LASER AND PROTON RADIATION TO REDUCE UVEAL MELANOMA–ASSOCIATED EXUDATIVE RETINAL DETACHMENTS

BY ***Devron H. Char MD,**** *Riley Bove BA*, AND *Theodore L. Phillips MD*

ABSTRACT

Purpose: To assess whether laser-induced hyperthermia in conjunction with proton irradiation of choroidal melanoma may more rapidly decrease exudative retinal detachments.

Design: Case-control study.

Methods: This was a single-center prospective phase 1 study of choroidal melanoma patients with exudative retinal detachments. These tumors did not overhang the optic disc, involve the fovea, or have greater than 40% involvement of the ciliary body. Patients were treated with laser-induced hyperthermia and proton radiation; results were compared with those of similar patients treated at the same institution with only proton radiation. Patients were followed up in an identical manner for loss of subretinal fluid, visual acuity change, and visual field alterations.

Results: All 11 patients treated with combined laser and proton therapy had resorption of subretinal fluid with a mean duration of retinal detachment of 193 days, compared with 263 days in the group treated with only proton therapy ($P<.04$). At 1 year, visual acuity was similar in both groups.

Conclusions: Combined laser-induced hyperthermia and proton radiation may dissipate exudative detachments more rapidly than radiation alone.

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INTRODUCTION

Many patients with uveal melanoma are treated with radiation with the intent to destroy the tumor and preserve both the eye and visual function.[1] We and others have shown that with charged-particle radiation, a local control rate of more than 98% can be achieved, but significant ocular morbidity can occur.[2-4] Some factors associated with poor visual outcome are innate, such as patient age, melanoma proximity to the fovea, and increased tumor thickness.[2-6] Other factors associated with poor visual outcome, such as a pretherapy exudative detachment, may be amenable to treatment.

Historically, it was thought that visual loss was not as likely to be permanent with an exudative, as compared with a primary rhegmatogenous, retinal detachment that involved the macula.[7] Unfortunately, preradiation exudative detachments in eyes with uveal melanomas are associated with larger, more aggressive tumors and significantly worse visual outcome.[2,6,8]

Several different strategies could be used to diminish exudative detachments in eyes with choroidal melanomas. These include surgical drainage and various forms of laser. We performed a phase 1 study to determine whether 810-nm laser treatment delivered shortly after the surgery for tantalum marker ring localization would diminish exudative detachment and possibly improve visual outcome in patients undergoing charged-particle radiation.

DESIGN

This was a case-control study.

METHODS

Patients were entered into this phase 1 trial after informed consent was obtained. We have complied with federal and state laws regarding the use of human subjects in medical research. Patients had choroidal melanomas with an exudative retinal detachment that involved at least 15% of

From the Tumori Foundation CPMC, San Francisco, Calif (Drs Char and Bove); the Department of Radiation Oncology, University of California, San Francisco (Dr Phillips); and the Department of Ophthalmology, Stanford University, Stanford, Calif (Dr Char).
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*Presenter.
Bold type indicates AOS member.

the fundus. No patient had prior eye tumor therapy. Tumors that overhung the optic nerve, were either contiguous to the fovea or subfoveal in location, or had greater than 40% involvement of the ciliary body were excluded.

Eleven patients were treated in this study; six were males. Mean patient age was 45 years. The mean largest tumor diameter was 12.3 mm (range, 8-15 mm), and the mean quantitative ultrasonographically measured thickness was 6.3 mm (range, 4.2-12.7 mm). Tumors were located entirely posterior to the equator in eight cases and were within 3 mm of the optic nerve and/or fovea in five patients. Patients were treated with confluent 810-nm laser spots over the tumor surface in the first weeks after tantalum marker ring placement. Laser spot size was generally 3,000 μm; a few tumors less than 3 mm from the fovea received some laser, at the posterior tumor edge, with 2,000-μm spots. The power density used was between 600 and 900 mW for 1 minute to achieve gradual gray-white appearance detectable after 45 seconds of treatment. Patients were treated with 56 gray equivalents (GyE) of proton radiation generally between 1 and 2 weeks later. Mean postradiation follow-up is 13.6 months (range, 2-35 months).

Historic controls that matched the previously described criteria were chosen from the charged-particle treatment database. The same doctors treated these 45 patients with 56 GyE of proton radiation without laser therapy. Radiation and follow-up were performed in the same manner throughout the study.

We examined the patients 3 months after therapy, then at 3-month intervals for the first year, 4- to 5-month intervals for the second year, twice in the third year after treatment, then yearly.

