Enucleation Following Transpupillary Thermotherapy of Choroidal Melanoma: Clinicopathologic Correlations

Transpupillary thermotherapy (TTT) is being used increasingly for the treatment of small and some medium-sized choroidal melanomas. Although several studies have outlined the complications following TTT, such as tumor recurrence, vascular occlusions, visual field defects, and retinal detachment, there are only a few studies dealing with histopathologic findings following TTT. In this article, we present clinicopathologic correlations in 10 eyes that required enucleation after TTT in an attempt to improve our understanding regarding potential limitations of TTT.

Methods. We prospectively collected data from all patients with a diagnosis of uveal melanoma who were treated with planned TTT at the Ocular Oncology Service at Wills Eye Hospital (Philadelphia, Pa) between January 1995 and September 2001. Only those patients who eventually required enucleation formed the basis of the present study. Institutional review board approval was obtained.

Tumor progression was defined as any increase in tumor thickness or basal diameter detected by ophthalmoscopy, fundus photography, or ultrasonography during the first 3 treatment sessions, without any documented regression. Tumor recurrence was defined as tumor growth after a period of stable regression. All eyes were fixed in neutral buffered formalin and processed routinely for light microscopy. All available histopathologic sections of each globe were reviewed retrospectively by an experienced ophthalmic pathologist. The findings at the site of primary treatment, margins, and away from the primary site were assessed, tabulated, and correlated with clinical findings.

Results. The general information regarding patient demographics and tumor characteristics is presented in Table 1. Among 357 consecutive patients who received TTT as primary treatment of choroidal melanoma, 10 patients (2.8%) eventually required enucleation (Figure 1). Two tumors were clinically amelanotic. Eight tumors touched the optic disc and were classified as juxtapapillary in location. The mean size of the choroidal melanomas was 7.4 mm in basal diameter and 3.1 mm in thickness, requiring an average of 3 sessions of thermotherapy.

Of the total 10 cases requiring enucleation, 8 cases (80%) were related to the failure of the primary tumor to respond, which was either due to tumor progression (3 cases) or to tumor recurrence (5 cases). One case each was enucleated because of persistent rhegmatogenous retinal detachment and neovascular glaucoma (Figure 2). The mean interval between TTT and enucleation was 19.4 months (range, 6-70 months).

The histopathologic findings based on multiple sections from each globe are summarized in Table 2. At the site of thermotherapy application, well-demarcated, full-thickness retinal atrophy and retinal and choroidal fibrosis were observed in all cases (Figure 3). The extent of fibrosis was variable; in 8 cases, fibrosis was minimal, and in 2 cases, it was massive, extend-
ing from the level of the retinal pigment epithelium to the underlying choroid. Viable-appearing choroidal melanoma was observed within the areas of TTT application in 5 cases and was noted at the margins of the treatment area in 6 cases. Tumor cells were evident intrasclerally in 3 cases, and 4 cases had extrascleral extension (Figure 3). The tumor was present within the lumina of the intrascleral emissary canals, or had directly infiltrated the scleral lamellae or both.

Comment. The level of hyperthermia during TTT is influenced by many variables such as duration, power, and spot size of the laser beam, and tumor characteristics such as thickness and extent of pigmentation.1 The potential complications of TTT can be anticipated by effects of hyperthermia on the overlying retina and retinal vessels. The sclera is known to be resistant to hyperthermia.9

In all cases in our study, TTT treatment sites were characterized by well-demarcated and abruptly margined areas of retinal atrophy and fibrosis. The underlying sclera seemed normal in cases without extrascleral extension.8 In one of our cases, complete atrophy of the overlying retina led to irreparable rhegmatogenous retinal detachment. In 2 cases, there was exuberant retinal fibrosis that obscured the ophthalmoscopic view of the underlying choroidal melanoma that was noted histopathologically. In one case, tumor recurrence was seen only extraocularly without any intraocular component. Although retinal vascular occlusions involving small vessels are fairly common (69%-83% of cases) following TTT, retinal neovascularization is relatively uncommon.4 In one of our cases, florid retinal neovascularization led to neovascular glaucoma.

Overall tumor-related complications such as progression and recurrence accounted for the majority of enucleations. Recurrent tumor following TTT can be managed by additional thermotherapy, plaque radiotherapy, or enucleation based on location and extent of the recurrent tumor and the visual potential. The post-TTT enucleation rate of 2.8% in our series compares favorably with the published rates of 2.6% to 7.0%.4,10,11

In general, the risk of tumor recurrence (about 4% at 1 year and 22% at 3 years) can be minimized by proper case selection and treatment beyond the visible tumor margins.3 The mean time to recurrence is almost 2 years after the initiation of TTT, implying the need for careful long-term follow-up of the patients.3 In our series, 8 cases (80%) were juxtapapillary in location at initial visit—a risk factor identified to predispose to tumor recurrence.3 It is not known whether the risk for re-
currence with juxtapapillary tumors is due to difficulty in treating tumors at this location or whether such tumors are inherently more aggressive.

