Visual Outcomes in the Subfoveal Radiotherapy Study

A Randomized Controlled Trial of Teletherapy for Age-Related Macular Degeneration

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Objective: To determine whether teletherapy with 6-mV photons can reduce visual loss in patients with subfoveal choroidal neovascularization in age-related macular degeneration.

Design: A multicenter, single-masked, randomized controlled trial of 12 Gy of external beam radiation therapy delivered to the macula of an affected eye vs observation only.

Setting: Three United Kingdom–based hospital units.

Participants: Patients with age-related macular degeneration, aged 60 years and older, who had subfoveal choroidal neovascularization and a visual acuity of 20/200 (logMAR 1.0) or better.

Methods: Two hundred three patients were randomly assigned to radiotherapy or observation. Treatment was undertaken at designated radiotherapy centers, and patients assigned to the treatment group received a total dosage of 12 Gy of 6-mV photons in 6 fractions. Follow-up was scheduled at 3, 6, 12, and 24 months. After excluding protocol violators, the data from 199 patients were analyzed.

Main Outcome Measures: The primary outcome measure was mean loss of distance visual acuity in the study eye at 12 and 24 months. Other outcome variables analyzed were near visual acuity and contrast sensitivity. The proportions of patients losing 3 or more or 6 or more lines of distance and near acuity and 0.3 or more or 0.6 or more log units of contrast sensitivity at each follow-up were also analyzed.

Results: At all time points, mean distance visual acuity was better in the radiotherapy-treated group than in the control group, but the differences did not reach statistical significance. At 24 months, analysis of the proportions of patients with loss of 3 or more (moderate) \((P = .08)\) or 6 or more (severe) \((P = .29)\) lines of distance vision showed that fewer treated patients had severe losses, but there was no statistically significant difference between groups. For near visual acuity, although there was no evidence of treatment benefit at 12 and 24 months, a significant difference in favor of treatment was present at 6 months \((P = .048)\). When analyzed by the proportions of patients losing 3 lines of contrast sensitivity, there was a significant difference in favor of treatment at 24 months \((P = .02)\). No adverse retinal effects were observed during the study, but transient disturbance of the precorneal tear film was noted in treated patients.

Conclusion: The results of the present trial do not support the routine clinical use of external beam radiation therapy in subjects with subfoveal choroidal neovascularization in age-related macular degeneration.

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CHOROIDAL neovascularization (CNV) as a complication of age-related macular disease has a poor visual outcome, with 60% of affected patients becoming severely visually impaired within 3 years.\(^1\) Reports\(^2\-^5\) from randomized controlled clinical trials, starting in the 1980s, indicated that photocoagulation benefited the small proportion of patients found to have extrafoveal or juxtafoveal classic CNV. Unfortunately, because recurrence of new vessel growth occurred in most cases, treatment served only to delay visual loss in most.\(^6\-^8\) In patients who have occult CNV\(^7\) or a mixture of classic and occult disease, there is no evidence of benefit by argon laser therapy.\(^6\) One study\(^8\) implied that laser photocoagulation treatment confers benefit even when the neovascular complex is subfoveal. In this study, 24 months

Author affiliations are listed at the end of this article.
PATIENTS AND METHODS

DESIGN AND INCLUSION
AND EXCLUSION CRITERIA

This trial was conducted in accord with the tenets of the Declaration of Helsinki, 1996, for studies on human subjects. The SFRADS was undertaken in 3 ophthalmic units in major National Health Service hospitals located in Belfast, Northern Ireland, and in London and Southampton, England. The trial design was developed by the steering committee and approved by the local ethics committee at each center before commencement of the study. Patients with a presumptive diagnosis of subfoveal CNV due to ARMD were screened in special study clinics. A full medical history was obtained for each subject. This included current medications, history of hypertension, respiratory and cardiovascular status, prior major surgery, malignant disease, and smoking status.