Three experimental parameters were assessed: time to subretinal fluid resorption, visual acuity 1 year after treatment, and visual field changes. Visual acuities were obtained from automated refractions. Visual fields were done with the same automated perimetry throughout the study. Both parametric and nonparametric statistical analysis was performed.

RESULTS

A comparison of the 11 patients (experimental group) who received proton radiation and laser and the 45 control patients who were treated with only proton radiation is shown in the Table. The patients who received only radiation were older; other pretreatment parameters were similar.

The mean time to fluid resorption, in patients whose fluid dissipated, was 192 days in the experimental group versus 263 days in the control group; this difference was statistically significant ($P<.04$). No patient in the combined treatment group and 11 patients in the irradiated group continued to have an exudative detachment throughout their follow-up; four of these latter patients underwent enucleation. As shown in the Table, there was no difference in visual acuity loss in the combined versus the control group. Four of eight retained greater than 20/30 vision at the time, while four had acuity of 20/200 or worse. There was no significant difference in visual field scotoma in the two groups.

DISCUSSION

In this phase 1, nonrandomized study, we noted that exudative retinal detachments dissipated significantly more rapidly after a combination of laser-induced hyperthermia and proton radiation as compared with proton radiation alone. The early visual outcome of the experimental group did not appear to be different from that of historic controls, although follow-up time for many of the laser patients has not been sufficient.

It is uncertain whether laser-induced hyperthermia has a beneficial or an adverse impact on radiation vascular complications; mean onset of clinically detectable radiation retinopathy is between 24 and 36 months, and too few patients have this length of follow-up to ascertain the effect on that complication.[2,6,9]

Several other issues are unresolved by this study. Data on the mechanism of tumor cytotoxicity with 810-nm laser therapy of uveal melanoma is limited. In a small number of cases, it appears that the depth of tumor penetration by sufficient laser energy to be cytotoxic is less than 4 mm.[10-12] It is likely that the diminution of subretinal fluid is due to closure of leaking superficial tumor vessels, since our melanomas were too thick for the laser energy to penetrate through the entire tumor.

It is possible that the laser therapy could have either deleterious or beneficial effects on tumor control. We and others have noted significant enhancement of radiation effects from heat in animal models of uveal melanoma.[13] Several investigators[14-17] have used a combination of this form of laser-induced hyperthermia plus brachytherapy to treat uveal melanomas. In a recent study, Shields and colleagues[17] noted increased tumor control, nearing that achieved with charged particles when this form of laser is used after I-125 brachytherapy. Although charged-particle radiation is less influenced by tumor oxygenation compared with either I-125 brachytherapy or conventional photon radiation, if laser therapy decreased blood flow or oxygenation, it is possible that it might result in less efficient tumor cytotoxicity.[18]

This report expands the potential uses of this form of laser therapy in uveal melanoma. Some patients with small, posterior choroidal melanomas can be treated with

laser therapy alone.[19,20] The long-term efficacy of this approach is uncertain. We have used this laser modality as a solitary treatment mainly in tumors that are in close proximity to the optic nerve or fovea but do not involve those structures. In many such cases, by using very tight margins, we can obliterate the tumor and retain good vision. In most series, there is a short-term control rate of about 95% for small melanomas and high-risk nevomas, but long-term results and the incidence of complications will probably vary depending on tumor selection parameters, how tight the margins are, and whether or not the technique is used to try to retain vision.[20]

We and others have also used this laser approach to salvage patients who had developed small, flat marginal recurrences after radiation.[21] Too few cases have been reported to determine the efficacy of this laser technique. In small numbers of cases, we have salvaged about 60% of selected cases.

In this study, we have shown that laser may be used as an adjuvant to radiation to more rapidly decrease exudative detachments; however, the long-term efficacy is uncertain.

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TABLE: COMPARISON OF PATIENT AND TUMOR CHARACTERISTICS

CHARACTERISTIC	RADIATION + LASER (11 PATIENTS)	RADIATION ONLY (45 PATIENTS)
Age, yr	45.4	60.5
Sex	6 male (55%)	22 male (48%)
Tumor anterior margin		
1 - Posterior fundus, posterior to equator	8 (73%)	27 (60%)
2 - Posterior fundus, anterior to equator	1 (9%)	9 (20%)
3 - In ciliary body	2 (18%)	9 (20%)
Tumor posterior margin		
1 - Posterior fundus, posterior to equator	11 (100%)	42 (93%)
2 - Posterior fundus, anterior to equator		1 (2%)
3 - In the ciliary body		2 (4%)
Tumor location completely posterior to equator	8 (73%)	27 (60%)
Tumor location within 3 mm of optic nerve or fovea	5 (45%)	24 (53%)
Largest diameter	12.3 mm (8-15)	12.6 mm (6-22)
Largest diameter >10 mm	9 (82%)	36 (80%)
≤10 mm	2 (18%)	9 (20%)
Ultrasound thickness	6.3 mm (4.2-12.7)	6.0 mm (1.9-12.6)
Ultrasound thickness >5 mm	7 (64%)	26 (58%)
≤5 mm	4 (36%)	19 (42%)
Mean days to resorption (excluding nonresorbers)	192	263
Follow-up, mo	13.6 (1.6-34.5)	30.8 (3.3-89.3)
Change in VA at 1 yr	(N=8)	(N=42)
(Log 1-yr VA to Log preproton VA)	0.599 (0.000 to 0.806)	0.584 (–0.699 to 2.000)