Intrascleral choroidal melanoma was noted histopathologically in 3 cases, and 4 cases developed extrascleral extension. Tumor infiltration of scleral lamellae has been observed in approximately 50% of eyes undergoing primary enucleation.12 Melanoma cells sheltered in posterior intrascleral emissary canals or scleral lamellae are a potential source of tumor recurrence.5 Tumor recurrence may occur intraocularly or extraocularly. Therefore, patients treated with TTT should routinely undergo B-scan ultrasonography to detect extrascleral extension even if they demonstrate satisfactory ophthalmoscopic appearance of regression. Concerns regarding the lack of efficacy of TTT against intrascleral melanoma5,7,8 have led to a concept of “sandwich therapy.”2,11,13 It is proposed that the combination of TTT and plaque radiotherapy may reduce the risk of tumor recurrence following TTT.14 Currently, guidelines for use of this sandwich therapy have not been clearly established.

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Table 2. Histopathologic Findings in 10 Eyes Undergoing Enucleation Following Transpupillary Thermotherapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Treatment Site</th>
<th>Melanoma</th>
<th>Fibrosis</th>
<th>Retinal Atrophy</th>
<th>Sclera</th>
<th>Marginal Melanoma</th>
<th>Intrasceral Melanoma</th>
<th>Extrascleral Melanoma</th>
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<td>Absent</td>
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<tr>
<td>3</td>
<td>Absent</td>
<td>Fine</td>
<td>Present</td>
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<tr>
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</tr>
<tr>
<td>5</td>
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Figure 3. A, A 48-year-old woman with a juxtapapillary choroidal melanoma in her left eye. Fundus appearance after a single session of thermotherapy. B, Stable regression following multiple sessions of thermotherapy. C, B-scan ultrasonography suggestive of extrascleral extension. D, Melanophages buried by postthermotherapy collagenous scar are seen at higher power in insets. Bleach section discloses bland nuclei and low nuclear-cytoplasmic ratio (main figure: hematoxylin-eosin, original magnification ×50; top inset: hematoxylin-eosin, original magnification ×100; bottom inset: bleach, original magnification ×100). E, Extrascleral nodule of melanoma adheres to the back of the globe, deep to the choroidal aggregate of melanophages seen in part D. Constituent mixture of spindle and epithelioid cells is evident at higher magnification on the right (hematoxylin-eosin, original magnification ×10 [left] and ×250 [right]).
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Fibrovascularization of Porous Polyethylene Orbital Floor Implants in Humans

Porous polyethylene (Medpor; Porex Surgical Inc, Newnan, Ga) orbital implants are increasingly popular and used commonly as sheets, blocks, or spheres for volume replacement in the anophthalmic socket and for orbital wall repair in orbital wall fractures. Synthetic orbital implants are generally less expensive than natural coral implants and are also biocompatible and nontoxic, with interconnecting pores and channels.1-3

Fibrovascular tissue growth from adjacent orbital tissue into spherical porous polyethylene orbital implants is well established and has been demonstrated4,5 using several techniques (histopathologic findings,6,7 technetium isotope scanning,8,9 computed tomography,8 and magnetic resonance imaging1,7,8). Vascularization usually occurs from the periphery of the implant toward the center of the sphere and aids integration of the implant into host tissues. This is believed to reduce infection, extrusion, and exposure of the implant. Porous polyethylene sheets or blocks are increasingly being used as orbital floor implants (especially in augmenting orbital volume postenucleation and in reconstructive surgery following orbital trauma2,9) with studies demonstrating fibrovascular tissue in-growth into Medpor orbital floor implants in an animal model.10 We demonstrate histologic evidence of fibrovascular tissue growth into the anterior aspect of porous polyethylene orbital floor implants in humans in 3 cases in which the implant required trimming.

Report of Cases. Case 1. A 36-year-old man had undergone right enucleation of a blind eye as a result of trauma, 10 years after injury. A secondary spherical orbital implant (18-mm porous polyethylene) was placed 8 years later. One year later, the orbit required further volume augmentation. Seven layers of stacked 0.85-mm-thick porous polyethylene sheets (total height, 5.95 mm) were inserted into the subperiosteal space on the orbital floor via a conjunctival incision. The surgery was performed by an oculoplastic trainee, and the perioseal closure to the arcus marginalis may have been incomplete, as 3 months later the patient had a prominent bump from the anterior edge of the stack, giving an irregular contour to the lower eyelid. This remained stable, and 1 year after insertion, the orbital floor implant was trimmed via a conjunctival approach for aesthetic reasons. The anterior few millimeters of the implant was excised by cutting down with a 15 Barde Parker blade.

Case 2. A 56-year-old man had a blunt injury resulting in a left orbital floor fracture, diplopia, and enophthalamos. Maxillofacial surgeons repaired the fracture by inserting a porous polyethylene block into the subperiosteal space via a conjunctival incision. His diplopia and enophthalamos improved. However, postoperatively he had lower eyelid retraction, and anterior displacement of the floor implant was noted 6 months after surgery, resulting in an irregular inferior orbital margin contour. Two years after insertion, the anterior protruding edge was excised via a conjunctival incision, and the adhesions causing the eyelid retraction were simultaneously freed.

Case 3. A 35-year-old man was shot in his right orbit. He had inferior and medial orbital wall fractures, and his eye was enucleated with a primary spherical orbital implant placed without repair of the fractures. Two years later, he was referred to the Oculoplastic and Orbital Service (The Western Eye Hospital, London, England) for treatment of his volume-deficient socket. Stacked porous polyethylene sheets were used to repair the floor defect and augment the orbital volume. Eight 1.5-mm-thick sheets (total height, 12 mm) were inserted via a conjunctival incision by an oculoplastic trainee. Perioseal closure to the arcus marginalis was difficult due to previous eyelid...