Transpupillary Thermotherapy

Results in 50 Patients With Choroidal Melanoma

Jendo A. Oosterhuis, PhD, MD; Hanneke G. Journée-de Korver; Jan E. E. Keunen, PhD, MD

Objective: To evaluate the efficacy and safety of transpupillary thermotherapy in treating choroidal melanoma.

Methods and Patients: To perform transpupillary thermotherapy, infrared diode laser energy at 810 nm was used with a beam diameter of about 3 mm and 1-minute exposure time. All 50 patients had choroidal melanoma. We performed transpupillary thermotherapy in 21 tumors that had responded insufficiently to 800 Gy ruthenium 106 brachytherapy; it was combined with 800 Gy 106Ru brachytherapy for 10 tumors greater than 5 mm in height and with 600 Gy for 19 tumors 5 mm or less in height.

Results: All but 1 tumor exhibited reduction in tumor height within a mean follow-up of 20.5 months (range, 6-49 months). In 41 eyes (82%), the tumor flattened completely. Visual acuity was 20/60 or better in 43 eyes (86%) before treatment and in 14 eyes (28%) at the last examination because of radiation vasculopathy. Neovascular glaucoma developed in 1 eye, and total retinal detachment developed in 2 eyes. Tumor recurrence was observed in 1 patient.

Conclusions: Although long-term results are necessary to properly appraise this new therapy, transpupillary thermotherapy may be useful as a complementary modality to brachytherapy.


**RESULTS**

All but 1 tumor exhibited reduction in tumor height; in 41 patients (82%), the tumor flattened completely after TTT within a mean follow-up period of 20.5 months (range, 6-49 months). Visual acuity was 20/60 or better in 43 eyes (86%) before treatment and in 14 eyes (28%) at the last examination.

Results of TTT on 21 patients with melanoma that had insufficiently responded to 800 Gy 106Ru brachytherapy are shown in Table 1. The mean period between the 2 treatment modalities was 14 months (range, 5-65 months). Of these tumors, 18 (86%) flattened completely by a mean of 8.3 months (range, 1-29 months) after TTT. The mean tumor height reduction 3 months after TTT was 1.6 mm (range, 0.1-3.3 mm). Visual acuity was 20/60 or better in 18 eyes (86%) before 106Ru plaque treatment but in only 4 eyes (19%) at the last examination.

**TRANSPUPILLARY** thermotherapy (TTT) is a new approach for the treatment of choroidal melanoma. We used infrared radiation at 810 nm, which produced optimal penetration into tissue but very low absorption by ocular media. Deep penetration of heat was also promoted with use of a large 3-mm-diameter radiation beam and a long 1-minute exposure time. Calculated intratumoral temperatures were 45°C to 60°C, which provided heat that would exert a direct destructive effect on tumor cells. Tumor necrosis was up to 6 mm deep in animal experiments and up to 3.9 mm in human choroidal melanoma. Thermotherapy differs from hyperthermia in that the latter is performed at temperatures of 42°C to 44°C, which do not cause permanent tumor damage but enhance the effect of radiotherapy. It also should not be confused with photocoagulation, which only causes superficial tumor necrosis of 0.2 to 1.0 mm.

The initial results of TTT in patients with choroidal melanoma have been promising. This report describes the results of ruthenium 106 brachytherapy and TTT, which we named sandwich therapy, in 50 patients with choroidal melanoma after a follow-up period of 6 months or more.

From the Department of Ophthalmology, Leiden University Medical Center, the Netherlands.
PATIENTS AND METHODS

We treated 50 adult patients, 25 men and 25 women, with $^{106}$Ru brachytherapy and TTT. Patient age at first treatment was 59 years (range, 35-80 years). The tumor was located in the right eye in 29 patients and in the left eye in 21 patients. Mean tumor diameter was 11.2 mm (range, 5.8-15 mm). In 21 tumors, the central border was more than 3.0 mm from the fovea, in 29 it was 3.0 mm or less, and in 5 it was 0.5 mm or less from the fovea.

There were 3 categories of patients: (1) 21 were treated with TTT when regression of the melanoma height at 14 months (range, 3-65 months) after $^{106}$Ru plaque treatment was insufficient; (2) 10 patients with a tumor more than 5 mm in height were treated by an episcleral dose of 800 Gy $^{106}$Ru brachytherapy and TTT; and (3) 19 patients with a melanoma of 5 mm or less in height were treated by a radiation dose of 600 Gy and TTT. The mean interval between both treatment modalities was 27 days (range, 2-67 days).

The treatment endpoint was a complete flattening of the tumor as shown on B-scan echography and absence of fluorescence as shown on angiography. The effect of TTT, measured as a reduction of tumor height, required 3 to 4 months. Flattening of large tumors required 2 or 3 TTT treatments.

The present study was approved by the Medical Ethical Committee of the Leiden University Medical Center (the Netherlands), and informed consent was obtained from each patient after the nature of the procedure had been fully explained.

