

**Proton Therapy for Exudative Age-Related Macular Degeneration:**

**A Randomized, Sham-Controlled Clinical Trial**

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Supported by the Indiana Lions Club, an unrestricted grant from Research to Prevent Blindness, Inc, New York, and Intercampus Research Grant from Research and University Graduate School, Indiana University and the Pearl Vision Foundation

Dr. Ciulla is a recipient of a career development award from Research to Prevent Blindness, Inc., New York

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**Abstract**

**Purpose:** To examine the effect of proton beam irradiation on subfoveal choroidal neovascular membranes (CNVM) in age-related macular degeneration (AMD).

**Methods:** Thirty-seven subjects with subfoveal CNVM due to AMD were enrolled in a prospective, randomized, double masked trial of 16 Gy of proton irradiation delivered in two fractions, 24 hours apart, versus sham control treatment. Eligibility criteria include subjective visual acuity impairment of less than six months duration, and best corrected visual acuity between 20/40 and 20/400. The radiation treatment involved a total dose of 16 Gy in two fractions. Masked assessment of angiography and visual acuity was performed at 3, 6, 12, 18 and 24 months. Recruitment was halted at 37 subjects for ethical reasons regarding randomization to sham treatment when FDA-approval of Visudyne was anticipated.

**Results:** Both treated and sham-treated control groups exhibited stable vision, on average, at 12 months. Data for the second year is more preliminary and there are fewer data points due to dropout. Proton irradiation was associated with a trend towards stabilization of visual acuity, but this did not reach statistical significance. No correlations were found within the fluorescein angiography data, including greatest linear dimension of CNVM total size, area of active leakage, area of associated sub-retinal hemorrhage, and intensity. This radiation protocol appears to cause no great harm in subfoveal CNVM due to AMD.

**Conclusion:** With the introduction and acceptance of photodynamic therapy for subfoveal,

predominately-classic CNVM for AMD, future studies will require more complex and larger design, in order to determine if radiation can play either a primary or adjunctive role in treating these lesions.

Since choroidal neovascular membranes (CNVM) are composed of endothelial cells, which are proliferating more rapidly than the endothelial cells of the retina, they are more radiation sensitive than the retinal vasculature. In the mid-1990's, early pilot studies of radiation therapy for exudative age-related macular degeneration (AMD) indicated stabilization or regression of CNVM treated with radiation.[1-17] One of these early studies suggested that higher doses of radiation may have a more beneficial effect in maintaining a stable visual acuity and CNVM on fluorescein angiography.[18, 19] Given this apparent dose response effect, several groups designed studies to deliver ionizing radiation to the macula using modalities that limited the exposure of ionizing radiation to normal radiosensitive structures of the eye, such as the optic nerve or lens. These methods included stereotactic external photon beam irradiation of the posterior pole, gamma knife therapy,[20] brachytherapy, during which radioactive plaques are sutured to the posterior pole of the eye and explanted several days later,[1, 21] and proton beam irradiation,[12] This current report describes a prospective, randomized, controlled double-masked study of proton radiation for exudative AMD to evaluate the efficacy of radiation therapy versus no treatment in patients with exudative AMD. Control subjects were randomized to sham treatments. At the time of recruitment for this study photodynamic therapy for subfoveal CNVM was not approved.

## **Methods**

### *Subject Recruitment*

Patients were recruited from the retina referral practice, general ophthalmology clinics at Indiana University Medical Center, and the optometry clinics at Indiana University School of Optometry.

Eligible patients were asked to participate and sign a consent form. Subjects were randomized to proton therapy or sham therapy in a double masked fashion. Eligibility criteria were as follows:

*Inclusion Criteria*

1. Subfoveal CNVM due to age-related macular degeneration, as defined by the international classification system
2. Subjective visual acuity impairment of affected eye less than six months duration
3. Best corrected visual acuity of affected eye equal to or less than 20/40 and better than or equal to 20/400

*Exclusion Criteria*

1. Inability to maintain steady fixation with either eye
2. Pre-existing microangiopathy, including diabetic retinopathy[22]
3. Media opacity sufficient to preclude examination and follow-up
4. Inability to give informed consent
5. Inability to comply with follow-up regimen

Patient enrollment began in June, 1998 and ceased in January of 2000. Recruitment was halted at 37 subjects for ethical reasons regarding randomization to sham treatment when FDA-approval of Visudyne was anticipated.

### *Subject Assessment*

All patients underwent a baseline examination to evaluate their visual function and to document their ocular health. Best corrected visual acuity was measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) charts and the best corrected refraction was achieved through a standardized refraction protocol. Near reading performance was measured using the MNREAD Acuity Charts and a timer whenever possible. The examination included, intraocular pressure determination, cataract grading, and dilated fundus examination. Fundus examination included direct, indirect, and contact lens techniques as necessary. Stereo fundus photography and fluorescein angiography were performed within 1 week of proposed treatment. The location and dimensions of the CNVM were confirmed on fluorescein angiography.

Treated and control patients underwent visual function reassessment (according to the techniques noted above) along with photography and fluorescein angiography at 3, 6, 12, 18 and 24 months. Masked assessment of angiography and analysis of visual acuity between groups was

performed. Masked assessment of the angiograms included measurement of the greatest linear dimension of the choroidal neovascular lesion; angiograms were graded as improved, stable, or worsened compared to baseline with regard to total lesion size, intensity of leakage, area of active leakage, and area of associated subretinal fluid and hemorrhage.

