Objective: To report our longer-term follow-up observations in patients with small choroidal melanomas primarily treated with transpupillary thermotherapy (TTT).

Methods: In this noncomparative interventional case series, 40 patients with small melanocytic tumors of the choroid (thickness <3.5 mm) underwent TTT. Follow-up examinations including ophthalmoscopy, ultrasonography, and fundus photography were conducted at 24 to 48 hours, 2 to 6 weeks, and 6-month intervals after treatment.

Results: Forty patients (mean age, 58 years) with small melanocytic tumors underwent TTT. Mean follow-up in all patients was 42 months. In most cases TTT resulted in tumor regression. Thirty-one (77.5%) of 40 tumors did not recur after initial treatment with TTT. In 5 (12.5%) of 40 tumors with initial basal diameters ranging from 4.25 mm to 7.5 mm and a mean initial thickness of 2.0 mm, edge recurrences developed, which were satisfactorily treated with additional TTT (4 cases) or cryotherapy (1 case). The mean interval between initial TTT and recurrence in this subgroup was 15 months (range, 7-22 months). Of 36 eyes that were successfully treated with TTT or cryotherapy, 26 eyes (72%) had posttreatment visual acuity better than or equal to pretreatment visual acuity. Four (10%) of 40 tumors were not controlled with TTT and eventually required brachytherapy (n=1), proton radiation (n=1), or enucleation (n=2). The initial basal diameters of these tumors ranged from 7.5 x 7.5 mm to 9 x 7.5 mm, with a mean initial thickness of 2.6 mm. The mean interval between treatment and determination of treatment failure was 22 months (range, 7-30 months).

Conclusions: Transpupillary thermotherapy resulted in tumor regression of most small melanocytic choroidal tumors. Tumor edge recurrences were successfully treated with additional TTT in most cases. Four tumors required irradiation or enucleation because of treatment failures with TTT. Transpupillary thermotherapy as a stand-alone therapy is insufficient for some small choroidal melanomas.


T HE FIRST CLINICAL STUDY OF transpupillary thermotherapy (TTT) in the management of choroidal melanoma was published by Oosterhuis et al1 in 1995. In TTT, a wide beam of an 810-nm diode laser is delivered to the choroidal tumor through a contact lens. Journee-de Korver et al2 demonstrated histopathologic evidence of tumor necrosis up to a depth of 3.9 mm in human choroidal melanoma caused by a TTT-generated temperature increase to 45°C to 60°C within the tumor. Subsequently, TTT has been used by several investigators to treat selected small to medium choroidal melanomas. Short-term follow-up studies have reported tumor regression and local control in most cases. We began using TTT in 1996 as a primary treatment of selected small melanocytic choroidal tumors presumed to be small melanomas with a thickness of less than 3.5 mm. In 1999, we published the results in the first 20 patients with small choroidal melanomas.3 Since then, we have treated an additional 20 patients. This article summarizes our extended follow-up observations in the original 20 patients and our experience with 20 more recently treated patients.

METHODS

In accord with an investigational protocol approved by the Institutional Review Board of the Mayo Clinic, Rochester, Minn, from 1996 through 2002, we enrolled men and women 18 years or older for primary treatment with TTT if they had suspected small choroidal melanoma (thickness <3.5 mm) that had been
either observed to grow or had features suggesting growth (subretinal fluid and lipofuscin) (Figure 1). Exclusion criteria were eyes with a maximum pupillary diameter of less than 6 mm; eyes with choroidal lesions in the peripheral fundus, where delivery of TTT would be difficult; eyes with media opacities preventing a clear view of the lesion; eyes with confounding fundus disorders; and patients who were unable to give informed consent.

Before treatment, a complete ophthalmologic examination was performed. The diagnosis of suspected choroidal melanoma was based on results of the clinical examination, including slitlamp biomicroscopy, indirect ophthalmoscopy, and ultrasonography. The basal dimensions and the thickness of the tumor were determined with indirect ophthalmoscopy and ultrasonography, respectively. Patients in the study agreed to return for scheduled follow-up examinations, including fluorescein angiography and ultrasonography. Systemic evaluation before treatment included a chest radiograph, determination of serum liver function enzyme levels, and computed tomography or ultrasonography of the abdomen.