After giving informed consent, suitable patients were recruited into the study and were randomized to the treated (EBRT) or control (observation only) group. Patients in the treated group were scheduled to receive radiotherapy within 14 days of entry, and both groups were examined at 3, 6, 12, and 24 months after randomization, when standard efficacy and safety variables were recorded. The optometrists who undertook visual assessments were unaware of the treatment status of the patients; however, neither the treating physicians nor the patients were masked.

Enrollment commenced November 1995, and was completed July 1998. Patients were required to be aged 60 years or older and have evidence of subfoveal CNV (some classic CNV or a vascularized pigment epithelial detachment) on a fundus fluorescein angiogram performed within 1 week of randomization. Visual acuity at baseline was required to be 20/200 or better in the study eye.

Exclusion criteria were (1) inability to give informed consent; (2) angiographic evidence of late leakage of indeterminate origin only; (3) presence of blood under the geographic center of the fovea; (4) presence of additional ocular disease, including high myopia in excess of −6.0 diopters in any axis; (5) diabetes mellitus, uncontrolled hypertension, or any life-threatening disorder at the initial visit; (6) concurrent enrollment in any other ophthalmic clinical trial; and (7) prior radiotherapy to either eye.

Patients who might benefit from foveal ablation according to the Macular Photocoagulation Study (MPS) criteria were made aware of this option and were invited to participate in the SFRADS only if they declined photocoagulation.

MEASURES OF VISUAL FUNCTION

All patients underwent assessment of visual function by a trained optometrist, using a protocol adapted from the MPS Manual of Procedures. All measurements were performed on each eye. Following refraction, best-corrected DVA was measured on the logMAR scale, using the backlight Early Treatment of Diabetic Retinopathy Study charts. The line with the smallest letters in which at least 3 of the letters were correctly identified was entered as the line acuity for that eye. The number of letters read was also recorded to give a letter score for that eye. Best corrected near visual acuity (NVA) in each eye at 25 cm was obtained using the Bailey-Lovie near-reading chart. Contrast sensitivity was measured for each eye using the Pelli Robson chart, with the patient seated at the recommended distance of 1 m.

Slitlamp biomicroscopy of anterior and posterior segments and intraocular pressure measurement were carried out on both eyes of every patient. High-dose radiotherapy is known to have adverse effects on the conjunctiva, lens, and retina. Detailed monitoring of these tissues was carried out at baseline and each subsequent visit. The conjunctiva was examined for vascular changes, such as microaneurysms and telangiectasia. The lacrimal system was evaluated as follows: The state of the preocular tear film and the cornea were examined by slitlamp biomicroscopy. The tear film breakup time was measured and the Schirmer test was performed. Lens clarity was monitored using a clinical grading system and red-reflex anterior segment photography. The retina and its vasculature were monitored for radiation retinopathy by biomicroscopic examination, electrophysiological assessment, and scrutiny of fundus photographs and fluorescein angiograms. The presence of retinal vessel microaneurysms or hemorrhage remote to the CNV was recorded.

ANGIOGRAPHY

Most patients referred to the study clinic had been previously assessed angiographically by their referring physician. A routine angiogram was usually sufficient to assess eligibility. On entry into the study, if not already performed for eligibility purposes, a study angiogram was undertaken. The photographic protocol specified the taking of bilateral color stereopair and red-free photographs centered on the macula. During angiography, stereo-pair photographs of the macula of the study eye were taken throughout the transit phase. Stereo pairs of the study eye and the fellow eye were captured during the later phases of the angiographic procedure, defined as 2 to 5 minutes after injection.

