

Preliminary Results of Combined Simultaneous Transpupillary Thermotherapy and ICG-Based Photodynamic Therapy for Choroidal Melanoma

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■ **BACKGROUND AND OBJECTIVE:** To evaluate whether the combination of simultaneous hyperthermia by transpupillary thermotherapy and indocyanine green–based photodynamic therapy is an effective treatment for small and medium choroidal melanomas.

■ **PATIENTS AND METHODS:** Twenty-five patients with small and medium choroidal melanomas were treated with combined simultaneous transpupillary thermotherapy and indocyanine green–based photodynamic therapy.

■ **RESULTS:** The median age of the 25 patients was 64 years (range, 35 to 88 years). The pretreatment volume of the tumors ranged from 15.9 to 653.5 mm³ (mean, 118.7

± 146.6 mm³). After a mean of 2.4 treatments (range, 1 to 5 treatments), all of the tumors but one showed a significant volume reduction without clinical evidence of recurrences. The follow-up ranged from 6 to 59 months (mean, 12 ± 14 months). Complications included retinal vascular occlusions, edema and superficial scarring of the macula, and rhegmatogenous retinal detachment.

■ **CONCLUSIONS:** The effects of combined simultaneous transpupillary thermotherapy and indocyanine green–based photodynamic therapy appears to be effective in achieving local tumor control in selected small and medium choroidal melanomas.

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INTRODUCTION

Choroidal melanoma is the most common intraocular malignant tumor of the adult eye.¹ Several methods for the management of choroidal melanoma

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have been described, including enucleation, plaque brachytherapy, charged-particle radiotherapy, local resection, laser photocoagulation, hyperthermia, and observation.²⁻¹⁰ Recently, the Collaborative Ocular Melanoma Study reported that there is no difference in survival when medium choroidal melanomas are treated with either enucleation or I-125 brachytherapy.¹¹

The ideal treatment for choroidal melanoma would eradicate the tumors locally while preserving ocular function. Radiation therapy has replaced enucleation as the most common treatment for medium choroidal melanoma. However, chronic radiation-induced complications, including cataract formation, radiation retinopathy, optic neuropathy, and neovascular glau-

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coma, may eventually impair ocular function or even result in loss of the eye.¹²

Hyperthermia delivered by transpupillary thermotherapy (TTT) has been used successfully in the treatment of choroidal melanomas and other intraocular tumors.^{3,13-18} TTT involves a near-infrared radiation therapy (810 nm) from a diode laser delivered to the tumor through a dilated pupil. Experimental models show that the temperature of the tumor increases to 45°C to 60°C (intermediate-level hyperthermia) with an exposure of 1 minute or longer inducing a direct cytotoxic effect to tumor cells.¹⁹

Photodynamic therapy has been used in the treatment of choroidal melanomas, ocular tumors, and other localized cancers.²⁰⁻²² This treatment strategy is based on the preferential uptake and retention of a photosensitizing molecule by tumors and their vasculature.²³ Subsequent irradiation of the tumor area with light wavelengths specifically absorbed by the photosensitizer generates highly reactive oxygen species that induce irreversible damage to neoplastic cells and vessels.²⁴

Indocyanine green (ICG) is a water-soluble anionic dye that was approved by the U.S. Food and Drug Administration for indocyanine angiography in ophthalmology decades ago.²⁵ Indocyanine green is safe, inexpensive, exhibits an absorption spectrum in the infrared band, and has been associated with only isolated case reports of adverse reactions.²⁶ In experimental models and clinical studies of choroidal melanoma, hyperthermia in combination with indocyanine green-based photodynamic therapy acts synergistically to almost double the tissue-destructive effect compared to using TTT alone.²⁷⁻³¹ ICG-based photodynamic therapy has been shown to be effective in the treatment of choroidal neovascularization from age-related macular degeneration and would also be expected to achieve similar destruction of tumor vasculature that arises from the choroid.³²

In this preliminary report, we describe our experience in treating 25 patients with small and medium melanomas using combination simultaneous transpupillary thermotherapy and ICG-based photodynamic therapy (CSTIP).