The diagnosis of choroidal melanoma was based on the results of ophthalmoscopic examination, ultrasonography, and perimetry. Fluorescein angiography was performed with special attention to the presence of cystoid edema and microvascular changes in the macula. The basal dimensions of the tumor were determined by B-scan ultrasonography; tumor height was determined by A- and B-scan ultrasonography.

Before treatment, the pupil was dilated with 5% phenylephrine hydrochloride and 0.25% tropicamide eyedrops. Parabulbar anesthesia was achieved with an injection of 2 mL of 2% prilocaine hydrochloride (Citanest) via a Greenbaum cannula, for immobilization and to preclude pain.

To perform TTT, an infrared diode laser (Iris, Mountain View, Calif, or Nidek, Tokyo, Japan) was attached to a slit lamp (Haag-Streit, Bern, Switzerland). The optical system of the laser allowed a beam diameter in the range of 1.0 to 4.5 mm. For the laser lens we used an infrared-coated panfunduscope (Rodensonch, Munich, Germany), the Mainster lens (Ocular Instruments, Bellevue, Wash), and the quadraspheric and the transseptator lenses (Volk, Mentor, Ohio).

In most patients, the diameter of the irradiation beam was 3.0 to 3.5 mm; a diameter of 2.0 to 2.5 mm was used when treating tumors close to the fovea or optic disc. We started treatment at the center of the tumor with a relatively low energy level that showed little or no visible effect after a 1-minute exposure. The energy level was then raised stepwise until edema turned the tissue grayish at the end of the 1-minute exposure. We avoided energy levels that might produce an early photocoagulation effect, as increased reflection and scatter reduce the rate of transmission into the tumor. Because of the variations in beam diameter, the energy output of the laser was calculated in watts per square centimeter on the target area. Energy levels ranged from 6.0 to 13.0 W/cm$^2$; in 54% 8.0 to 9.5 W/cm$^2$. The number of applications ranged from 5 to 15, depending on the diameter of the tumor.

After TTT, mydriatic and 0.1% dexamethasone eyedrops were administered twice daily for 1 week.

### Table 1. Results of TTT in Choroidal Melanoma Insufficiently or Not Responding to Plaque Therapy With Ruthenium 106

<table>
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<tr>
<th>Patient No.</th>
<th>No. of TTT†</th>
<th>Tumor Height Before TTT, mm</th>
<th>Tumor Height at 3 mo, mm</th>
<th>Time Until Tumor Flat, mo</th>
<th>Final Tumor Height, mm</th>
<th>Control Period, mo</th>
<th>Before Therapy</th>
<th>Last Control</th>
<th>Location‡</th>
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<td>20/25 20/200</td>
<td>+</td>
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<td>6</td>
<td>20/60 20/60</td>
<td>+ (E)</td>
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* TTT indicates transpupillary thermotherapy; CF, counting fingers; LP, light perception; NG, neovascular glaucoma; E, enucleation; and ellipses, not applicable.
† Number in parentheses is the interval in months between the first and second TTT treatments.
‡ The distance of the tumor margin in millimeters from the fovea is designated as follows: − indicates >3.0; +, ≤3.0; and ++, ≤0.5.
The results for 10 patients with melanoma more than 5.0 mm in height after 800 Gy \(^{106}\)Ru brachytherapy and TTT are shown in Table 2. The mean tumor height before TTT was 6.5 mm (range, 5.2-8.4 mm). The mean tumor height reduction 3 months after TTT was 3.0 mm (range, 1.3-4.5 mm). Seven tumors (70%) flattened completely by a mean of 11.7 months (range, 5-22 months) after both treatments. Visual acuity of 20/60 or better was present in 8 eyes (80%) before treatment but in only 2 eyes (20%) at the last examination.

The results for 19 patients with melanoma of 5 mm or less in height after 600 Gy \(^{106}\)Ru brachytherapy and TTT are shown in Table 3. The mean tumor height before TTT was 3.6 mm (range, 2.0-4.8 mm); mean tumor height reduction 3 months after TTT was 2.3 mm (range, 0.7-4.5 mm). Sixteen tumors (84%) flattened completely; 8 were already flat after 1 month. Visual acuity was 20/60 or better in 17 patients (89%) before treatment, and in 8 (42%) at the last examination.

Radiation vasculopathy associated with considerable loss of vision was the most important complication. The anterior chamber and vitreous may sometimes show a slight flare and some cells, but clinically manifest inflammation was not observed. A localized white...
subcapsular cataract developed in 2 patients when the radiation beam accidentally touched the iris border, but did not progress over time or interfere with vision. A transient serous retinal detachment over the tumor was sometimes noticed small hemorrhages in the transition zone between viable and necrotic parts of the tumor where heat was sufficient to damage the vessel wall but insufficient to cause thrombosis.

Signs of intraocular inflammation after TTT were minimal, owing to the low absorption of radiation of 5% by clear ocular media. When retinal vessels constrict during TTT, occlusion can be prevented by discontinuing TTT and restarting treatment at a lower energy level.

