Laser Treatment in Fellow Eyes with Large Drusen: Updated Findings from a Pilot Randomized Clinical Trial

The Choroidal Neovascularization Prevention Trial Research Group

Purpose: To update the findings from the Choroidal Neovascularization Prevention Trial (CNVPT) with respect to resolution of drusen, incidence of choroidal neovascularization, and visual function.

Design: A multicenter, randomized, controlled, pilot clinical trial.

Participants: The 120 patients enrolled in the CNVPT. Patients had signs of choroidal neovascularization or retinal pigment epithelial detachment in 1 eye and had ≥10 large (>63-μm) drusen in the contralateral, or fellow, eye.

Intervention: The fellow eye of 59 patients was assigned randomly to argon green laser treatment consisting of multiple 100-μm spots at least 750 μm from the center of the fovea. The fellow eye of the remaining 61 patients was assigned randomly to observation.

Main Outcome Measures: Change in visual acuity was the primary outcome measure. Incidence of choroidal neovascularization, resolution of drusen, change in contrast threshold, change in critical print size for reading, and incidence of geographic atrophy were secondary outcome measures.

Results: Throughout 4 years of follow-up, there were no statistically significant differences in change in visual acuity, contrast threshold, critical print size, or incidence of geographic atrophy. With additional follow-up, the large increase in the incidence of choroidal neovascularization observed within 18 months of treatment was maintained; however, by 30 months, the incidence in the two treatment groups was the same. Most drusen resolution in treated eyes occurred within 24 months of the initial treatment. Treated eyes that received higher-intensity laser burns had an increased risk of choroidal neovascularization. Among eyes developing choroidal neovascularization in each treatment group, most lesions (two thirds or more) were composed of occult neovascularization only.

Conclusions: Laser treatment as applied in the CNVPT caused an excess risk of choroidal neovascularization in the first year or so after treatment. The increased early incidence of choroidal neovascularization was not associated with either a harmful or beneficial effect in this pilot study. *Ophthalmology 2003;110:971–978 © 2003 by the American Academy of Ophthalmology.*

In 1998, the Choroidal Neovascularization Prevention Trial (CNVPT) Research Group reported short-term findings from two randomized clinical pilot trials of argon green laser treatment in eyes at risk of vision loss from choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).[1] The Bilateral Drusen Study was composed of patients who had ≥10 large (>63-μm) drusen in each eye. One eye of these patients was selected randomly for laser treatment, and the contralateral eye was observed. The Fellow Eye Study (FES) was composed of patients who had exudative AMD in 1 eye and ≥10 large drusen in the contralateral, or fellow, eye. The fellow eye was randomly assigned to either laser treatment or observation. Enrollment in these pilot studies was suspended under recommendation by the Data and Safety Monitoring Committee (DSMC) because there was a higher incidence of CNV within 12 months of study enrollment in laser-treated eyes than in observed eyes, predominantly in the FES. Through 12 months of follow-up, visual acuity and contrast threshold were similar in the treated and observed eyes in both the Bilateral Drusen Study and the FES.

Follow-up of the CNVPT patients continued through the originally planned 2 years. Patients were then asked to commit to an additional 2 years of follow-up. The purpose

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of this article is to present the effects of laser treatment on drusen resolution, vision, and incidence of CNV through the 4-year follow-up period. Only results from the FES are provided, because the ongoing Complications of Age-related Macular Degeneration Prevention Trial, involving 1052 patients, is designed to provide definitive information on the value of low-intensity argon laser treatment for patients with bilateral large drusen.

Patients and Methods

The design and methods of the CNVPT FES have been described in detail in previous reports.[1–3] Only the aspects of the study design that are important for interpretation of the data presented in this report are provided below. The study design, informed consent statements, and subsequent communications to study participants about study results were approved by the institutional review board serving each participating clinical center.

