

The Age-Related Macular Degeneration Radiotherapy Trial (AMDRT): One Year Results from a Pilot Study

THE AMDRT RESEARCH GROUP*

- **PURPOSE:** To assess the short-term safety and efficacy of treating subfoveal choroidal neovascularization (CNV) with external beam radiation delivered in 5 × 4 Gy fractions among patients having age-related macular degeneration (AMD).
- **DESIGN:** A multicenter prospective randomized controlled pilot study.
- **METHODS:** Eighty-eight patients were enrolled through 10 sites and were randomized to radiotherapy (20 Gy delivered in 5 daily fractions of 4 Gy each; 6 MV [N = 41]) or no radiotherapy (sham radiotherapy [N = 22] or observation [N = 25]). Eligibility criteria included visual acuity of at least 20/320 and subfoveal CNV not amenable to treatment. Randomization was stratified by lesion type (new or recurrent CNV) and blood (<50% or ≥50% of the lesion [N = 13]). The primary outcome measure was loss of ≥3 lines of visual acuity. Secondary outcome measures were angiographic response and side effects.
- **RESULTS:** At baseline, patient and ocular characteristics were similar between treatment groups. At six months, 9 radiated eyes (26%) and 17 eyes not radiated (49%) lost ≥3 lines of visual acuity ($P = .04$; stratified χ^2 test). At 12 months, 13 radiated eyes (42%) and 9 observed eyes (49%) lost ≥3 visual acuity lines ($P = .60$). The radiated group demonstrated smaller lesions and less fibrosis than the nonradiated group ($P = .05$ and $.004$, respectively) at 12 months. Radiation-induced complications were not observed except for one radiated eye with numerous cotton wool spots and possible radiation retinopathy.

- **CONCLUSIONS:** External beam radiation at 5 × 4 Gy may have a modest and short-lived (six month) benefit in preserving visual acuity. (Am J Ophthalmol 2004;138: 818–828. © 2004 by Elsevier Inc. All rights reserved.)

RADIODTHERAPY POSSESSES ANTIANGIOGENIC, ANTI-fibrotic, and antineoplastic properties^{1–9} and has, therefore, been proposed as a treatment for choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). Numerous nonrandomized and uncontrolled clinical studies have been performed with varying results and recommendations. Most studies have used external beam radiation with standard fractions of 2 Gy to a total of 10 to 20 Gy for subfoveal CNV. Some studies report minimal or no therapeutic radiotherapy effect,^{10–12} while others report a moderate benefit with standard fractions.^{13–16} Higher fractions and doses of external beam radiation,¹⁷ brachytherapy,^{16,18} or proton therapy^{19–21} have also been examined. Angiographic regression of CNV has been observed with higher fractions, especially after proton beam radiation, although radiation retinopathy occurs at a substantial frequency.²⁰

There have been eight randomized clinical trials with published results comparing radiotherapy to observation. Results from three trials that employed higher, nonstandard fractions indicate that radiotherapy may be beneficial.^{22–24} The evidence of visual benefit using standard 2 Gy fractions is less compelling. Two Gy fractions to a total dose of 8 or 16 Gy²⁵ and to 20 Gy²⁶ have been reported to decrease the rate of visual loss. However, three studies with standard 2 Gy fractions to total doses of 12, 14, and 16 Gy failed to demonstrate a beneficial effect.^{27–29}

We initiated a multicenter, randomized pilot trial comparing external beam radiation with nonstandard fractions (5 fractions of 4 Gy) vs no active intervention. Results from the pilot study on safety and the nature of response of neovascular lesions to larger doses of radiation were intended to provide information needed to determine whether a large-scale, definitive trial was warranted. In addition, the pilot study allowed refinement of procedures for a clinical trial relying on collaboration between ophthalmologists and radiation on-

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TABLE 1. AMDRT Patient Inclusion Criteria

Age 50 or older	
New or recurrent CNV secondary to AMD	
Occult CNV or minimally classic or predominately classic subfoveal CNV*	
CNV not amenable to laser treatment or patient refuses	
<50% fibrosis	
No ocular histoplasmosis	
No ocular conditions precluding good photography	
No other ocular condition likely to affect visual acuity in 2 years	
Myopia \leq 8 diopters	
Acuity \geq 20/320	
Exclusion Criteria	
Diabetes	
Prior ocular/periocular radiation	
CNV secondary to non-AMD causes	
Prior or current chemotherapy	
History of macula affecting drugs	
*Patients with predominately classic CNV were enrolled prior to FDA approval for PDT with verteporfin for predominately classic CNV. After FDA approval, patients with predominately classic CNV were enrolled only if the lesion was not amenable to photodynamic therapy or if the patient refused.	

cologists and assessment of the feasibility of sham radiotherapy.