Angiograms were scrutinized by the principal investigators (U.C., P.M.H., A.C.B., and I.H.C.) at each center, who ascertained eligibility using a checklist of inclusion and exclusion criteria. The CNV was classified based on the fluorescein angiographic appearance of a lesion by the reading center based in Belfast. The size of the lesion (defined as any abnormal fluorescence, elevated blocked fluorescence, or contiguous blood) and the area of classic hyperfluorescence were measured in disc areas according to MPS criteria. Lesions were classified as wholly or predominantly classic (≥50% of the lesion), minimally classic (1%-49% of the lesion), occult (0%), or vascularized pigment epithelial detachment. Of the 203 baseline angiograms, 110 were read by a senior MPS-certified grader from The Scheie Eye Institute Photographic Reading Center, Philadelphia, Pa. Agreement between Belfast graders and the MPS-certified grader was high, with a κ value of 0.89. Discordance was primarily because of differences in the grading of mixed lesions, with Belfast graders classifying more cases as minimally classic than the MPS grader. There was no disagreement between graders in lesions classified as either purely classic or purely occult.

RANDOMIZATION

Eligible subjects were counseled and informed consent was obtained. The randomization code was kept at the...
coordinating center (Belfast) and released by telephone on receipt of patient details. To ensure balance within each of the 3 centers, the randomization was blocked. Two hundred three patients were recruited from 477 screened, and the detailed flowchart depicting study participation is shown in Figure 1.

RADIOTHERAPY TECHNIQUE

Patients in the treatment arm were assessed in the radiotherapy unit in each center by the designated radiotherapist. All centers used a 6-MV photon beam from a linear accelerator, and the dosage of radiotherapy selected for this study was 12 Gy given as 6 equal fractions on consecutive working days.

The treatment plan was based on a high-definition computed axial tomographic scan, taken with the patient’s head immobilized using a custom-made bexoid beam direction shell. Fine radiopaque tubing was placed on the beam direction shell marking the sagittal and coronal planes to establish reference points for the treatment port. The tomogram selected for treatment planning was one that clearly showed the lens, medial and lateral recti, and optic nerve of the ipsilateral eye in the same slice and included a clear view of the lens and optic nerve of the contralateral eye. The whole length of the optic nerve may be demonstrated in 1 slice when the chin is raised to bring the orbitomeatal line to an angle of 16° to the vertical. The patient was instructed to keep his or her eyes closed while the scan was performed. The treatment plan was constructed using a computer-based software program (Theraplan 500 series; Theratronics, Ottawa, Ontario) for 6-MV photons prescribed to the 90% isodose. In the generation of the treatment plan, care was taken to minimize exposure to the optic nerves of both eyes and the ipsilateral lens. The 90% isodose curve included the macula and optic disc, with less than 50% of the maximum dose falling on the posterior lens capsule.

The eye was irradiated through a single lateral port measuring 3 × 3 cm. The beam was angled 10° posteriorly to avoid the lens of the contralateral eye. Cursor measurements were made from the surface reference marks on the beam direction shell to localize the lateral beam entry port. This port was marked on the beam direction shell using a treatment simulator. Before treatment, or following the first treatment session, a monitoring computed axial tomographic scan, taken with the patient constructed to keep his or her eyes closed while the scan was performed. The treatment plan was constructed using a computer-based software program (Theraplan 500 series; Theratronics, Ottawa, Ontario) for 6-MV photons prescribed to the 90% isodose. In the generation of the treatment plan, care was taken to minimize exposure to the optic nerves of both eyes and the ipsilateral lens. The 90% isodose curve included the macula and optic disc, with less than 50% of the maximum dose falling on the posterior lens capsule.

The null hypotheses of primary interest were that there was no difference in change in DVA between treated and control groups at 12 and 24 months. As this is a longitudinal study, we also routinely report outcome at 3 and 6 months and the group trajectories over time after randomization for each of the outcome measures.

As a means of comparing the results with those of previous studies, we also analyzed the number of lines of acuity lost from baseline to the 12- and 24-month examinations in the 2 groups. Losses of 3 or more or 6 or more lines of DVA and NVA (which reflects a doubling or a quadrupling of the visual angle) were used as binary outcomes. Similarly, for CS, losses of 0.3 log units (2 triplets) or 0.6 log units (4 triplets) were used as binary outcomes. A decrease of 0.3 log units or 2 triplets on the Pelli Robson chart represents a halving of the contrast threshold from the baseline value. Therefore, these latter measures may be regarded formally as comprising a second set of secondary outcomes of interest.