Initial Evaluation and Enrollment

The major inclusion criteria for the FES were patient age ≥50 years, evidence of CNV or serous retinal pigment epithelial detachment in the nonstudy eye, visual acuity ≥20/40 in the study eye, and ≥10 large (>63-μm diameter) drusen within 3000 μm of the center of the foveal avascular zone in the study eye. The major exclusion criteria were signs in the study eye of CNV, serous retinal pigment epithelial detachment, or geographic atrophy within 500 μm of the center of the foveal avascular zone and signs of other ocular disease that might affect visual acuity in the study eye.

Visual acuity, contrast threshold, and critical print size for reading were measured, color stereo fundus photographs of the macula and disc were taken, and fluorescein angiography was performed at baseline before the study eye was randomly assigned to treatment or observation. Visual acuity for each eye was measured by using Early Treatment Diabetic Retinopathy Study visual acuity charts after a standardized refraction.[4] Contrast threshold was measured with Pelli–Robson charts at 1 m.[5] Critical print size (the print size at which reading speed decreases) was measured with MNRead Charts, a series of text passages that decrease in size by 0.1 logarithm of the minimum angle of recession with each successive passage.[6] After the enrolling ophthalmologist reviewed the angiograms, an eligibility checklist was reviewed over the telephone with a member of the CNVPT Coordinating Center (Philadelphia, PA), and a randomized treatment assignment was allocated to the patient. Between October 1994 and December 1996, 120 patients were enrolled in the FES; 59 were assigned to laser treatment, and 61 were assigned to observation.

Staff members, who were masked to treatment assignment, at the CNVPT Fundus Photograph Reading Center (Philadelphia, PA) assessed the baseline color photographs and fluorescein angiograms of enrolled patients for compliance with the eligibility criteria. In addition, photographs were graded for features of drusen, pigmentary disturbances, and atrophy according to a protocol based on a modification of the International Classification and Grading System for Age-Related Maculopathy and Age-Related Macular Degeneration.[7]

The distributions of patient and ocular characteristics were well balanced between the two treatment groups except for cigarette-smoking history. More patients in the treated group (39 [66%] of 59) reported having smoked cigarettes than in the observed group (33 [54%] of 61).

Laser Treatment

Three different laser treatment protocols eventually were used in the FES. Most patients assigned to treatment (49 [83%] of 59) were treated with the Laser 20 protocol. The Laser 20 protocol was used in all clinical centers from the beginning of patient enrollment through at least April 1996. The Laser 20 protocol specified that 20 laser burns, 100 μm in diameter, be placed in a pattern of 3 rows between the 12- and 6-o'clock positions beyond the temporal perimeter of the fovea. The innermost row of burns was to be placed no closer than 750 μm from the foveal center, and 300 μm was to be between each row. The duration of each burn was to be 0.1 second, with the goal of creating a light gray/white lesion. At 6 months after the initial treatment, a second laser treatment of 20 burns was required to be placed on the nasal side of the fovea in a mirror-image pattern to the first treatment if there had been a <50% reduction in the amount of macular drusen. In April 1996, the CNVPT Research Group decided to evaluate alternative treatment protocols because of a high percentage of patients requiring additional treatment at 6 months. The Laser 24 protocol was applied to 9 (15%) of 59 eyes assigned to treatment. This protocol specified 2 concentric rings of 12 burns centered on the foveola, with the innermost ring no closer than 750 μm from the foveal center and with 200 μm between rings. The spot size, duration, and intensity of the burns were to be the same as for the Laser 20 protocol. A third protocol, Laser 6, was used on only 1 (2%) of the 59 treated patients. The Laser 6 protocol specified 1 ring of 6 burns at least 1000 μm from the center of the fovea. The spot size and duration of the burns were to be the same as for the Laser 20; however, the intensity was to be greater, similar to the intensity used for panretinal photocoagulation. Additional treatment was applied at 6 months to 22 eyes originally treated under the Laser 20 protocol before laser treatment was suspended in December 1996. None of the eyes assigned to the other laser treatment protocols had been retreated before that time.

