Small Choroidal Melanomas Treated With Transpupillary Thermotherapy and Cryotherapy

The management of small choroidal melanomas continues to be controversial.1 Although radiotherapy with either charged particles or ionizing radiation can be effective in providing local control of these tumors, radiation complications (radiation retinopathy and optic neuropathy) that cause loss of vision have led some investigators to consider alternative forms of treatment. One alternative treatment that has been studied by a number of investigators is transpupillary thermotherapy (TTT).2,3 Although initial results using TTT to treat selected uveal melanomas were optimistic, a longer follow-up and a relatively high tumor recurrence rate have dampened the initial enthusiasm for TTT as a stand-alone therapy. To minimize the tumor recurrence rate after TTT, adjunctive cryotherapy has been proposed.2 The purpose of this report is to review a small cohort of patients who were prospectively treated with a combination of TTT and cryotherapy.

Report of Cases. The institutional review board of the Mayo Medical School approved this study, which was performed in accordance with Health Insurance Portability and Accountability Act regulations. This study is a noncomparative interventional case series. Five patients with small melanomas of the choroid (thickness range, 1.2-2.8 mm) that were located 1.5 mm or more from the optic nerve and the macula underwent TTT. The anterior edge of each tumor was more than 2 disc diameters posterior to the equator. Other criteria for selecting tumors for TTT and the TTT treatment variables have been outlined in a previous publication4; all tumors in this series had demonstrated growth or had significant risk factors of growth that included subretinal fluid. Patients who consented to treatment with TTT were advised that their tumors would also be treated with cryotherapy 3 to 4 months after TTT. For the cryotherapy, the surgical site was anesthetized with sub-Tenon lidocaine, and the cryotherapy was delivered under indirect ophthalmoscopic control using a standard retinal cryoexy probe. The tip of the probe was introduced into the sub-Tenon space through a small slit in the conjunctival fornix. In each case, the full tumor thickness was maintained within the freeze for 45 seconds before it was thawed. A subsequent freeze at the same location was given. The probe was then repositioned and additional applications were administered until the entire tumor and a 1-mm perimeter of tumor-free tissue were treated. I delivered all the cryotherapy applications. Follow-up examinations were conducted at 24 to 48 hours, 2 to 6 weeks, and 6-month intervals.

The 5 patients, ranging in age from 35 to 75 years (mean age, 56 years), were treated with combination therapy (TTT and cryotherapy) and followed up from 44 months to 5 years. The tumors ranged in thickness from 1.2 to 2.8 mm. Maximum base dimensions ranged from 6 to 9 mm.

In 2 patients, a recurrence of the tumor was observed despite the combination therapy. One of the patients had lost an eye from trauma. He developed a melanoma in his only eye. A recurrence of the tumor was noted at the edge of the treatment site 40 months after the original combination treatment. This recurrence was treated with additional TTT, and no additional recurrence was found during a further follow-up of 6 months. The tumor recurrence in the other patient was observed 10 months after the original combination treatment. After the TTT but before the cryotherapy, the tumor thickness was reduced from 1.7 mm to less than 0.5 mm. Then, its base was treated with cryotherapy. Seven months after cryotherapy, the tumor was observed to expand in both thickness (1.6 mm) and base dimension (7 mm). The tumor was treated with iodine 125 brachytherapy, and growth of the tumor was arrested. Its thickness remained stable (1.6-1.7 mm), and no further basal expansion of the tumor occurred. However, at the 48-month follow-up, the patient had metastatic melanoma in the liver. One patient developed a macular epiretinal membrane 1 year after treatment of the melanoma. Despite pars plana vitrectomy and successful membrane peeling, the patient’s visual acuity has remained compromised at 20/80.