OUTCOME MEASURES

The primary outcome measure, change in DVA in the study eye, was chosen because of its traditionally accepted role as a marker for visual function. We also measured NVA and CS as a set of secondary outcomes. With respect to patient-centered outcomes, we collected information on self-reported visual functioning and health-related quality of life; these measures are reported elsewhere (M.R.S., P.M.H., A.C.B., I.H.C., and U.C., unpublished data, 2002).

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STATISTICAL METHODS

Design

The study was designed to be 93% confident in detecting a minimum mean difference in DVA of 2 lines on the logMAR scale between treated and control groups with 90% power. Initial power calculations were made using data from the pilot study, and the sample size was determined to be 240 observations (120 per arm). Revised calculations based on the generalized Laird-Ware model allowed a subsequent reduction in sample size to 200 without loss of power. The study was not powered to investigate NVA, CS, or the second set of secondary outcomes.

Analysis

Standard univariate methods (χ² and t tests and parametric and nonparametric analyses of variance) were used to analyze the data. The 5% level of statistical significance was adopted throughout to construct tests of hypotheses and confidence intervals (CIs). In relation to the outcomes of DVA, NVA, and CS, longitudinal multiple linear regression modeling was used, which allowed us to adjust the treatment effect for factors measured at baseline and the trend over time. In longitudinal studies, repeated measurements are recorded for each individual are correlated, and alternative models are required that allow for this correlation. Accordingly, we adopted a specially modified Laird-Ware model that allows for correlation between the repeated measures when the individual follow-up examinations are irregularly spaced in time. The effects of the following factors were considered in these analyses: (1) treatment indicator, (2) time trend after randomization, (3) treatment by time interaction, (4) baseline value of the outcome measure, (5) CNV composition (classic or predominantly classic vs other), (6) center, and (7) whether both eyes were affected.

Scheduled follow-up examinations necessitate that information accruing over time is interval-censored and does not accurately reflect time to event. In the Kaplan-Meier-based presentations of the cumulative proportions of patients losing 3 or more or 6 or more lines of visual acuity, we used the scheduled, rather than the observed, visit times, and this is in accord with most previously published randomized clinical trials in this field.
after enrollment, mean losses of 3.0 and 4.4 lines of distance visual acuity (DVA) were recorded in treated and control eyes, respectively. Greater benefit was seen with maintained contrast sensitivity (CS) and reading speed at the same time point. As central vision is substantially reduced immediately after foveal ablation, any benefit is therefore only detectable in the longer term.

Because of the disappointing outcome with or without intervention in this common ophthalmic condition, several novel therapeutic approaches have been proposed for the treatment of subfoveal CNV during the past decade. Recent studies shown that photodynamic therapy with verteporfin reduces the risk of moderate and severe vision loss in patients with subfoveal CNV in age-related macular degeneration (ARMD). This treatment exploits the property of verteporfin uptake by the endothelia of the CNV, and targeted activation of the dye, using an infrared laser, results in occlusion of the neovascular complex, with minimal or no initial damage to the adjacent retinal neuropile.

The use of ionizing radiation to cause involution of the CNV is another possible therapeutic approach. Clinical studies have been undertaken, with some identifying a visual benefit, and others suggesting a lack of benefit and adverse outcome due to teletherapy. However, none of these studies incorporated a concurrently recruited control group with visual and angiographic baseline characteristics similar to those of the treated group.

A small randomized controlled trial consisting of 74 patients showed that a total dose of 24 Gy (in 4 fractions) of 6-mV photons delivered as external beam radiotherapy (EBRT) to the macula of eyes with CNV resulted in benefit of maintained DVA in the treated group.