Patient Follow-up

Visual acuity was measured and color stereo photographs were taken at every follow-up visit. Contrast threshold was measured at 3 months and annually. The critical print size for reading was measured annually. Fluorescein angiography was performed annually and whenever necessary to evaluate symptoms or changes in the fundus that were suggestive of CNV. Staff from the CNVPT Reading Center graded photographs and angiograms for development of CNV, serous detachment of the retinal pigment epithelium, geographic atrophy, and drusen and pigmentation characteristics. CNV was considered present only if leakage of dye could be documented on fluorescein angiography. Eyes that had developed exudative AMD at or before a given follow-up visit were excluded from the grading of drusen and pigmentary features for that visit and all future visits. Side-by-side comparisons of color photographs were used to determine the location and magnitude of changes in drusen and pigmentary features between baseline and follow-up visits. New areas of geographic atrophy were considered present if a new area of geographic atrophy developed or if there was an expansion of preexisting geographic atrophy.

Information on visual function and photographs from ophthalmologists not participating in CNVPT were accepted for patients who were unable or unwilling to return to CNVPT clinical centers for their follow-up examinations. Ten patients, 7 in the observed group and 3 in the treated group, had information for a total of 23 visits reported in this way.

Table 1. Number of Patients Who Completed Follow-up at the Specified Time

Time after Randomization (mos)	Laser		Observed	
	Alive (n)	*Complete, n (%)*	*Alive (n)*	*Complete, n (%)*
0	59	59 (100.0)	61	61 (100.0)
3	57	55 (96.5)	61	59 (96.7)
6	57	55 (96.5)	61	59 (96.7)
12	57	57 (100.0)	61	58 (95.1)
18	57	49 (86.0)	60	47 (78.3)
24	57	46 (80.7)	58	47 (81.0)
30	57	37 (64.9)	58	45 (77.6)
36	57	35 (61.4)	58	38 (65.5)
42	56	28 (50.0)	57	33 (57.9)
48	56	33 (58.9)	57	37 (64.9)

Data Analysis

This report is based on information from data collection and photograph grading forms received by October 22, 2001. Patients were analyzed in the patient group to which they were originally assigned. The Kaplan–Meier method was used to estimate the cumulative proportion of patients with a 50% reduction in drusen and the proportion of patients who developed CNV. Differences in the Kaplan–Meier curves were evaluated with the log-rank statistic. Adjustments for possibly confounding covariates were made by using the discrete time version of the Cox proportional hazards model. Distributions of measurements of visual function and change in visual function from the initial visit were compared between treatment groups with Wilcoxon's ranked sum test. SAS version 8.0 (SAS Institute, Inc., Cary, NC) was used for all computations.

Results

The number of patients completing scheduled examinations is given in Table 1. Seven patients (6%), three in the treated group and four in the observed group, died during the 48-month follow-up period. Missed-visit percentages for individual visits were <5% through the first 12 months of follow-up and were 19% at 24 months. Fifty-one (89%) of 57 treated patients alive at 24 months consented to additional follow-up, and 52 (90%) of 58 living patients assigned to observation consented. The 12 patients who did not consent to additional follow-up were considered as missing all visits after 24 months. Missed-visit rates for follow-up visits scheduled from 30 to 48 months ranged from 22% to 50% and were approximately equal for each scheduled visit for the two treatment groups. Thirty-three (59%) treated patients and 37 (65%) observed patients had follow-up at 48 months. Comparison of the characteristics of living patients who completed the 48-month visit to those of patients who did not showed that those who completed the visit in each treatment group tended to be younger (mean, 72 vs. 74 years; $P = 0.08$) and that those in the laser-treated group were more likely to be current cigarette smokers (18% vs. 0%; $P < 0.05$).

