red-orange choroidal tumor associated with an overlying serous retinal detachment, a fluorescein angiogram showing early filling of the tumor with dye with gradually intense hyperfluorescence and leakage of dye in the subretinal space during the late phase, early hyperfluorescence on indocyanine green angiography with a washing-out aspect during the late phase, and B-scan ultrasonography showing a highly reflective hyperechoic tumor with no choroidal excavation (Figures 1, 2, and 3).

The treatment technique was the same as that used for proton therapy of uveal melanomas. The tumor was visualized intraoperatively using indirect ophthalmoscopy, and 4 tantalum rings were sutured to the sclera using 5/0 Dacron sutures (Alcon Laboratories Inc, Fort Worth, Tex). The 3-dimensional coordinates of the clips were obtained from pairs of x-ray films during a simulation and were then introduced into the treatment-planning program, which provides a model of the eye and the tumor. A 200-MeV proton beam was degraded to 70 MeV and modulated to administer a uniform dose to the target volume. Each eye received a total of 20 CGEs (CGE: phys-

Figure 1. Choroidal hemangioma along the superior temporal vessel with secondary serous retinal detachment. The patient had a visual acuity of 20/200.

Figure 2. Ultrasonographic study, A, showing a solid choroidal lesion, high internal reflectivity, and a thickness of 2.5 mm. B, Echographic aspect 3 years after proton beam therapy. The tumor is almost flat; the patient’s final visual acuity was 20/25.

Figure 3. Fluorescein angiogram with late frames of the same eye before (A) and 3 years after (B) proton beam therapy. A, Hyperfluorescence within the choroidal tumor, associated with leakage of dye in the subretinal space. B, Inactive atrophic choroidal lesion and resolution of the subretinal fluid. The patient had a visual acuity of 20/25.
cal dose × 1.1 estimated relative biological effectiveness of protons compared with photons) delivered in four 15-second fractions of 5 CGEs over 4 days. During irradiation, the patient’s head was immobilized using a stereotactic head-holding device, and voluntary visual fixation was requested. A macular shield was used when the tumor involved the macula. Choroidal hemangiomas do not represent a malignant condition. Macula-sparing radiotherapy was decided on and the macula received less than 50% of the total dose. Dosimetry was established to evaluate the individual amount delivered to the macula, the optic disc, and the lens.

Patients were informed about the study and gave their consent in accord with the Declaration of Helsinki. The study was not submitted to institutional review board approval.

The Pearson-Spearman $r$ test was used for statistical analysis.

**RESULTS**

Follow-up examinations were performed on days 30 and 90, at 6 and 12 months after treatment, and yearly thereafter. Ophthalmologic parameters assessed included best-corrected visual acuity in the affected eye and fellow eye, tested at a distance of 5 m with standard visual acuity charts, intraocular pressure measurement, slitlamp examination, and indirect ophthalmoscopy. B-scan ultrasonography was performed at 3 and 6 months and yearly thereafter. Fluorescein angiography and indocyanine green angiography were performed yearly. Follow-up examinations verified that irradiation complications such as cataracts, neovascular glaucoma, and radiation retinopathy had not occurred. The mean (SD) follow-up was 52 (58) months (range, 36-90 months).

All patients were initially seen with diminished best-corrected visual acuity (Table) related to serous retinal detachment (Figure 1). Cystoid macular edema was present in 1 eye. The time elapsed between the onset of the first symptoms and treatment varied between 1 month and 7 years (mean, 11 months; median, 4 months); none of the eyes had undergone previous laser treatment.

The clinical characteristics of the 17 hemangiomas are detailed in the Table. Most eyes were initially seen with a tumor located in the temporal part of the choroid (15 eyes), the macula was involved in 7 eyes, and the lesion was juxtapapillary in 2 eyes. The mean (SD) tumor thickness was 3.6 (0.9) mm. The mean initial tumor diameter was 6.82 mm (range, 3.2-12.1 mm). The right eye was involved in 7 cases and the left eye in 10 cases.