More recently, 2 additional randomized controlled trials of EBRT vs sham irradiation demonstrated no visual benefit in subjects observed for up to 1 year.

We commenced a prospective, longitudinal, multicenter, randomized controlled trial November 1995, to investigate the hypothesis that 12 Gy of EBRT would limit the loss of visual function in patients with ARMD in whom CNV involved the fovea. The acronym used to designate the Subfoveal Radiotherapy Study is SFRADS. Patients were observed for 24 months, and the visual outcomes are reported herein.

**RESULTS**

**PATIENTS ANALYZED**

Two hundred three patients were randomized into this study, and the numbers from each center are shown in Table 1. Of the 203, 4 were subsequently found not to satisfy all study entry criteria. One patient was aged 56, and 3 patients had baseline DVAs of 1.1 logMAR or worse. Three of these 4 were allocated to the treatment group. These 4 patients were excluded from the analysis. One other patient was randomized to the control group but subsequently received treatment according to protocol. This patient was analyzed as if she had been allocated to the treatment group. The baseline angiograms of the study eyes were graded for CNV composition, and the lesions were classified as purely or predominantly classic (145 [72.9%]), minimally classic (45 [22.6%]), occult with no classic (3 [1.5%]), or fibrovascular pigment epithelial detachment (6 [3.0%]). Although the reading center classified the study eyes of 3 patients as having no classic CNV at baseline, these subjects were not excluded from the analysis, as this was not considered a protocol violation. This is because the criterion specifying the presence of at least some classic CNV is subjective, and arbitration may be used in the event of disagreements between reading center staff and investigators. The flow chart (Figure 1) shows the route to the final numbers of participants analyzed within the treatment and control groups.

**BASELINE CHARACTERISTICS**

Randomization achieved prior similarity between the treated and control groups (Table 2). Most patients in
the study (72.9%) had wholly or predominantly classic CNV.

**COMPLETENESS OF FOLLOW-UP**

During the study, 48 visits were missed, and the numbers of missed visits and withdrawals were similar among treatment groups and centers.

**VISUAL OUTCOMES**

**Distance Visual Acuity**

**Table 3** shows that the primary null hypotheses could not be rejected at 12 and 24 months. Although the difference between the groups at 12 and 24 months favored treated patients, the magnitude of the difference, less than 1 line of DVA, was small and did not reach statistical significance. The findings were similar at 3 and 6 months. The longitudinal regression analysis was conducted by systematically removing redundant terms from the model, and this showed that the treatment indicator remained nonsignificant throughout.

Analysis of the data on the basis of lines of acuity lost showed that a greater proportion of patients in the control group lost 3 or more or 6 or more lines at each follow-up visit, but the differences did not reach statistical significance (**Table 4**). These findings are corroborated by examination of the cumulative proportions of patients losing 3 or more or 6 or more lines of DVA in the treatment and control groups (**Figure 2** and **Figure 3**).

**Near Visual Acuity**

At the primary follow-up visits, at 12 and 24 months, no statistically significant difference between the groups was detected. However, the difference between treated and control groups was statistically significant at 6 months (t test, \( P = .048 \) (**Table 5**), when the magnitude of the change was \(-0.102\), which is equal to 1 line of NVA (95% CI, 0.001-0.203). As noted previously with DVA, the direction of the mean change from baseline in NVA always favored treated patients during the study, and this is shown in **Figure 4**. When the data were analyzed by longitudinal regression, no treatment benefit was found. In only one regression analysis did the treatment effect (\( \beta \)) approach statistical significance (\( \beta = -0.07, \ SE = 0.04, \ t = -1.94, P \) value is between .05 and <.10), when adjusting for time and baseline NVA.
When the proportions of patients losing 3 or more or 6 or more lines of NVA were examined, statistically significant differences were detected at 3 and 6 months but not at 12 or 24 months (Table 6). Kaplan-Meier–based graphs show the cumulative proportions of patients losing 3 or more or 6 or more lines of NVA over time (Figure 5 and Figure 6).