Reduction in Area of Drusen

The reduction in the area of drusen within 3000 μm of the foveal center relative to baseline was graded for eyes that had not yet developed CNV. The Kaplan–Meier estimates of the proportion of eyes that ever had a documented 50% reduction in drusen area are displayed in Figure 1. Within the 6 months after initial treatment, the proportion increased sharply in treated eyes from 17% (9 of 52) at 3 months to 43% at 6 months. Eyes assigned to laser treatment that did not have a 50% reduction in drusen area at 6 months were to have treatment on the nasal side of the fovea; however, 11 patients who had their 6-month visit after the DSMC recommended suspending treatment had no additional treatment even though they did not have a 50% reduction. The proportion of treated eyes that had had a 50% reduction increased from 50% at 12 months to 69% at 48 months. Because the proportion of patients with missed visits or CNV was high in the later months of follow-up, the analysis was repeated to include only those patients who completed the 48-month visit. The same pattern of a sharp increase in the proportion of eyes with a 50% reduction within the first 6 months, with a plateau at approximately 30 months, was observed in this subset of eyes.

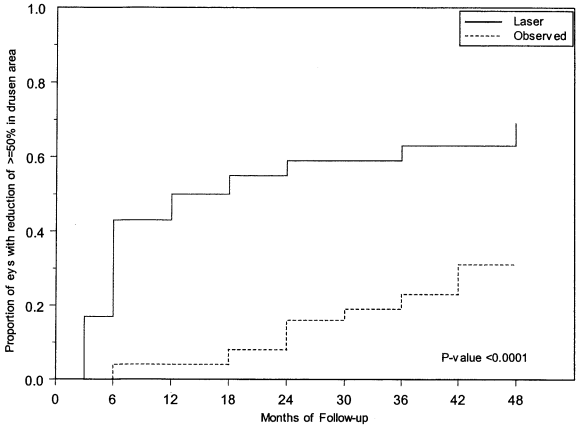

Figure 1. Estimated cumulative proportion of eyes with a 50% reduction in drusen area by treatment group.

A 50% reduction in drusen area was rarely documented through 12 months in eyes assigned to observation; <5% of eyes had a 50% reduction in that time period. However, the proportion that had ever had a 50% reduction increased steadily through 42 months to the level of 32%.

The percentages of eyes with less drusen area within 1500 μm of the foveola and with greater drusen area relative to baseline were also examined in each treatment group over time (Table 2). At 3 months after initial treatment, 62% (32 of 52) of treated eyes had at least some reduction in central drusen area, whereas only 9% (5 of 54) of eyes assigned to observation had less central drusen. The percentage of treated eyes with some reduction in central drusen area increased over time, reaching approximately 76% at 36 months. Over the period of follow-up, 6% to 19% of treated eyes had a greater central drusen area than at baseline. Conversely, a high percentage of observed eyes had a greater central drusen area during follow-up; nearly 50% of eyes had a greater area at 3 years.

Incidence of CNV

The incidence of CNV over time is displayed in Figure 2. The incidence in the treated group was greater initially such that at 12 months, the incidence was approximately five times higher in treated eyes than in observed eyes (23% vs. 5%). However, by 30 months, the cumulative incidence was nearly the same in treated and observed eyes (33% vs. 32%). The incidence was similar thereafter, with the cumulative incidence reaching 43% in the treated group and 38% in the observed group at 48 months.

Table 2. Area of Foveal Drusen Relative to Baseline by Treatment Group and Visit

	3 mos		12 mos		24 mos		36 mos		48 mos	
Area	*Laser, n (%)*	*Observed, n (%)*	*Laser, n (%)*	*Observed, n (%)*	*Laser, n (%)*	*Observed, n (%)*	*Laser, n (%)*	*Observed, n (%)*	*Laser, n (%)*	*Observed, n (%)*
Greater	3 (6)	11 (20)	5 (13)	30 (57)	4 (13)	16 (47)	4 (19)	10 (48)	1 (6)	10 (48)
Same	17 (33)	38 (70)	2 (5)	9 (17)	2 (7)	4 (12)	1 (5)	4 (19)	4 (22)	2 (10)
Less	32 (62)	5 (9)	33 (83)	14 (26)	25 (81)	14 (41)	16 (76)	7 (33)	13 (72)	9 (43)
n	52	54	40	53	31	34	21	21	18	21