Comment. In a recent study by Win et al,3 tumor recurrences after TTT of small melanomas were observed in 23% of the cases. This recurrence rate was comparable to the Kaplan-Meier 3-year estimated recurrence rate reported in a series of patients with small melanoma treated by Shields et al.2 These observations, along with the posttreatment occurrence of extrascleral extension in 1 of my patients, led me to begin treating such tumors with transscleral cryotherapy approximately 3 months after TTT. The choice of cryotherapy as an adjunct to TTT was based on the documented success of cryotherapy in destroying small choroidal melanomas when used as a primary treatment.3 I also used cryotherapy successfully to destroy 1 small-sized melanoma. Because of these observations, I theorized that adjunctive transscleral cryotherapy might minimize the potential for both tumor recurrence and extrascleral extension by destroying mela-

noma cells in the deep portion of the tumor that were possibly beyond the kill depth of TTT. Peripapillary tumors and those within 1.5 mm of the optic disc were excluded from consideration of treatment with transscleral cryotherapy. Because of the disparity between the small size of the optic disc and the larger size of the extrascleral portion of the optic nerve, it was concluded that cryotherapy could not properly treat the episcleral tissue behind a tumor located in the peripapillary region without injuring the optic nerve. My observation that primary treatment of even a small choroidal melanoma (≤3.0-mm thickness) could be followed by severe intravitreous hemorrhage led to the decision to apply the cryotherapy only after a post- TTT interval of 3 months. My observations of tumors treated with TTT verified that 3 months after TTT both the vascularity of the tumor and the tumor bulk were greatly reduced. The reduced tumor bulk would enable the cryotherapy to be more capable of successfully treating the entire thickness of the residual tumor, and the reduced vascularity would decrease the likelihood of causing hemorrhage.

In the present series, the development of 2 recurrences in 5 cases, despite combination therapy, was disappointing. Clearly this combination therapy will not always be successful in preventing tumor recurrences. One might argue that the depth and completeness of the freezes with the cryotherapy applications were inadequate. However, the freezes were easy to observe with indirect ophthalmoscopy; in each case, the treatment appeared to adequately and completely cover the perimeter of the tumor base. The observed freeze from the cryotherapy application extended approximately 1 mm beyond the perimeter of the TTT, which, in turn, was delivered to encompass not only the tumor base but also 1 mm of clinically normal-appearing tissue around the tumor margin.

The failure of this combined treatment may be looked on as a reason to discontinue the use of cryotherapy as an adjunctive treatment. However, the known effectiveness of primary cryotherapy in the treatment of some small melanocytic tumors and the effective management of an edge recurrence with cryotherapy after an initial treatment with TTT as in an unreported case, as well as the potential value in preventing extrascleral extensions, argue for continuing to explore the use of cryotherapy as an adjunctive treatment in selected cases of small melanomas. Of the 2 tumors that developed recurrences after the use of combined therapy with TTT and cryopexy, effective management appears to have been accomplished with additional TTT in 1 tumor. Brachytherapy was used to treat the other tumor recurrence. This was followed by local control of the tumor for several years, but the treatments failed to prevent metastases. Although meaningful survival statistics cannot be drawn from this small series, the development of metastatic melanoma in 1 of the 2 patients with tumor recurrence serves to remind us that a trend toward reduced survival has been demonstrated following local tumor failure after brachytherapy. It remains a goal to eliminate tumor recurrences. One eye developed an epiretinal membrane with resulting visual impairment despite successful pars plana vitrectomy and membrane peeling. Although epiretinal membrane formation can be seen after TTT alone, cryopexy has also been shown to produce epiretinal membrane, especially when used with heavy applications as in this case series. It remains uncertain whether the epiretinal membrane in this series was induced from TTT, cryotherapy, or both.

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**Functional Use of Hyaluronic Acid Gel in Lower Eyelid Retraction**

Hyaluronic acid gel is a nonanimal, naturally occurring polysaccharide found in the extracellular matrix of connective tissue and is well suited as a soft-tissue filler in cosmetic surgery. Cross-linked hyaluronic acid gel is identical in composition across species with a low risk of allergic reaction. It is a transparent, viscous, injectable tissue filler that can be found in varying particle sizes and whose effect lasts up to 9 months. Lower eyelid retraction with exposure keratopathy and lagophthalmos is a challenging clinical problem. While symptoms of corneal exposure can be medically managed, traditional long-term treatments generally involve surgical intervention. We used hyaluronic acid gel as a minimally invasive nonsurgical alternative to treat secondary lower eyelid retraction causing corneal exposure and keratopathy in 5 patients with varying etiologies. This treatment formed part of the patients’ clinical management and did not require institutional review board approval.

**Report of Cases.** Injection location and volume were determined in the preoperative visit. Preinjection and postinjection photographs were taken with standard position and lighting by the same surgeon with a Nikon Coolpix 990 camera (Nikon, Melville, New York). Each injection was done by the