Contrast Sensitivity

Table 7 shows that the primary null hypotheses could not be rejected at 12 and 24 months. As before, mean changes in CS from baseline favored treated patients throughout the study but did not reach statistical significance. The longitudinal regression analysis revealed a marginally significant treatment effect when time and baseline CS were entered into the model: (B=0.09, SE=0.04, t=2.0, P value is between .02 and .05).

At all time points, the proportion of patients losing 0.3 or more or 0.6 or more log units of CS was lower in the treatment group than in controls (Table 8). At 12 months, the difference was not significant; 34 patients (37.4%) had lost 0.3 or more log units of CS in the treatment group, compared with 45 patients (49.5%) in the control group (difference, 12.1%; 95% CI, −1.9% to 26.1%). At 24 months, there was evidence of a significant difference in the loss of 0.3 log units of CS in favor of treatment (treated, 43.5%, vs controls, 60.9%; difference, 17.4%; 95% CI, 3.4%-31.4%) (Figure 7 and Figure 8).

Table 5. Estimated Treatment Benefit to Near Visual Acuity (NVA)*

<table>
<thead>
<tr>
<th>Follow-up, mo</th>
<th>Benefit</th>
<th>SE</th>
<th>No. of Participants</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>−0.066</td>
<td>0.042</td>
<td>186</td>
<td>.12</td>
</tr>
<tr>
<td>6</td>
<td>−0.102</td>
<td>0.051</td>
<td>179</td>
<td>.048†</td>
</tr>
<tr>
<td>12</td>
<td>−0.061</td>
<td>0.052</td>
<td>161</td>
<td>.25</td>
</tr>
<tr>
<td>24</td>
<td>−0.076</td>
<td>0.057</td>
<td>172</td>
<td>.19</td>
</tr>
</tbody>
</table>

*Data are given as logMAR near acuity. Benefit indicates the difference between group averages (treatment minus controls) in change in NVA from baseline. The number of participants varies according to the number of completed visits.
†P<.03 in nonparametric testing.
SAFETY OUTCOMES

The analysis of the angiographic outcomes will be the subject of a detailed further report. No patients were found to develop features of radiation retinopathy in the 24 months after trial entry. As we did not carry out indocyanine green angiography, we could not rule out radiation-induced choroidopathy.

Treatment and control groups had similar tear film breakup times at baseline (mean, 11.6 and 11.3 seconds, respectively). At 3 months, this decreased in the treatment group by a mean (SD) of 1.7 (0.8) seconds, compared with an increase of 0.6 (0.8) seconds in the control group (P=.03). A similar finding was noted at 6 months (P=.04) but not at subsequent time points. Statistically significant differences in Schirmer test results were also noted between treatment and control groups at 6 and 12 months. At baseline, mean Schirmer test values were 11.84 and 12.74 mm, respectively, but at 6 months, the mean (SD) in the treatment group had decreased by 0.83 (0.94) mm, whereas in the control group the mean increased by 1.98 (0.94) mm (P=.04). By 12 months, the mean in the treated group had decreased by 2.27 mm from baseline, compared with an increase in the control group of 0.92 mm (P=.02).

The present study and most other clinical trials in ophthalmology have used DVA as a principal outcome measure. This measure of vision is based on the eye’s ability to resolve targets at a distance, and it is generally accepted that threshold visual acuity, measured using the logMAR chart to standardized protocols, provides a useful yardstick for monitoring outcome for research purposes. However, the validity of using DVA alone has been questioned in assessing the benefits of treatment for ocular disorders, including ARMD. For this reason, 2 addi-

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**Table 6. Lines of NVA Lost by 3, 6, 12, and 24 Months of Follow-up**