PATIENTS AND METHODS

Between October 1998 and December 2003, we evaluated 25 eyes of 25 patients with small and medium choroidal melanomas treated with CSTIP in a

retrospective, noncomparative interventional study.

Patient and Tumor Evaluation

Each patient underwent a complete ophthalmologic examination including refraction, tonometry, fundus examination with a dilated pupil, fundus photography, fluorescein angiogram, and serial ultrasonography. Systemic evaluation by an internist, and routine chest radiography (both anteroposterior and lateral views), serum liver enzyme levels, and abdominal computed tomography scans and a bony gammagraphy did not show any evidence of metastatic spread or signs of other malignancy before treatment of any of these patients. The same scheme was used twice a year during the follow-up to rule out metastatic disease. Informed consent was obtained from patients after a detailed explanation of the therapeutic alternatives and characteristics and limitations of CSTIP.

The data collected included patient age, race, gender, and visual acuity at initial and final examination. Data related to the tumor included bidimensional tumor base size and height. Tumors were classified as small (1 to 3 mm in the apical height and 5 to 16 mm in the largest basal diameter), medium (2.5 to 10 mm in the apical height and 6 to 16 mm in the largest basal diameter), and large (larger than 10 mm in the apical height and larger than 16 mm in the largest basal diameter). Also recorded were the relation with the optic disc and fovea, location (superonasal, superotemporal, inferonasal, inferotemporal, or subfoveal), pigmentation (amelanotic, light pigmented, and heavy pigmented), morphology (sessile, dome-shaped, or mushroom-shaped), the presence of subretinal fluid, orange pigment or drusen over the tumor, and fluorescein angiographic characteristics.

Ultrasonographic evaluation included both A-scan and B-scan measurements. Calipers were used to measure the tumor base (bidimensional) in addition to tumor height. The technique used to measure the tumors included aligning the probe so that the highest tumor elevation was centered for best resolution. The measurement was taken from the apex of the lesion to the inner scleral surface with both electronic and handheld calipers. This apical measurement was compared for accuracy on both transverse and longitudinal sections, and then compared with the measurement obtained from the diagnostic A-scan image. The basal dimensions were measured with both electronic and hand-

held calipers from the bi-dimensional B-scan images. Correlations with indirect ophthalmoscopy and ultrasound images were made.

Tumor volume was calculated from the measurement of three orthogonal diameters according to the formula $V = 4/3 \pi D1/2 D2/2 D3/2$.¹⁷

Inclusion and Exclusion Criteria

The eligibility criteria for treatment included primary choroidal melanoma measuring 16 mm or less in the largest basal diameter and 6 mm or less in the apical height, location posterior to the equator of the eye, and documented growth or tumor risk factor for metastasis (thickness > 2 mm, symptoms, tumor margin at the optic disc, and documented growth). Criteria also included growth with thickness greater than 2 mm, sub-retinal fluid, symptoms, orange pigment, and tumor margin at the optic disc,^{18,19} and absence of drusen or areas of retinal pigment epithelial changes adjacent to the tumor.²⁰

Exclusion criteria were recurrent choroidal melanoma, evidence of metastatic disease, pupil diameter of less than 6 mm, poor fundus view precluding clear visualization or adequate treatment of the tumor, evidence of retinal or scleral invasion, patients with lesions in the midperipheral fundus, and an indisposition to comply with follow-up program.

CSTIP Technique

Before treatment, the pupil was dilated with neosynephrine 2.5%, cyclopentolate hydrochloride 1.0% and tropicamide 1.0%. Topical anesthesia was achieved with tetracaine hydrochloride 0.5%. Retrobulbar anesthesia was preferred for pain control and consisted of an intraocular injection of 5 mL of 0.75% bupivacaine.