Characteristics of the lesion at the time of detection were examined among the 40 eyes that developed CNV after baseline. This analysis included the 12 eyes with CNV described in a previous publication.[2] The neovascular lesion, contiguous blood, increased blocked fluorescence, or serous retinal pigment epithelial detachment was subfoveal at the time of detection in 12 (55%) of 22 treated eyes and 8 (44%) of 18 observed eyes. Two (9%) of the treated eyes and none (0%) of the observed eyes showed a pattern of fluorescein leakage associated with purely classic CNV, whereas 17 (77%) of the treated eyes and 12 (67%) of the observed eyes showed a pattern of purely occult CNV. The remaining five (14%) treated eyes and five (28%) observed eyes showed a pattern of both classic and occult CNV. Among the eyes with additional follow-up after detection of CNV, 4 of 28 eyes (2 eyes in each treatment group) with purely occult CNV developed classic CNV. Further examination of the eyes with follow-up after the detection of CNV showed that although the angiographic appearance of some occult lesions became less pronounced (less fluorescein leakage over the same or smaller area), all eyes retained signs of CNV in the form of dye leakage, fibrous tissue, or both.

Analyses presented in a previous report showed that eyes that had received laser treatment with higher-intensity laser burns were more likely to develop CNV than eyes that had received less-intense burns.[8] However, the trends were of borderline statistical significance (*P* values between 0.05 and 0.10). An additional two eyes with laser burn intensity ratings developed CNV after the analyses for the previous article were completed. The integrated burn rating (IBR), the summation over all pixels corresponding to the laser burns of the difference in brightness between pretreatment and posttreatment color photographs, and the maximum difference in brightness (MAX) were used as indices of treatment intensity. Without adjusting for any factors associated with the risk of developing CNV, the risk ratio for an increase of 1 natural logarithm of intensity was 1.56 (95% confidence interval, 0.94–2.58; $P = 0.09$) for IBR and was 2.21 (95% confidence interval, 1.08–4.53; $P = 0.03$) for MAX. The association between treatment intensity and risk of developing CNV changed little after adjustment for the presence of focal hyperpigmentation and the extent of very large (>125-μm) drusen. The adjusted risk ratios were 1.90 (95% confidence interval, 1.09–3.33; $P = 0.02$) for IBR and 2.07 (95% confidence interval, 1.00–4.28; $P = 0.05$) for MAX.

Visual Function

The median visual acuity at baseline in each group was 20/25; all eyes but one eye in the observed group of eyes had visual acuity of ≥20/40. The distribution of visual acuity over time in each treatment group showed an overall decline (Table 3). At each annual visit through 48 months, there was a higher percentage of treated eyes with visual acuity of ≥20/20 and, except at 12 months, a lower percentage of treated eyes with ≤20/200 than observed eyes. However, none of the differences in visual acuity were statistically significant. Review of the distribution of change in visual acuity from baseline at each annual visit shows a higher percentage of treated eyes with an increase of one or more lines and a similar percentage of eyes with a loss of three or more lines (Table 4). None of the differences in change in visual acuity were statistically significant. At 48 months, approximately 30% of each group had lost three or more lines of visual acuity.

The amount of contrast required to recognize letters on the Pelli–Robson chart increased in each treatment group over time from baseline (Table 5). The proportion of eyes that were considered worse because they required more contrast to read the letters on the chart was similar in both treatment groups, increasing to approximately 50% at 48 months. The distribution of change in critical print size showed that eyes required larger print size over

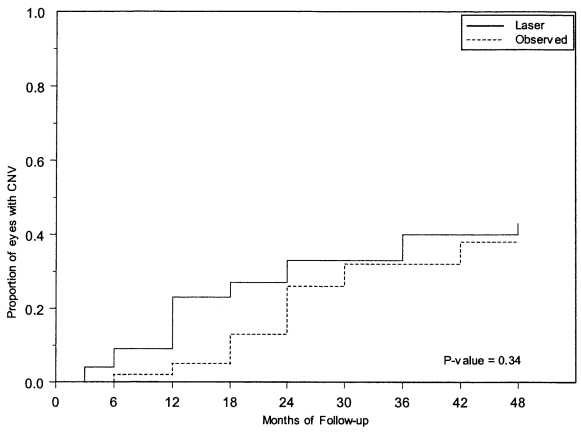

Figure 2. Estimated cumulative proportion of eyes developing choroidal neovascularization by treatment group.