METHODS

• **PARTICIPANTS:** Patients for the Age-Related Macular Degeneration Radiotherapy Trial (AMDRT) were recruited and followed at 10 clinical sites in the United States (see the appended credit roster). Financial support for the trial was provided in part by the National Eye Institute and in part by each of the participating institutions. Each clinical center represented collaboration between academic or community based retina practices and Departments of Radiation Oncology. At the outset, each center had the option to choose sham radiotherapy or observation only as the control treatment for active radiotherapy. Three centers chose sham radiotherapy. The AMDRT Coordinating Center and Fundus Photograph Reading Center (FPRC) certified at least one ophthalmologist, clinic coordinator, visual acuity examiner, and photographer in each center and the Radiologic Physics Center (RPC) certified at least one radiation oncologist and radiation physicist. Each clinical center was required to obtain local Institutional Review Board (IRB) approval for the protocol and consent forms. Participants were provided with information about the clinical trial and had the opportunity to ask questions before signing consent forms.

Patient enrollment began in January 2000 with a goal of 100 patients. One center had been conducting a single

center clinical trial with the same protocol and consent procedures and had enrolled 23 patients before their multi-center certification; these patients are included in the analysis. In September 2001, the Data and Safety Monitoring Committee (DSMC) recommended that recruitment be halted because of a low rate of enrollment.

• **PARTICIPANT SELECTION:** Patients with new or recurrent (following prior thermal photocoagulation) subfoveal CNV secondary to AMD were eligible for enrollment. Major eligibility criteria included a lesion comprised of occult CNV, minimally classic CNV or predominantly classic CNV,³⁰ with fibrosis (if present) comprising <50% of the lesion, and visual acuity \geq 20/320 in the study eye. Patients enrolled into the Recurrent CNV arm of the study were required to have both historic and ophthalmoscopic evidence of thermal photocoagulation for CNV in the study eye. A diagnosis of AMD was confirmed by drusen $>63 \mu\text{m}$ or focal hyperpigmentation in either eye or evidence of CNV, geographic atrophy, or serous detachment of the pigment epithelium in the nonstudy eye. Other specific eligibility requirements are listed in Table 1.

• **ENROLLMENT AND RANDOMIZATION PROCEDURES:** After required examinations and photography were completed, an eligibility checklist was faxed to the Coordinating Center. The enrolling ophthalmologist and clinic coordinator verbally confirmed eligibility of the patient by telephone with a Coordinating Center staff member.

Randomized treatment assignment schedules, stratified by lesion type (new or recurrent) and status of blood (<50% or \geq 50% of the lesion), were generated for each clinical site. For centers performing sham radiotherapy, sealed, black-lined, security envelopes containing a randomized assignment were provided to the ophthalmology clinical staff. At enrollment, the clinic coordinator confirmed with the Coordinating Center the assignment of the patient to the next sequentially numbered envelope for the appropriate strata. The sealed envelope was sent to the Radiation Oncology Department and opened by the radiation oncologist and radiation physicist immediately before treatment. For centers not performing sham radiotherapy, the coordinator called the Coordinating Center to obtain the treatment assignment. For all patients, the Coordinating Center compared the treatment the patient actually received (active radiation, sham radiation or observation) with the treatment assigned.

• **OUTCOME MEASURES:** The primary outcome measure was a decrease in visual acuity (\geq 3 lines). Secondary outcome measures were lesion size as graded on fluorescein angiography and incidence of side effects.