The retina reattached within 1 month after treatment in 11 eyes and, in 3 patients within 3 months; in 2 patients, a flat retina was seen 6 months after treatment. Retinal detachment disappeared in 1 patient after 12 months (mean, 2 months; median, 1 month). A decrease in tumor thickness was observed in all eyes. Tumors lost at least 50% of their initial thickness 6 months after treatment in 10 eyes (47%) (Figure 2). Twelve months after treatment tumors regressed completely in 8 eyes and a flat scar 0.4 to 1.6 mm thick remained in 6 eyes. A recurrence occurred in 1 eye, 1 year after treatment. The hemangioma was located in the juxtapapillary area. This region did not receive irradiation at the initial treatment. Thickening of the juxtapapillary hemangioma occurred and was complicated by a cystoid macular edema. Proton beam irradiation was successfully delivered to the juxtapapillary area. One year after re-treatment the lesion had completely disappeared and cystoid macular edema had regressed.

One month after treatment visual acuity improved to 2 Snellen lines or more in 9 patients, was stable in 6 eyes, and decreased in 2 eyes. Two years after treatment

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Abbreviation: HM, hand motion.

*Retinal reattachment was attained in all cases after a mean period of 2 months.
visual acuity improved to 2 Snellen lines or more in 16 eyes, was stable in 1 eye (Figure 4), and reached 20/40 or more in 12 eyes (70.6%) (Table). We did not observe a decrease of visual acuity.

Two years after treatment visual acuity was significantly correlated with initial visual acuity (Pearson-Spearman $r$ test, 0.77, $P<.001$). The time elapsed between the onset of the first symptoms and treatment was significantly correlated with final visual acuity (Pearson-Spearman $r$ test, −0.60, $P = .02$). The patients treated earlier tended to have a better final visual acuity.

Initial visual impairment seems to be correlated with the location of the hemangioma. When the tumor manifests a subfoveal extension, initial visual acuity was less than 20/50. However, tumor thickness was not correlated with initial visual acuity. Three patients exhibited some granularity of the retinal pigment epithelium 4 years after treatment, and mild subretinal fibrosis was present at the periphery of the site occupied by the original tumor in 1 eye, 3 years after irradiation. No visual impairment was reported and no radiation treatment complications, such as cataract, irradiation retinopathy, or neovascular glaucoma, were observed during follow-up.

Figure 4. Evolution of visual acuity after treatment. PBI indicates proton beam irradiation.

COMMENT

Usually, choroidal hemangiomas are not progressive tumors, but slight enlargements have been reported, albeit rarely. Although choroidal hemangiomas are usually asymptomatic and require no treatment, they may be sight threatening when they involve the macula or when they are associated with serous retinal detachment or macular edema and, thus, may constitute a therapeutic dilemma. The spectrum of treatment options is limited when tumors are centrally located and in close proximity to the optic nerve and the fovea.

Laser therapy has been recommended in eyes with visual impairment due to an exudative retinal detachment overlying a choroidal hemangioma, the aim being to induce chorioretinal adhesion thereby enabling retinal detachment. However, because laser therapy failed to achieve tumor eradication, it is no longer recommended for this disorder. Photodynamic therapy does not specifically target this type of nonproliferative vessel of choroidal vascular tissue could, in fact, cause the recurrence of subretinal fluid with progressive impairment of vision. Such therapy achieved retinal reattachment in 82.5% of the eyes, but relapses were reported in 51.5% of the patients within a mean period of 24 months. Moreover, even when modified to a mild scatter technique, laser photocoagulation failed to maintain visual acuity above 20/50 in 75% of treated eyes and irreversible scotoma may occur when the choroidal lesion is close to the optic disc or the macula. Such a procedure is applied easily, except in cases of bullous retinal detachments that occasionally have required drainage of subretinal fluid before photocoagulation.

Low doses of fractionated external irradiation or brachytherapy are both effective and achieve retinal reattachment and tumor regression. External x-ray irradiation delivers a virtually homogeneous dose to the entire choroid. Brachytherapy allows more precise irradiation of the hemangioma, but the dose to the tumor is not homogeneous, with the base receiving a higher dose than the apex, and suturing the radioactive plaque posteriorly may be difficult.

Radiation therapy–induced retinopathy following fractionated treatment is not expected with doses below 30 to 40 Gy. The late carcinogenic effect of irradiation with an increased risk of developing radiation therapy–induced malignant tumors is well known. Radiotherapy for benign lesions should, therefore, consider each individual case carefully and if unavoidable, irradiation of the smallest area is preferable.