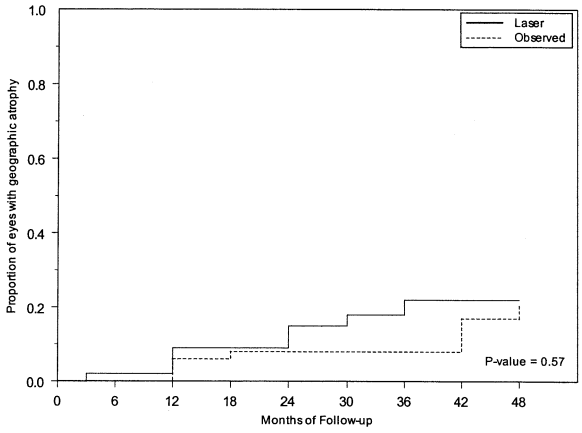

Figure 3. Estimated cumulative proportion of eyes developing geographic atrophy by treatment group.

Table 3. Visual Acuity by Treatment Group and Visit

Visual Acuity (20/*x*)	Baseline		12 mos		24 mos		36 mos		48 mos	
	Laser, *n* (%)	*Observed*, *n* (%)	*Laser*, *n* (%)	*Observed*, *n* (%)	*Laser*, *n* (%)	*Observed*, *n* (%)	*Laser*, *n* (%)	*Observed*, *n* (%)	*Laser*, *n* (%)	*Observed*, *n* (%)
12–20	25 (42)	28 (46)	28 (49)	18 (31)	22 (48)	12 (26)	15 (43)	14 (37)	12 (36)	8 (22)
25–40	34 (58)	32 (52)	24 (42)	38 (66)	16 (35)	26 (55)	12 (34)	14 (37)	11 (33)	16 (44)
50–160	0 (0)	1 (2)	3 (5)	2 (3)	6 (13)	6 (13)	5 (14)	4 (11)	7 (21)	7 (19)
≥200	0 (0)	0 (0)	2 (4)	0 (0)	2 (4)	3 (6)	3 (9)	6 (16)	3 (9)	5 (14)
n	59	61	57	58	46	47	35	38	33	36
*P**	0.81		0.27		0.15		0.84		0.55	

*From Wilcoxon's two-sample test.

time and that the changes were similar in the two treatment groups (Table 6).

Development of Geographic Atrophy

By 48 months, the estimated incidence of geographic atrophy was 22% among treated eyes and 21% among observed eyes (Fig 3; $P = 0.57$). Although the overall percentages were very similar in the two treatment groups, atrophy developed from treatment burns in four of the eight treated eyes that developed geographic atrophy. New geographic atrophy was within 1500 μm of the foveal center in all cases and was 1 disc area or larger in 6 (40%; 2 in treated eyes and 4 in observed eyes) of 15 eyes. Four of the six eyes with more than a disc area of geographic atrophy lost either two or three lines of visual acuity.

Discussion

Additional follow-up of the 120 patients enrolled in the FES of the CNVPT showed that although some of the short-term findings persisted, there were also some important new findings. As in the initial report, there were no major differences between treated and observed eyes with respect to visual acuity, contrast threshold, or critical print size. Scores on all three measures of visual function decreased over follow-up time, but to a similar extent in each treatment group (Tables 3–6). In contrast, the proportion of eyes that developed CNV was initially much higher among treated eyes, but with additional follow-up time, the cumulative proportion in each treatment group reached approximately 33% at 30 months after treatment (Fig 2).