In 41 (82%) of 50 patients, the tumor flattened completely after \(^{106}\text{Ru}\) treatment and TTT. Visual acuity was 20/60 or better in 43 eyes (86%) before treatment and in 14 eyes (28%) at the last examination.

The mean height reduction 3 months after TTT in melanomas greater than 5 mm was 3.0 mm (range, 1.3-4.5 mm), which corresponds with histological findings of 1.3- to 3.9-mm depth of necrosis in human choroidal melanomas after TTT before enucleation. The mean tumor height reduction in melanomas 5 mm or less in height after combined treatment was 2.3 mm (range, 0.7-4.5 mm). The mean decrease in height after TTT in tumors that responded insufficiently to \(^{106}\text{Ru}\) treatment was 1.6 mm (range, 0.1-3.3 mm), significantly less than in melanomas more than 5 mm in height (P = .003; Student t test). This may be attributed to partial tumor necrosis, which had developed during the period of 14 months (range, 5-65 months) between brachytherapy and TTT. This was evident in the necrotic melanoma that failed to shrink after TTT (Table 1, patient 21).

For the treatment of choroidal melanoma, transscleral hyperthermia is performed by microwave, localized current field, ultrasound, and ferromagnetic thermoseeds at a tumor temperature of 42°C to 44°C for 30 minutes or more to enhance the effect of radiotherapy. We designated temperatures of 45°C or more as thermotherapy because that temperature exerts a direct cytotoxic effect on cells, and additional radiotherapy is not required.

Necrosis and vascular occlusion in heat-damaged tissue develop rapidly, within 24 hours in hamster melanoma and within 2 days in human choroidal melanoma. Clearance of necrotic debris takes 3 to 4 months and is evident as reduction in tumor height on ultrasonography.

After radiotherapy, cell damage and tumor regression develop gradually and may continue for several years. Despite progressive vascular occlusion, large vessels may remain perfused many years after irradiation.

Fluorescein angiography after TTT shows a rather sharp demarcation between the nonfluorescent heat-treated area and the surrounding normal fluorescence, as also found on histological examination, because the choroid adjacent to the field of thermotherapy, which has a high blood perfusion rate, acts as a heat sink. Conversely, after brachytherapy the treated area is surrounded by zones of nonperfusion of the choriocapillaris layer and atrophy of the retinal pigment epithelium.

Occlusion of tumor vessels in the heat-treated area restricts the development of hemorrhages and subretinal exudation, which after TTT was less than after brachytherapy. On histopathological examination we sometimes noticed small hemorrhages in the transition zone between viable and necrotic parts of the tumor where heat was sufficient to damage the vessel wall but insufficient to cause thrombosis.

Table 1 includes information on 3 patients who were treated with \(^{106}\text{Ru}\) plaque treatment and 3 transpupillary thermotherapy procedures on an 8.0-mm elevated tumor (Table 2, patient 6); s indicates sclera.
Absence of pigmentation in amelanotic melanomas allows for increased penetration of infrared radiation into tissue and for a decreased volume uptake of radiation converted into heat. The mean energy required for the treatment of amelanotic melanomas was 15% higher than for pigmented tumors; the reduction of tumor height 3 months after TTT was 33% more in amelanotic than in pigmented tumors.

Macular edema and microvascular damage, the fluorescein-angiographic evidence of radiation vasculopathy, were associated with loss of visual acuity because it was 20/60 or better in 86% of eyes before treatment and only 28% at the last examination. Radiation vasculopathy might be induced by thermotherapy or brachytherapy. The latter may be of more importance because loss of visual acuity mostly occurred 6 months or more after treatment, and better visual results were reported when TTT was performed as the sole treatment. Macular capillaries are very susceptible to radiation; moreover, macular microangiopathy may already be present in eyes with peripheral choroidal melanomas. Para-macular tumors are at considerable risk for evoking radiogenic vasculopathy with loss of central vision.

For tumor treatment, we combined TTT with 106Ru plaque treatment, because in 51% to 64% intrascleral and in 11% to 13% episcleral, tumor cells are found that may be a source of local and extrascleral outgrowth. The incidence of tumor recurrence after transscleral melanoma resection was significantly higher in eyes without than with adjunct plaque radiotherapy. The high incidence of tumor recurrence with extraocular tumor extension after melanoma resection and after photocoagulation treatment supposedly originate from intrascleral tumor cells. In 1 eye that received TTT before enucleation, histopathological examination showed total tumor necrosis up to the sclera, but in the sclera, a cluster of melanoma cells without signs of necrosis was evident. When TTT is performed as sole treatment, heating of the sclera must be sufficient to destroy intrascleral tumor cells. Transscleral thermotherapy holds promise in the treatment of choroidal melanoma as an effective nonsurgical outpatient procedure that can be repeated. The 2 treatments, TTT and brachytherapy, named sandwich therapy, are complementary because the effect of the TTT is maximal at the top of the tumor and that of the brachytherapy at its base. However, long-term results are necessary to properly appraise this new form of therapy.

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