Before treatment, the pupils were dilated with a combination of 1% cyclopentolate hydrochloride and 10% phenylephrine hydrochloride. Retrobulbar anestesia was accomplished with administration of 4 mL of 2% lidocaine hydrochloride. The beam of a diode laser (wavelength, 810 nm), focused on the tumor surface, was delivered through a 3-mm aperture of a slitlamp adapter and a corneal contact lens. The 3-mm laser beam provided a retinal exposure 1.5 mm in diameter. A smaller beam diameter was sometimes used when treating near the macula. Overlapping treatment spots were applied to cover the entire tumor surface, including at least 1 mm of clinically normal tissue around the margin of the tumor. Treatment was initiated using a 60-second exposure and an energy level of 550 mW, while adjusting the energy level stepwise in 50-mW to 100-mW increments until the surface of the tumor turned gray during the second half of the 60-second exposure. An attempt was made to avoid high-energy levels that produced an early white coagulation effect within the first 30 seconds of exposure. The response was considered optimal when the treated tissue became gray to white during the last 15 to 20 seconds of exposure. The treatment applications were repeated to confluently cover the entire surface of the tumor.

Follow-up examinations were conducted 24 to 48 hours after treatment to look for evidence of protein and cellular reaction in the anterior chamber and vitreous cavity, injury to anterior ocular structures, and any changes in the amount of subretinal fluid. Two to 6 weeks after treatment, patients were reevaluated with ophthalmoscopy, ultrasonography, and fundus photography. Additional follow-up at 6-month intervals included ultrasonography, fundus photography, and visual field examination (either tangent screen or Goldmann perimetry).

RESULTS

Forty patients (23 men and 17 women), ranging in age from 26 to 82 years (mean, 58 years), underwent TTT for treatment of a small melanocytic choroidal tumor. The initial basal diameter of the tumors ranged from 4.0 × 2.75 mm to 10.5 × 8 mm. The thickness of the tumors ranged from less than 1.0 to 3.2 mm (mean, 2.0 mm). Follow-up in all patients ranged from 5 to 90 months (mean, 42 months; median, 40 months). The mean follow-up in the original 20 patients was 57 months and in the recent 20 patients was 28 months. Thirteen tumors were followed up for more than 60 months. After treatment, there was no evidence of inflammation in the anterior segment; the cornea, iris, and lens remained unchanged.

Twenty-three (57.5%) of 40 tumors were reduced to a flat scar within 6 months. In our early experience with TTT, we treated 4 tumors with additional TTT because of what we presumed to be an inadequate early treatment response. After observing several tumors that developed progressive atrophy for more than 1 year after a single treatment with TTT, we concluded that the early retreatment of these 4 tumors may have been unnecessary. Thirty-one (77.5%) of the 40 tumors did not recur after initial treatment with TTT (Figure 2).

Of the original 20 treated tumors, edge recurrences developed in 3, which were satisfactorily controlled with additional TTT (Figure 2). One tumor was re-treated at 14 months, 1 tumor at 22 and 39 months, and 1 tumor at 13, 35, and 71 months after the initial TTT. One tumor failed to respond to 3 TTT sessions, and brachytherapy was required because of progressive increase in tumor thickness 28 months after the initial TTT.

Among the 20 recently treated tumors, there were 3 failures; 1 eye was enucleated because of a progressive increase in both base di-
mension and thickness at 7 months, 1 eye was enucleated because of extraocular extension that was recognized at ultrasonography 30 months after TTT despite regression of the intraocular portion of the tumor to a flat scar, and 1 eye was treated with proton beam radiation at 23 months because of an inadequate response to the initial TTT. The 5 (12.5%) tumors with edge recurrences that were satisfactorily controlled with additional TTT or cryotherapy had a mean initial thickness of 2.0 mm (range, 1.0-2.7 mm) and initial basal dimension ranging from 4 × 2.75 mm to 7.5 × 6 mm. The mean interval between initial TTT and first recurrence was 15 months (range, 7-22 months). The 4 (10%) tumors that could not be controlled with TTT had a mean initial thickness of 2.6 mm (range, 2.4-2.7 mm) and initial basal dimension of 7.5 × 7.5 mm to 9 × 7.5 mm. The mean interval between initial TTT and failure was 22 months (range, 7-30 months).

Of 36 eyes that were ultimately successfully treated with TTT or cryotherapy, 26 eyes (72%) had posttreatment visual acuity equal to (±1 line) or better than pretreatment visual acuity (Figure 3). The posttreatment visual acuity in 6 eyes improved from pretreatment (gain of ≥2 lines on the visual acuity chart) as a result of resolution of subretinal fluid involving the central macula. In 10 (28%) of the 36 eyes with tumor regression, posttreatment visual acuity declined (decrease of ≥2 lines on the visual acuity chart) as a result of development of central macular scar or atrophy in cases in which the tumor was located under the central macula or the papillomacular bundle (n=5), epiretinal membranes (n=4), and macular edema with subfoveal retinal pigment epithelial changes (n=1).