The effects of laser treatment on resolution of drusen and, possibly, on formation of new drusen seem to be long-standing. Even with the great majority of treated patients (83%) having initial treatment applied only temporal to the fovea, 43% of patients had ≥50% of the drusen throughout the macula resolved by 6 months (Fig 1). Most eyes that ever had a 50% reduction in the area of drusen had done so by 24 months after initial treatment. The time course of such a substantial reduction in drusen in treated eyes was very different from the course in eyes that were in the observed group. There was a small but steady increase in the proportion through the follow-up period, so that by 42 months, 32% of the eyes that had not developed CNV had a 50% reduction in drusen. If only drusen in the central macula within 1500 μm of the fovea were considered, then the great majority of treated eyes had less central drusen at all times in follow-up than at baseline. Previously, our group reported that eyes with resolution of central drusen were more likely to have a small improvement in visual acuity than eyes without resolution of central drusen.[3] Among observed eyes, there was a small proportion of eyes with less central drusen at baseline, and approximately half of the eyes had more central drusen than at ≥12 months. At this point, we do not know whether the spontaneous resolution of drusen in observed eyes is a sign of progression to a more severe stage of AMD or a sign of improved status.

Laser treatment seemed to accelerate the development of

Table 4. Change in Visual Acuity by Treatment Group and Visit

Change in Visual Acuity (Lines)	12 mos		24 mos		36 mos		48 mos	
	Laser, *n* (%)	*Observed*, *n* (%)	*Laser*, *n* (%)	*Observed*, *n* (%)	*Laser*, *n* (%)	*Observed*, *n* (%)	*Laser*, *n* (%)	*Observed*, *n* (%)
≥1 increase	17 (30)	12 (21)	10 (22)	6 (13)	7 (20)	7 (18)	6 (18)	4 (11)
<1 change	17 (30)	18 (31)	15 (33)	16 (34)	11 (31)	12 (32)	7 (21)	7 (19)
1, 2 decrease	19 (33)	25 (43)	14 (30)	16 (34)	9 (26)	9 (24)	10 (30)	13 (36)
3–5 decrease	2 (4)	3 (5)	4 (9)	4 (9)	2 (6)	2 (5)	5 (15)	7 (19)
≥6 decrease	2 (4)	0 (0)	3 (7)	5 (11)	6 (17)	8 (21)	5 (15)	5 (14)
n	57	58	46	47	35	38	33	36
*P**	0.45		0.39		0.71		0.55	

*From Wilcoxon's two-sample test.

Table 5. Contrast Threshold Change by Treatment Group and Visit

Change in Log Contrast Threshold	12 mos		24 mos		36 mos		48 mos	
	Laser, n (%)	*Observed, n (%)*	*Laser, n (%)*	*Observed, n (%)*	*Laser, n (%)*	*Observed, n (%)*	*Laser, n (%)*	*Observed, n (%)*
0.15 better	2 (4)	5 (9)	2 (5)	2 (5)	3 (10)	1 (3)	2 (7)	2 (7)
No change	37 (69)	43 (75)	24 (56)	24 (55)	14 (45)	18 (55)	13 (46)	13 (43)
0.15 worse	11 (20)	8 (14)	11 (26)	11 (25)	7 (23)	9 (27)	5 (18)	10 (33)
0.30 worse	4 (7)	1 (2)	6 (14)	7 (16)	7 (23)	5 (15)	8 (29)	5 (17)
n	54	57	43	44	31	33	28	30
*P**	0.36		0.82		0.99		0.76	

*From Wilcoxon's two-sample test.

clinically detectable CNV; however, the cumulative risk was similar in treated and untreated eyes by ≥30 months. The estimated 4-year incidence rate of approximately 40% is in keeping with estimates of incidence from other case series of patients with multiple large drusen and areas of focal hyperpigmentation.[9,10] Approximately two thirds of the observed eyes that developed CNV had an angiographic pattern of only occult CNV. Lesions with an angiographic pattern of only classic CNV were found in just 9% of observed eyes and no treated eyes. Additional follow-up time and the development of CNV in a few more patients beyond the cutoff date for our previous article on laser burn intensity and risk of CNV strengthened the reported association between higher intensity and increased risk.[8] These findings, together with reports of a higher incidence of CNV with visible burns applied with a diode laser than with subthreshold burns applied with the same instrument, provide evidence that the gray/white lesions specified in the CNVPT treatment protocol may have been too intense to effectively reduce the risk of loss of vision in fellow eyes.[11] However, the intensity of laser treatment used in the CNVPT did not seem to increase the risk for development of geographic atrophy.