### *Proton Radiation Treatment Methods*

The proton radiation treatment arm included a total dose of 16 Gy in two fractions on two consecutive days. This dose was selected because the preliminary reports from the Lima Linda study showed no early radiation retinopathy with 8 Gy protons in a single fraction, but did show some radiation retinopathy at 14 Gy in a single fraction.[23, 24] Treatment planning, simulation, and bite block fabrication were performed at the Indiana University Cyclotron Facility. Head fixation with bite block augmentation was used for anatomical immobilization. Eye gaze fixation on a lighted cross hair target and real time treatment observation achieved a localization accuracy of 0.5mm. Video magnification x 12 allowed direct function interruption by the treating oncologist. Treatment was paused should the position limit be exceeded.

**Results**

Thirty seven subjects with subfoveal CNVM from exudative AMD, symptomatic for fewer than 6 months and with visual acuity no worse than 20/400, were randomized to sham treatment or proton treatment with 2 fractions of 8 Gy in a prospective double masked fashion.

As noted above, recruitment was halted at 37 subjects when FDA-approval of Visudyne was anticipated. The median age of the entering subjects was 71.1 years and the mean entering best corrected visual acuity measured 0.6 +/- 0.3 logMAR units.

Of the 37 subjects enrolled in this investigation, there were 14 women and 23 men. No data was recovered from 7 subjects, due to 4 baseline discrepancies, 1 off-protocol treatment due to equipment failure, and 2 discontinuations prior to the first treatment. One subject suffered retinal detachment not associated with the treatment, one exhibited non-impairing optic neuropathy. There were no cases of radiation retinopathy noted to date. Of the remaining subjects in whom angiograms were interpretable, baseline CNVM morphology included 13 classic, 11 mixed classic and occult, and 4 occult CNVM. The CNVM morphology was not considered in the randomization scheme. The mean greatest linear dimension of the CNVM at baseline measured 3796 microns.

The average visual acuity data for both the treated and the sham group is presented in the table. The average visual acuity for the untreated group was approximately 2 lines worse than that recorded for the sham group at the time of the entry into the investigation (0.5 logMAR units in 20 treated subjects compared to 0.7 logMAR units in 10 untreated control subjects). However, this difference

was not statistically significant. This relationship was maintained throughout the 24 months observation period

Both treated and sham-treated control groups exhibited stable vision, on average, at 12 months.

Data for the second year is more preliminary and there are fewer data points due to dropout. Proton irradiation was associated with a trend towards stabilization of visual acuity, but this did not reach statistical significance. No correlations were found within the fluorescein angiography data, including greatest linear dimension of CNVM total size, area of active leakage, area of associated sub-retinal hemorrhage, and intensity. There were no correlations between changes in visual acuity and changes in CNMV total size, area of active leakage, area of subretinal hemorrhage, or intensity of leakage.

## **Discussion**

Since the mid 1990's, there have been conflicting many reports regarding the efficacy of radiation therapy for exudative AMD. Some studies, for example, which used nonrandomized or historic controls, suggested no beneficial effect of low dose radiation therapy for exudative AMD,[27-30] while some recent small randomized[31, 32] and non-randomized[24, 33-38] trials suggested that radiotherapy was beneficial. With regard to CNVM morphology, some of these trials suggested a possible beneficial effect particularly with classic CNVM compared to occult CNVM.[39, 40] A small uncontrolled prospective trial suggested that radiation can stabilize occult subfoveal CNVM, [41] but another uncontrolled trial suggested no benefit in occult CNVM.[42] More recently, some relatively large randomized clinical trials suggested benefit[43] while others showed no statistically significant

benefit.[44, 45]

In this current study, a prospective, randomized, controlled double-masked study of proton radiation for exudative AMD was performed. Control subjects were randomized to sham treatments, as photodynamic therapy for subfoveal CNVM was not approved for use at the time of study recruitment (June, 1998 to January of 2000). However, recruitment was halted at 37 subjects when FDA-approval of Visudyne was anticipated, for ethical reasons regarding randomization to sham treatment. Consequently, although there was a trend toward stabilization of best-corrected visual acuity in the proton-treated group, the study was too small to show a statistically significant result. However, the study does suggest that proton radiation therapy causes no great harm in, or great benefit for, subfoveal CNVM due to AMD. With the introduction and acceptance of photodynamic therapy for subfoveal, predominately-classic CNVM for AMD, future studies will require more complex and larger design, in order to determine if radiation can play either a primary or adjunctive role in treating these lesions.

**Table: Best-Corrected Visual Acuity**

<b>THE AVERAGE VISUAL ACUITY FOR TREATED AND UNTREATED SUBJECTS OVER 24 MONTHS</b>						
	<b>Baseline</b>	<b>3 Months</b>	<b>6 Months</b>	<b>12 Months</b>	<b>18 Months</b>	<b>24 Months</b>
<b>Treated (LogMAR)</b>	0.5	0.7	0.6	0.6	0.7	0.6
<b>Range</b>	0.2 - 1.2	0.4 - 1.4	0.2 - 1.2	0.2 - 1.1	0.3 - 1.3	0.2 - 1.0
<b># Subjects</b>	20	18	17	16	12	8
<b>Control (LogMAR)</b>	0.7	0.8	0.9	1.0	0.9	0.7
<b>Range</b>	0.4 - 1.3	0.2 - 1.6	0.3 - 1.6	0.4 - 1.6	0.3 - 1.2	0.4 - 1.1
<b># Subjects</b>	10	10	9	8	7	5

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