All of the treatments were performed by the same surgeon (PEL) with a diode laser (IRIS Laser, Mountain View, CA) delivered through a slit-lamp focused on the tumor with a fundus contact lens (Mainster widefield; Ocular Instrument, Bellevue, WA). Fifteen milliliters of an aqueous solution containing 75 mg of ICG (IC-Green; Akorn, Inc., Buffalo Grove, IL) was administered as a single intravenous bolus into a cubital vein, followed by injection of a 10 mL saline flush, 10 minutes before the beginning of treatment with the laser. The laser application was initiated using a 60-second exposure and an energy level of 550 mW using the 3 mm diameter spot. The energy was raised step-wise

by 50 to 100 mW until the surface of the tumor developed a grayish color at the final second half of each exposure time.

The treatment applications were repeated to cover the entire surface of the tumor confluent. A smaller beam diameter was sometimes used when treating near the macula or the optic disc.

Follow-up

Systematic evaluations were performed at 1, 3, 6, 9, and 12 months and every 6 months thereafter. A complete ophthalmic evaluation that included Snellen visual acuity, indirect ophthalmoscopy, fundus photography, fluorescein angiography, and A-scan and B-scan ultrasonography was performed regularly at each visit.

Treatment Aim

A volume reduction with shrinkage of the tumoral tissue without clinical evidence of activity was the aim of the treatment. Additional treatment was performed if the fluorescein angiogram showed vascular activity in the tumor or if the lesion did not regress or showed evidence of growth.

Ocular side effects of CSTIP were documented, especially those that surround the uninvolved retina, choroids, lens, and sclera.

Statistical analysis was performed using SPSS 11.0 for Windows (SPSS, Inc., Chicago, IL). The Student's *t* test was used for the quantitative variables. Significance was defined as a *P* value of less than .05.

RESULTS

Patients and Tumor Characteristics

Twenty-five patients had a mean age of 64 ± 15 years (range, 35 to 88 years). All of the patients were white. There were 13 men and 12 women. The minimum follow-up was 6 months (mean, 12 ± 14 months; range, 6 to 59 months), with 15 (60%) of the eyes followed up for at least 12 months. Thirteen (52%) patients were asymptomatic at presentation, whereas 12 presented with decreased vision or distortion. One of the patients had ocular pain as the main complaint.

Seventeen tumors were classified as small and 8 were classified as medium choroidal melanomas. The tumor was subfoveal in 2 cases, occupied one of the superior quadrants in 11 cases, and occupied the inferior

TABLE 1
Tumor Localization and Pigmentation
 (N = 25)

Characteristic	No. of Patients (%)
Localization	
Superotemporal	8 (32)
Inferotemporal	8 (32)
Superonasal	3 (12)
Inferonasal	4 (16)
Subfoveal	2 (8)
Pigmentation	
Heavy	19 (76)
Light	4 (16)
Amelanotic	2 (8)

quadrants in 12 cases (Table 1). The tumor overhung a portion of the optic disc in 2 patients, and the mean distance between the proximal border of the tumor and the fovea was 3.4 mm (range, 0 to 10 mm).

Two of 25 eyes harbored amelanotic lesions (Fig. 1). Four were light pigmented and 19 were heavy pigmented tumors. The tumor was dome-shaped in 23 patients and mushroom-shaped in 2 patients. Eight patients displayed orange pigment over the tumoral surface. A double pattern circulation was detected in the fluorescein angiogram in 13 patients before treatment. A neurosensory detachment was present in association with the tumor in 7 (28%) eyes.

Tumor Height and Volume

Mean pretreatment height and major base diameter was 2.7 ± 1.01 mm (median, 2.5 mm; range, 1.6 to 6.0 mm) and 8.56 ± 3.87 mm (median, 8.0; range, 3 to 16 mm), respectively. Mean pretreatment volume was 118.7 ± 146.6 mm³ (median, 114.6 mm³; range, 15.9 to 653.5 mm³). The mean posttreatment volume was 54.7 ± 39.8 mm³ (median, 63.8 mm³; range, 8.4 to 110.5 mm³) at the final visit ($P < .05$) (Table 2).