Six of 40 eyes treated had juxtapapillary tumors. In all 6 eyes with juxtapapillary tumors, corresponding wedge-shaped visual field defects and sector optic disc pallor developed after treatment. Two eyes with tumors abutting the temporal margin of the optic disc 180° and extending under the macula demonstrated significant visual acuity loss as a result of development of a central macular scar after TTT. In 1 of those 2 eyes, edge recurrences developed adjacent to the optic disc margin 22 months after the initial TTT and on the temporal edge of the tumor 39 months after the initial TTT. However, with 2 additional TTT applications, the tumor recurrences were replaced with a flat scar.

Since our initial report of management with TTT of 20 small presumed choroidal melanomas, we have similarly treated another 20 tumors. The characteristics of the tumors in both series were similar in size, thickness, growth behavior, and location in the fundus. Initial treatment and follow-up were similar for all tumors.

Our earlier report of 20 patients with small choroidal melanomas treated with TTT reported a recurrence rate of approximately 8%. With extended follow-up, the recurrence rate rose to 23%, which is comparable to the Kaplan-Meier 3-year estimated recurrence that reported in a series by Shields et al. In our series of 40 tumors, 31 tumors (77.5%) were treated with TTT, without recurrence. Five (56%) of 9 recurrences were treated with additional TTT or cryotherapy. Although the initial recurrences in these 5 cases were recognized within 2 years of treatment with TTT, new edge recurrences continued to be observed with longer follow-up, namely, 39 months in 1 case and 71 months in another. Four tumors failed to respond to initial TTT and additional treatments, and were treated with enucleation (n=2), brachytherapy (n=1), or proton beam radiation (n=1); 1 failure occurred 7 months after the initial TTT, and 3 failures occurred 2 years or more after the initial TTT. The observation of an increasing incidence of tumor recurrences with longer follow-up reinforces the need to closely monitor all treated tumors.

In our series, 26 (72%) of 36 eyes with small choroidal melanomas successfully treated with TTT had equal or better visual acuity after TTT than before treatment. Improvement of vision was usually the result of the disappearance of subretinal fluid extending from the tumor into the fovea. Loss of vision after TTT was, in general, the result of destruction of the fovea or papillomacular nerve fiber bundle when the tumor was located under these structures or of macular pucker formation or vascular occlusions involving the macula. Other complications of TTT, as previously observed in our initial series of small choroidal melanomas managed with this treatment, were arcuate or wedge-shaped scotomas due to destruction of the nerve fiber layer overlying the tumor, branch retinal vessel obstruction, retinal traction, macular edema, and focal neovascularization.

Some investigators have expressed concern about treatment of juxtapapillary tumors with TTT. Juxtapapillary tumors have been reported to be associated with an increased risk for growth and metastasis. However, thus far, 5 of 6 juxtapapillary tumors in our series have been well controlled with 1 TTT application. The other juxtapapillary tumor developed an edge recurrence and remains controlled after additional treatment with TTT.

Our single case with extrascleral tumor extension detected at ultrasonography underscores the importance of continual monitoring of the treated tumors with ultrasonography, even though the ophthalmoscopic appear-
ance suggests complete tumor regression to a flat scar. It also points out the limitations of TTT in destroying the deep portions of the tumor tissue, particularly tumor cells that have invaded the emissary channels and sclera. Coupled with other reports of intrascleral and extrascleral extension of tumor cells in eyes enucleated after TTT,6-8 this case indicates that TTT as a stand-alone therapy is inadequate for treatment of some choroidal melanomas. This has led some investigators to combine TTT with brachytherapy.9 Brachytherapy, however, carries significant risk for vision-threatening adverse effects in the form of radiation retinopathy and neuropathy. Therefore, as an alternative to brachytherapy, we have been using adjunctive transscleral cryotherapy after TTT to treat tumors located more than 1.5 mm from the optic nerve, with the goal of destroying all tumor cells in the depths of the tumor and in the sclera. Although transscleral cryotherapy alone has been satisfactorily used to destroy selected small choroidal melanomas,10 one of us (D.M.R.) has observed extensive intravitreal cellular reaction or vitreous hemorrhage when cryotherapy was used as primary treatment. However, 2 to 4 months after initial treatment with TTT, most of the tumor bulk will have regressed and the tumor will be relatively avascular; when delaying the administration of cryotherapy several months after primary TTT, transscleral cryotherapy has been associated with minimal intravitreal cellular reaction. We are using a double freeze-thaw technique delivered under indirect ophthalmoscopic control. After administration of a local anesthetic, a small conjunctival incision in the fornix enables introduction of the cryoprobe. It is hoped that this combination treatment will reduce the incidence of edge recurrences and minimize the possibility of extrascleral tumor growth.

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REFERENCES