<table>
<thead>
<tr>
<th>Lines of NVA Lost</th>
<th>Treatment</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>By 3 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3†</td>
<td>19 (20.9)</td>
<td>35 (36.8)</td>
<td>54 (29.0)</td>
</tr>
<tr>
<td>≥6†</td>
<td>5 (5.5)</td>
<td>15 (15.8)</td>
<td>20 (10.8)</td>
</tr>
<tr>
<td>By 6 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3§</td>
<td>43 (46.2)</td>
<td>54 (62.8)</td>
<td>97 (54.2)</td>
</tr>
<tr>
<td>≥6§</td>
<td>12 (12.9)</td>
<td>21 (24.4)</td>
<td>33 (18.4)</td>
</tr>
<tr>
<td>By 12 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3¶</td>
<td>53 (57.0)</td>
<td>55 (62.5)</td>
<td>108 (59.7)</td>
</tr>
<tr>
<td>≥6¶</td>
<td>22 (23.7)</td>
<td>28 (31.8)</td>
<td>50 (27.6)</td>
</tr>
<tr>
<td>By 24 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3**</td>
<td>58 (66.7)</td>
<td>61 (71.8)</td>
<td>119 (69.2)</td>
</tr>
<tr>
<td>≥6††</td>
<td>27 (31.0)</td>
<td>36 (42.4)</td>
<td>63 (36.6)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of participants. The number of participants varies according to the number of completed visits.

NVA indicates near visual acuity.

†χ² = 5.75, P = .02.

§χ² = 5.13, P = .02.

¶χ² = 4.93, P = .03.

1 = 3.94, P = .05.

1 = 0.57, P = .45.

1 = 3.15, P = .02.

1 = 2.37, P = .12.

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**Figure 5.** Kaplan-Meier–based graph of proportions of eyes losing 3 or more lines of near acuity. Maximum separation between groups is seen between 3 and 6 months. This difference reached significance (P=.048).

**Figure 6.** Kaplan-Meier–based graph of proportions of eyes losing 6 or more lines of near acuity. At all time points, fewer eyes assigned to treatment lost 6 or more lines of acuity compared with the control group, although the difference did not reach significance (P=.17).

**Table 7. Estimated Treatment Benefit to Contrast Sensitivity (CS)**

<table>
<thead>
<tr>
<th>Follow-up, mo</th>
<th>Benefit</th>
<th>SE</th>
<th>No. of Participants</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>+0.082</td>
<td>0.046</td>
<td>184</td>
<td>.08‡</td>
</tr>
<tr>
<td>6</td>
<td>+0.056</td>
<td>0.062</td>
<td>178</td>
<td>.36</td>
</tr>
<tr>
<td>12</td>
<td>+0.102</td>
<td>0.065</td>
<td>182</td>
<td>.12‡</td>
</tr>
<tr>
<td>24</td>
<td>+0.052</td>
<td>0.067</td>
<td>172</td>
<td>.44</td>
</tr>
</tbody>
</table>

*Data are given as log contrast threshold. Benefit indicates the difference between group averages (treatment minus controls) in change in CS from baseline. The number of participants varies according to the number of completed visits.

†Nonsignificant on nonparametric testing (P = .10).

‡P=.06 in nonparametric testing.

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In the SFRADS, DVA was not statistically significantly different between the study groups at 12 or 24 months, when we believe a benefit would have been clinically useful. During the study, visual outcome was better on average in treated patients, but the differences observed were smaller than those considered likely to be clinically relevant, and most were not statistically significant. When considering mean differences between the groups, the only single measure of outcome that was significantly different was mean NVA at 6 months, and the magnitude of this difference was 1 logMAR line, the 95% CI being consistent with an effect size ranging from just above zero to 2 logMAR lines. The analysis of dichotomous variables in relation to NVA suggests the presence of an early therapeutic effect (not sustained beyond 6 months). This finding is more persuasive given that these differences were detected despite the fact that the SFRADS was not powered to investigate these aspects of visual outcome. However, the significant findings in relation to CS at 3 and 24 months are more difficult to explain and accordingly are less convincing.