VA, visual acuity.

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DISCUSSION

Dr D. Jackson Coleman. Dr Char presents a small case-control study on the use of long pulse diode laser photocoagulation as an adjunct to charged particle radiation for control of preexisting exudative detachment in uveal melanoma. He reports a significant increase in resorption rate in the photocoagulation plus group and no significant difference in the visual acuity loss between the two groups at one year.

The usual caveats must apply when considering a small case control study of this sort. The difficulty of obtaining good matching in the active and control groups can increase variance in the outcome variables and limit the overall usefulness of the results. In a larger study of the resolution of exudative retinal detachment after brachytherapy, Harbour et al., reported that 90% of patients had resolution at 1 year post-treatment with a mean time to resorption of 5.6 months.[1] This is similar to the rates reported by Dr Char of 6.4 months for the photocoagulation plus group, and 8.7 months for the proton beam only group.

While exudative detachments are prognostic for the propensity for growth in small melanomas.[2,3] Work by Kivela et al. suggests that they are nonsignificant for overall survival.[4] The concept of using high dose long pulse photocoagulation to alter the exudative ability of local tumor vasculature does have merit at least in the context of maintaining functional vision in these eyes. Larger studies are needed to confirm resorption rate improvement and the tradeoff of improved SRF resorption with additional laser induced damage to the retina and choroid, and its overall effect on vision.

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Dr Dennis Robertson. It is important to consider that the visual acuity you are hoping to modify is for the short term. For example, the long-term effects of radiation as

reported in the proton-beam study of Dr Evan Gragoudas demonstrate that 88% of the treated eyes have hand movement vision or worse at 10 years; and the results of brachytherapy are probably about the same. You have discussed a short-term effect of your therapy that may improve the visual acuity within the first couple of years after radiation, sometime before the visually damaging effects of the radiation have occurred.

Relative to your choice of intervention, I know that you are aware of the problems with transpupillary thermotherapy and presume that you're applying this fairly lightly if your aim is to promote resolution of subretinal fluid. If you are using heavy applications of transpupillary thermotherapy, such as might be used as a primary treatment of a small melanoma, then you are going to cause wedge-shaped field defects, and you may also cause some distant changes in the macula such as macular pucker or cystoid macular edema. So you might be adding short-term complications to the already known long-term complications of radiation.

If the aim is to reduce the subretinal fluid, why not apply a light surface dusting treatment over the tumor using argon laser (the indirect delivery system, for example) monitored by fluorescein angiography to identify the leakage sites? This works with small melanomas, and light applications of laser photocoagulation do not cause the collateral damage we often see with transpupillary thermotherapy.

Dr Devron H. Char. Dr. Coleman factiously mentioned that our paper's title was not on "TTT," but instead a variant of laser induced heating. I am reticent to use the term "thermotherapy," since there is a paucity of in vivo data on heating of uveal melanomas with these types of laser therapy. We showed in a rabbit hyperthermia eye tumor model years ago that to accurately obtain uniform and precise hyperthermia, we used as many as 12 thermisters in the tumor. As Dr Coleman knows well, on average, a change in the tumor temperature of half degree centigrade produces more than one log unit difference in tumor cytotoxicity. Since we do not have uveal melanoma "heat maps" I have chosen to use the terminology of "laser heating."

Now I'd like to make some comments about Dr Robertson's points. It's important to realize that you can model visual results, and, in fact, there's a subset of patients that, at 10 years after helium or after proton beam therapy, will have 20/40 or better vision. There's also a subset that will be worse. I wrote in the 1970s in an American Journal of Ophthalmology Editorial that two-thirds of the melanomas that we see around the country are within 3 millimeters of the nerve and fovea; anything you do to that group is going to deliver enough energy to those structures to have significant visual side effects. Dr Robertson's point about how to treat them is a very good one and using argon would probably also work. The reason we used laser induced heating was that we thought it might give us a greater effect since we were dealing with thicker tumors, but I think the other experiment would certainly be a reasonable one.