Considering the small and medium tumors in different analyses, both groups showed a statistically significant ($P < .05$) reduction in tumor height and volume during the follow-up and at the final visit. After a mean of 2.4 sessions of CSTIP (range, 1 to 5 sessions), all of the cases but one reached the aim of the therapy,

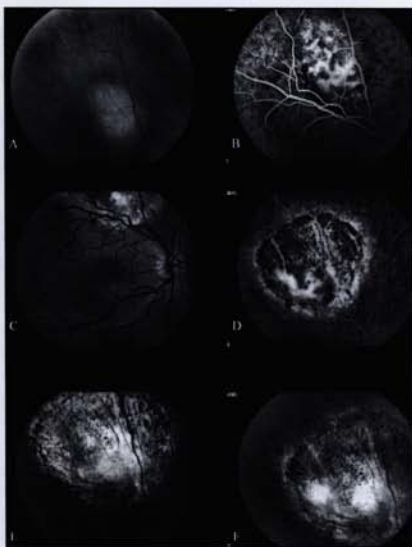


Figure 1. Case 19. (A) Color photograph of amelanotic choroidal lesion showing augmentation in size after successive controls; height = 2.4 mm by ultrasound. (B) Fluorescein angiogram with evidence of active intratumoral vascular complex. (C) Red-free photograph that notes the relationship between the posterior border of the treatment area and the optic disc and foveal area 3 months after treatment. (D) Late phase fluorescein angiogram showing staining of the wall of the retinal vessels, but without evidence of intratumoral vascular activity 3 months after treatment. (E) Color photograph of the atrophic residual tumoral tissue. (F) Final fluorescein angiogram phase with no evidence of tumor-related vascular activity 9 months after treatment.

which was to obtain a volume reduction with shrinkage of the tumoral tissue without clinical evidence of growth during the follow-up. Fifteen (88%) of the 17 small lesions and 4 (50%) of the 8 medium lesions showed a complete volume involution after treatment manifested clinically as flat scar tissue (Fig. 2).

In the rest of the cases, some grade of residual tumoral tissue was observed at the final visit. The aim of the treatment was achieved with 1 session in 5 (20%) patients. The rest of the cases required a mean of 2.75 treatments (range, 2 to 5 treatments). In almost all of the cases, the indication for re-treatment was some evidence of intratumoral vascular activity (generally fluo-

TABLE 2
Results of Transpupillary Thermotherapy Enhanced With Indocyanine Green in Choroidal Melanomas

Melanoma Size	Height Before Treatment (mm)	Volume Before Treatment (mm ³)	Tumor Height After Treatment (mm)			Volume After Treatment (mm ³)
			3 Months	6 Months	Last Visit	
Small	2.35 ± 0.41	52.89 ± 42.07	1.7 ± 0.4	1.1 ± 0.3	0.7 ± 0.4	19.94 ± 23.53
Medium	3.99 ± 1.01	258.48 ± 191.77	3.2 ± 0.6	2.2 ± 0.4	1.5 ± 0.7	93.33 ± 67.06
Both groups	2.70 ± 1.01	118.7 ± 146.6	2.2 ± 0.8	1.8 ± 0.6	1.1 ± 0.6	54.7 ± 39.8