Recently stereotactic radiotherapy with a linear accelerator was proposed as an alternative treatment for circumscribed choroidal hemangiomas. Kivela et al demonstrated resolution of retinal detachment within 6 to 20 months (median, 5 months) and a median decreased tumor height of 24% after 6 months. In our study disappearance of subretinal fluid usually occurred within 1 to 12 months following treatment (median, 1 month) and tumor height decreased 50% after 6 months, which compared favorably with the study of Kivela et al.

Proponents of transpupillary thermotherapy for primary treatment of circumscribed hemangiomas seemed to have gained ground. Although successful tumor regressions have been reported, they were often incomplete with conventional transpupillary thermotherapy. The mild thermal effect of transpupillary thermotherapy was found to be the cause of complete chorioretinal atrophy with a lack of photoreceptor recovery and an optimal visual outcome of only 20/50.

Photodynamic therapy is not dependent on a thermal effect but rather on a photochemical effect. Barbacetta and Schmidt-Erfurth and Robertson proposed photodynamic therapy as an attractive treatment option for choroidal hemangiomas. However, only 5 cases were reported with a limited follow-up. More recently Schmidt-Erfurth et al and Porrini et al corroborated their results in a prospective study. In age-related macular degeneration, the photosensitizer used is verteporfin, which accumulates preferentially in choroidal new vessels. However, it is thought that choroidal hemangiomas do not grow. Photodynamic therapy does not specifically target this type of nonproliferative vessel of cho-
roidal origin. The lack of neovascular selectivity may lead to focal overtreatment of large vascular lesions. Occlusion of the physiologic choroid may result from too many re-treatments, and an interval that is too short between the subsequent re-treatments. The advantage of proton beam irradiation is that a homogeneous dose can be delivered to the target while sparing the healthy tissue surrounding the tumor. 3,16,26

In 1997, we reported on 13 cases with choroidal hemangiomas in which serous retinal detachment was treated with proton beam irradiation. The total dose delivered was 30 CGEs. Retinal reattachment was obtained in all cases after a mean period of 52 days, tumor height regressed in all cases, and visual acuity improved to 2 Snellen lines or more in 8 (62%) of 13 eyes and attained 20/200 in 9 (69%) of 13 eyes. However, the mean duration of symptoms was 3 years. Four of the patients had previously undergone laser photocoagulation and had experienced retinal detachment recurrences. In this study, the total dose delivered was 20 CGEs in 15-second fractions of 5 CGEs over 4 days, regression of retinal detachment was obtained in all cases after a mean period of 2 months, tumor height regressed in all cases, and tumor flattening was obtained in 14 (82.0%) of 17 eyes. Visual acuity improved to 2 Snellen lines or more in 16 (94.0%) of 17 eyes and attained 20/40 in 12 (70.6%) of 17 eyes. However, the mean time elapsed before treatment was 11 months and no eyes had received any previous treatment. Better visual improvement should not be the only reason for reducing the total dose delivered; more adverse effects can also be avoided. Zografos et al.26 claimed that a total dose of 27.3 Gy induced radiation optic neuropathy, which reduced visual acuity and that a dose of 22.7 Gy can induce some retinal telangiectasis 5 to 7 years after irradiation. Doses lower than 18.2 Gy appear to be safer and tumor regression can be achieved within 2 to 4 years. Our results do not corroborate those of Lee and Hungerford26 who reported optic neuropathy and maculopathy in 2 patients treated with 18 Gy CGE within 32 months of proton beam irradiation. The risk for radiation-related complications depends on factors such as total dose, fractionation, and treated volume. Proton beam therapy allows reducing the irradiated volume.

The respective efficacy and safety and safety of photodynamic therapy and proton beam therapy should be compared through large randomized, prospective studies. This approach seems difficult because of the reduced prevalence of choroidal hemangiomas.

Although it is associated with inconvenience such as the need for surgery and its cost, proton beam irradiation (20 CGE) seems to be an attractive and effective option for treating circumscribed choroidal hemangiomas with exudative retinal detachment. Our study results indicate that the dose we chose is beneficial, especially in eyes with subfoveal involvement, and it is also tolerated at the posterior pole.

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