Therefore, when all outcome measures were considered, the data suggest that visual outcome was better in treated patients. That the data imply, but do not establish beyond doubt, that a therapeutic effect exists is consistent with the mixed conclusions of other studies using low-dose radiotherapy. Bergink et al concluded that 24 Gy of radiation given as 4 fractions of 6 Gy was effective in reducing moderate and severe visual loss in eyes with CNV in ARMD. However, more recent studies did not find any evidence of benefit from EBRT. The absence of a therapeutic effect in the latter studies is unlikely to be related to variation in dosage, as similar dosages were used (16 Gy and 14 Gy vs 12 Gy in the SFRADS). However, there are other factors that could account for the variation in outcome. In one study, most subjects (55.6%) had purely occult CNV, and in the other, fewer than 14% of subjects were graded at baseline as having classic CNV. Furthermore, the studies with negative findings were based on 12 months of data alone. Other small randomized controlled studies

### Table 8. Log Units of CS Lost by 3, 6, 12, and 24 Months of Follow-up*

<table>
<thead>
<tr>
<th>Log Units CS Lost</th>
<th>By 3 mo</th>
<th>By 6 mo</th>
<th>By 12 mo</th>
<th>By 24 mo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.3†</td>
<td>21 (23.6)</td>
<td>6 (6.7)</td>
<td>15 (15.6)</td>
<td>21 (11.4)</td>
<td></td>
</tr>
<tr>
<td>≥0.6‡</td>
<td>30 (33.0)</td>
<td>36 (41.4)</td>
<td>19 (21.8)</td>
<td>34 (19.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of participants. The number of participants varies according to the number of completed visits. CS indicates contrast sensitivity.

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### Figure 7. Kaplan-Meier–based graph of proportions of eyes losing 0.3 or more log units of contrast sensitivity. Proportionately fewer eyes assigned to treatment lost 0.3 or more log units of contrast compared with the control group, but the difference was not statistically significant (P=.005).

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### Figure 8. Kaplan-Meier–based graph of proportions of eyes losing 0.6 or more log units of contrast sensitivity. Proportionately fewer eyes assigned to treatment lost 0.6 or more log units of contrast compared with the control group, but the difference was not statistically significant (P=.11).
have used sources of radiotherapy that are more capable of precisely delineating the target area, including proton beam and plaque radiotherapy. Although the data from these studies are encouraging, the high dosages of radiation to the choroidal vasculature may result in greater damage to the choroid and retinal pigment epithelium, with the prospect of a worse visual outcome than that associated with the natural history. In this regard, several reports suggest that EBRT to CNV may cause abnormal vascular proliferations in the retinal and choroidal circulations.

The results of the present study indicate that radiotherapy to a subfoveal CNV given as 6 fractions to a total dosage of 12 Gy is not iminical and does not result in a worse visual outcome compared with the natural history. To our knowledge, none of the controlled trials thus far have reported radiation retinopathy or optic neuropathy, and similarly we found no serious adverse effects, although some temporary abnormality of tear film was recorded. Also, the value of the small differences noted in acuity and contrast between treatment and control groups may not translate into improvements in visual functioning. The magnitude of benefit detected indicates that EBRT will not resolve the problem of blindness from age-related macular disease. Whether the magnitude of the detected benefit warrants the use of this treatment is questionable. Most subjects enrolled in the SFRADS had wholly or predominantly classic CNV and thus fall into the category of patients who would benefit from photodynamic therapy with verteporfin. With photodynamic therapy, the need for successive treatments and the accompanying investigations have important implications for the patient. Also, there are health, economic, and cost-benefit issues to be considered when comparing treatments. However, the smaller proportion (28%) of eyes losing 3 lines of acuity in a predominantly classic subgroup treated with photodynamic therapy is considerably better than that achieved by EBRT in this study (58%). It is therefore our opinion that the present study has not identified a specific clinical role for 12 Gy of photon radiotherapy given as a series of 6 fractions in the management of CNV in ARMD.

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