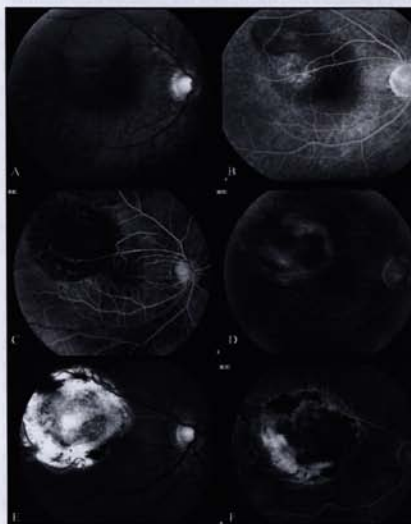


Figure 2. Case 23. (A) Color photograph of a suspicious pigmented choroidal lesion; height = 3.2 mm by ultrasound. Best-corrected visual acuity was 20/20. (B) Fluorescein angiogram showing a double pattern circulation. (C) Early frame in the fluorescein angiogram 4 weeks after the first session of combined simultaneous transpupillary thermotherapy and indocyanine green-based photodynamic therapy, showing central hypofluorescence of the tumor. (D) Late frame fluorescein angiogram showing residual exudation in the border of the lesion. (E) Red-free fundus photograph. (F) Middle frame fluorescein angiogram 3 months after the second session showing tumoral tissue without clinical evidence of activity. Best-corrected visual acuity was 20/60.

rescein leakage in the periphery of the tumor). In one patient, the indication for re-treatment was the lack of volume reduction in successive sessions. No recur-

TABLE 3
Visual Acuities Before and After Treatment

Visual Acuity	Before Treatment	After Treatment
20/20 to 20/40	17 (68%)	12 (48%)
20/50 to 20/100	4 (16%)	6 (24%)
< 20/100	4 (16%)	7 (28%)

rences were observed during the follow-up.

Visual Acuities

Preoperative visual acuity with correction ranged from 20/20 to 20/800. Seventeen (68%) of the 25 eyes had a preoperative visual acuity of 20/40 or better. Twelve (48%) eyes had a postoperative visual acuity of 20/40 or better. By the end of the follow-up, visual acuity had either improved or remained unchanged in 9 (36%) eyes (Table 3).

Complications

Retinal edema and intraretinal hemorrhages occurred immediately after the treatment in most of the patients. Vascular occlusion of the retinal vessels, either arterial or venous, occurred in 11 (44%) patients. In every case, the occlusion affected a second or third order retinal vessel on the surface of the tumor. The major macular complications were cystoid macular edema and epiretinal membrane formation. When the macular edema was secondary to a branch retinal vein occlusion, a positive response was observed to the injection of intravitreal steroids. One of the patients, with abundant subretinal fluid related to the tumor, developed a rhegmatogenous retinal detachment secondary to the treatment (case 8).

Evaluation for metastatic disease in all patients re-

vealed no sign of systemic dissemination at the time of treatment or during follow-up. At the time of writing, there had been no tumor-related deaths.

DISCUSSION

Many studies have indicated good results with TTT alone for small and medium intraocular tumors.^{6,14-20} The rationale to use CSTIP is to achieve a more complete level of tissue destruction by two mechanisms: the direct cytotoxic effect from hyperthermia and the photodynamic effect (ie, the generation of highly reactive oxygen species that induce irreversible damage to neoplastic cells and their vasculature).^{23,27,30,31} Many investigators believe hyperthermia with TTT is best achieved when the tumor is highly and uniformly pigmented.¹⁵ This is not the case in many choroidal melanomas due to variation in pigmentation and the presence of subretinal fluid.² The above two factors may cause some variability in the absorption of TTT. We believe the added effect of photodynamic therapy in these circumstances increases tumor destruction with negligible increase in expense or complications in the treatment.

In 24 (96%) patients, we observed at least 50% reduction of tumor size with treatment to the bare sclera in at least parts of the tumor. Most tumors in this series were an actively growing mass, as seen by fundus photographs, and had high-risk characteristics for continued growth or metastatic disease.³³⁻³⁵ In all but one patient, hypofluorescence at the treatment site was achieved as part of the end point. Additionally, all tumors except case 13 (discussed below) showed a change in A-scan, 8 of which were associated with loss of tumor vasculature and an increase in the internal reflectivity. No growth was seen in any of the tumors from the time of last treatment.