The estimates presented in this report for outcomes at 3 and 4 years of follow-up must be viewed with caution. A high proportion of enrolled patients did not complete clinic visits beyond 24 months. Although the percentage of such patients was similar in both treatment groups, those patients returning for their visits may not be representative of the entire set of enrolled patients. Returning patients in both treatment groups were somewhat younger than those who did not return; therefore, rates of CNV and vision loss may be underestimated. In addition, returning patients in the treated group were more likely to be current cigarette smokers; therefore, the rates for laser-treated patients may be overestimated. More than one factor may have been responsible for the difficulty in obtaining long-term follow-up. The CNVPT was designed as a pilot study to assess short-term safety and efficacy. At enrollment, patients made a commitment to 2 years of follow-up. The unexpected finding of a higher incidence of CNV among treated eyes in the FES led the investigators to try to obtain longer follow-up. Requesting that patients extend the period of their commitment and limited funding of clinical center staff to pursue patients who had moved, become ill, or developed other constraints on their ability to return for examinations may have contributed to the relatively low proportion of patients who completed the examinations at 3 and 4 years after enrollment.

These updated findings from the FES of the CNVPT demonstrate that the initial imbalance of CNV in laser-treated eyes was temporary and that a high percentage of both observed and laser-treated eyes will eventually develop CNV over 4 years. Even in light of the Age-Related Eye Disease Study findings that support micronutrient supplementation for patients with high-risk early AMD in one eye and advanced AMD in the other eye, the need for incremental prophylaxis remains great. It is interesting that at no time during the study were there significant differences in visual function between observed and laser-treated eyes

Table 6. Change in Print Size by Treatment Group and Visit

Change in Print Size	12 mos		24 mos		36 mos		48 mos	
	Laser, n (%)	*Observed, n (%)*	*Laser, n (%)*	*Observed, n (%)*	*Laser, n (%)*	*Observed, n (%)*	*Laser, n (%)*	*Observed, n (%)*
3 sizes smaller	4 (8)	4 (8)	5 (12)	5 (13)	0 (0)	2 (7)	2 (7)	3 (11)
1–2 sizes smaller	12 (24)	13 (25)	10 (23)	9 (23)	4 (14)	8 (27)	4 (14)	5 (18)
No change	10 (20)	17 (33)	8 (19)	5 (13)	8 (28)	6 (20)	7 (25)	5 (18)
1–2 sizes larger	18 (35)	16 (31)	12 (28)	10 (26)	8 (28)	6 (20)	6 (21)	9 (32)
3 sizes larger	7 (14)	2 (4)	8 (19)	10 (26)	9 (31)	8 (27)	9 (32)	6 (21)
n	51	52	43	39	29	30	28	28
*P**	0.11		0.11		0.26		0.69	

*From Wilcoxon's two-sample test.

despite different rates of development of CNV; explanations are speculative but could include a more benign natural course of laser-associated CNV, modest improved visual function in eyes with central drusen reduction, and, perhaps, bias introduced by lower rates of follow-up in years 3 and 4. Clearly, however, the laser treatment intensity information from this study, in combination with the diode laser treatment study observations, supports lower-intensity laser treatment goals for any future studies that use laser burns to this group of eyes. It is important that future preventive studies continue for this group of patients at greatest risk for central severe loss of vision because of advanced AMD.

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Answers for CME Credit.
1. C; 2. C; 3. A; 4. D; 5. B