• **EXAMINATION PROCEDURES:** The following data were recorded at the time of enrollment for each participant: age; gender; occupational status; racial and ethnic status; and status of treatment for systemic hypertension, if

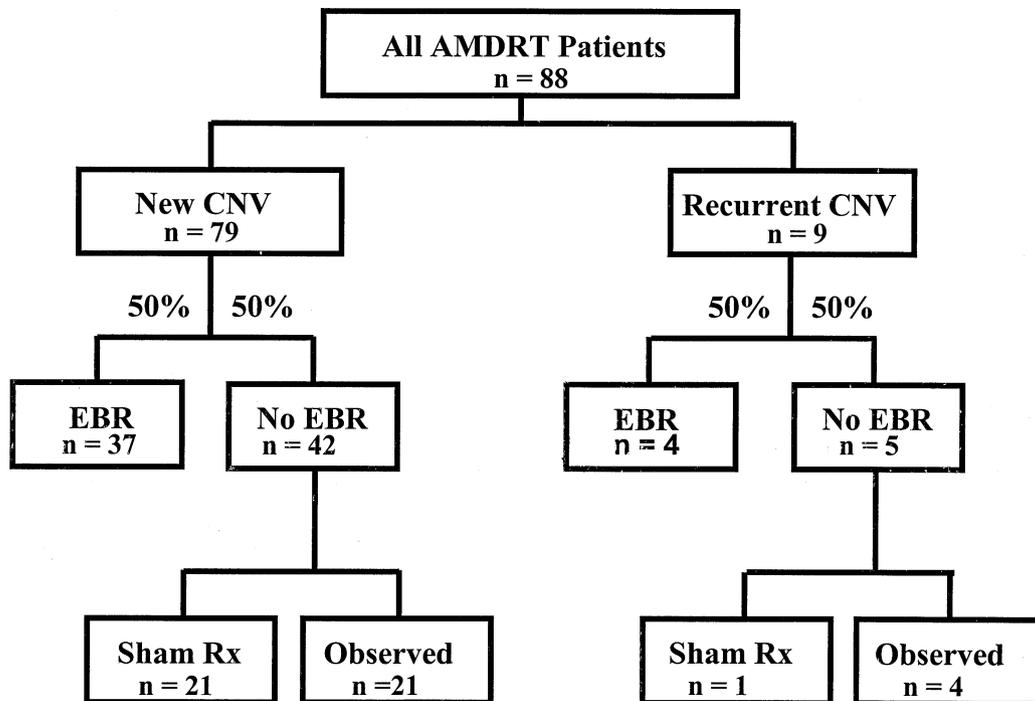


FIGURE 1. AMDRT Enrollment and Randomization Numbers.

present (blood pressure was determined by sphygmomanometry while the patient was seated).

Certified visual acuity examiners performed standardized refraction and visual acuity testing according to an adaptation of the protocol used in the Submacular Surgery Trial (SST).³¹ During follow-up, examiners were masked to the patient's treatment assignment. Certified ophthalmologists performed all ophthalmic examinations. Symptoms of ocular pain, discomfort, dryness, or irritation in the study eye; signs of conjunctival or episcleral inflammation and description of eyelashes in the study eye; and the lens status of both eyes were recorded. In addition to these conditions, nonstudy treatment of the study eye and development of ophthalmic conditions related to exposure to radiation were recorded during follow-up.

• **PHOTOGRAPHY AND FLUORESCEIN ANGIOGRAPHY:** Certified photographers performed all fundus photography and fluorescein angiography following SST protocols.³¹ Initial visit photography was required within 42 days of enrollment.

Expert readers at the FPRC, masked to treatment assignment, reviewed all baseline photographs and angiograms for eligibility. The study lesion was described by CNV type [classic CNV, occult CNV, serous pigment epithelial detachment (S-PED)] and the proportion of contiguous hemorrhage and/or fibrosis. Total lesion size was recorded in relative disc areas for the CNV component of the lesion as well as for all lesion components combined. Evidence of large drusen and/or focal hyperpigmentation

was also recorded. Signs of any retinal vascular changes that would be indicative of radiation retinopathy, such as cotton wool spots, nonperfusion, or microaneurysms were noted. At 12 months, the area of classic CNV and area of fibrosis were compared to baseline and classified as same, more, or less. The amount of fibrosis present at 12 months was graded as none, localized (not extending arcade to arcade), or fibrosis extending arcade to arcade. For participants with new CNV lesions, readers assessed changes from baseline to 12 months in lesion size and extent of blood and/or fluid on IVFA.