De Potter et al. presented data from a prospective, randomized controlled study comparing TTT melanoma treatment with and without ICG enhancement.²⁷ They believe that ICG administered before TTT does not seem to be beneficial in the tumor regression pattern. They speculate that because of blood circulation patterns and other biological mechanisms, the ICG solution may diffuse differently *in vivo* than *in vitro*, making the ICG-enhanced TTT in humans less efficient than in animal studies.

Our study parameters differed in several ways: the

timing of the laser treatment following the injection of ICG, the difference in the laser parameters used during the treatment, and the interval between treatments.

The temporal pharmacokinetic distribution of the photosensitizer between the tumor parenchyma and blood vessels may significantly alter the effect on the tumor by the photodynamic component of the therapy.^{23,24,27} Experimental data showed a two-part distribution phase related to the ICG pharmacokinetic.²⁹ The first is a phase of fast distribution lasting 2.12 ± 0.43 minutes and the second is a phase of slow elimination lasting 127 ± 40 minutes.

De Potter et al. started the treatment during the fast distribution phase (130 ± 35 seconds [range, 25 to 40 seconds]).²⁷ We prefer to deliver the laser treatment during the second, more prolonged, phase where the ICG reaches the highest concentration in the tumor mass.^{28,29,36} The time interval between the injection of ICG and treatment with thermotherapy was at least 30 minutes in our study. This additional time would allow ICG to be taken up more completely by the tumor and tumor vessel cells.

Irradiation of the tumor with TTT at this point initiates the production of reactive oxygen species to be formed in the tumor cells and their vasculature with resulting increasing tumor destruction independent from the hyperthermia effect alone.³¹ Our temperature dosimetry would be expected to be much higher in that we used a power setting between 800 to 1,300 mW with a median of 1,000 mW compared to 450 to 500 mW. Finally, our treatment cycles were every 4 weeks instead of every 3 months, to achieve adequate tumor response. Our experience indicates that waiting the additional 4 to 8 yields little further reduction in the tumor mass or vascularity.

We did see several complications in this combined treatment study that have previously been seen with TTT alone, including retinal vascular occlusions (arterial and venous), increase in the subretinal fluid immediately after treatment, subretinal pigment dispersion, macular edema and scar tissue formation over the macular region, and retinal atrophy over the treatment area that could lead to a retinal tear.^{2,3,15,18,27}

In our study, there were no anterior segment complications related to the treatment. Retinal vascular occlusion was seen in 11 (44%) patients in the treatment area. This complication seems to be more frequent in our series than in other reports, perhaps due

to the temperature dosimetry parameters used and the added photodynamic effect. Two patients in our series developed macular edema due to branch retinal vein occlusion in the treatment area. Both showed a positive response to the injection of intravitreal triamcinolone acetonide (4 mg/0.1 cc), with resolution of the edema and improvement of the visual acuity.

One patient (case 13) with extensive subretinal fluid associated with the tumor developed a rhegmatogenous retinal detachment from a break at the treatment site due to retinal necrosis. The patient was treated successfully with vitrectomy and scleral buckle and had a final visual acuity of 20/800. A power setting above 1,300 mW, as used in this patient, may cause retinal necrosis in the treatment site due to pooling of ICG in the subretinal fluid with increase in uptake of infrared light locally. Ocular and retrobulbar pain are often seen, but are easily managed with oral analgesic and typically resolve in 72 hours.

We believe CSTIP is effective in the treatment of small and medium choroidal melanomas and supports our previously reported experimental findings.³¹

This study has several limitations. As with any alternative treatment to enucleation, we cannot assume that the residual tumor is completely sterile and incapable of growth; therefore, a longer follow-up and periodic systemic examination are necessary to rule out tumor dissemination. Another weakness of the study is the retrospective design, which has no control group for comparison with the interventional group. Other drawbacks include the relatively short follow-up and the small sample size. Further studies, including a randomized, controlled clinical trial, are needed to study whether CSTIP may play a role as an alternative treatment for selected small and medium choroidal melanomas.

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