• **RADIATION THERAPY:** Certified radiation physicists and radiation oncologists planned and implemented, respectively, all external beam radiotherapy (EBR) and sham EBR sessions. Each EBR session consisted of a single ipsilateral field, delivered using CT-guided treatment planning to ensure accuracy in dose delivery and target coverage. Beam angling and block utilization were adjusted at the discretion of the physicists and radiation oncologists to minimize exposure of other ocular and nonocular structures. Treatment field sizes were kept as small as possible to completely treat the exudative macular lesion in its entirety and encompass the ipsilateral optic disc. A target dose of 20 Gy was delivered using the 6MV beam of a linear accelerator in 5 daily fractions of 4 Gy each over five to eight business days. The dose to the macula was calculated utilizing the treatment planning CT image, which facilitated placing the isocenter of the treatment beam coincident with the location of the macula. To

TABLE 2. Completeness of Patient Follow-up by AMDRT Treatment Group

Follow-up Visit Month	*EBR (N = 41)			†No EBR (N = 47)		
	N‡	Completed		N‡	Completed	
		n	Percent		n	Percent
03	41	32	(78.0)	46	39	(84.8)
06	40	36	(90.0)	46	35	(76.1)
12	40	31	(78.5)	44	31	(70.5)

*EBR = External Beam Radiation Therapy.
†No EBR = Sham Treatment or Observation.
‡Number of living participants.

restrict the movement of the macula as much as possible during treatment, patients were asked to focus on a specific point in the room. Dose to the lens was minimized by blocking, either by the placement of a lead-equivalent block of at least 5 cm thickness or use of an asymmetric independent anterior collimator jaw. Similar custom head-holding devices were employed during both EBR and sham EBR sessions, but no radiation was delivered during sham EBR sessions.

At two of the three centers performing sham EBR, all procedures surrounding sham EBR mirrored that of actual EBR: patients underwent a planning CT scan and received five simulated treatments. At one center performing sham EBR, patients randomized to sham EBR did not undergo a planning CT scan, and they received only one simulated treatment. At that site, all patients, regardless of treatment assignment, were told in advance that they would receive between one to five radiation treatments, and that the actual number would be determined by randomization.

RPC staff reviewed the treatment records for each treated patient. The treatment was reconstructed and the center's dosimetry calculations were compared with RPC calculations using either "standard dosimetry data" maintained for specific make/models of photon accelerators or measured data from RPC on-site dosimetry review visits to participating centers. Dosimetry data for each site's accelerator(s) used to treat the patients were also submitted to the RPC for comparison with their "standard" data. All patients were found to be treated per protocol specifications.

• **STUDY FOLLOW-UP VISITS:** A "safety visit" was performed at one month for all participants randomized to EBR or sham EBR treatment. The visit included a non-protocol determination of visual acuity, updated ophthalmic and medical history, and an ophthalmic examination. Procedures for study visits at 3, 6, 12, and 24 months after enrollment included updating the ophthalmic and medical history, measuring visual acuity according to protocol, and, beginning at month 6, protocol disc and macula photography and IVFA. Coordinators called patients at 18

months to maintain contact and check if there had been changes warranting a clinical examination.

• **DATA ANALYSIS:** Data received by July 31, 2003 are included. All patients would have completed their 12-month follow-up visit by this time. Results on visual acuity through 12 months are presented; however, results related to adverse events are presented for the entire period of patient participation. For the primary analysis of visual acuity, patients assigned to either sham EBR or to observation are combined into one group designated "No EBR." The small number of patients enrolled in the Recurrent CNV arm of the trial were precluded from analysis as an independent group; therefore the results of both arms have been considered simultaneously through use of analyses stratified by arm of the trial. Primary analyses were performed under the "intention-to-treat" principle in which patients are analyzed in the group to which they were randomly assigned, regardless of the treatment actually received.

Comparisons of categorical variables such as development of a 3-line loss in visual acuity were made using χ^2 tests or logistic regression methods, stratified by the arm of the study. Comparisons involving ordered categories used χ^2 tests for trend. Secondary analyses explored the impact of baseline imbalances in the treatment groups and of deviations from the randomly assigned treatment.

RESULTS

• **PATIENTS AND TREATMENT:** Eighty-eight participants enrolled into the AMDRT. Recruitment ranged between 1 and 32 patients/center, with a median of 6 patients/center. Seventy-nine patients were enrolled in the New CNV arm of the clinical trial with 37 assigned to EBR, 21 assigned to sham EBR, and 21 assigned to observation only (Figure 1). Nine patients were enrolled in the Recurrent CNV arm of the clinical trial with 4 assigned to EBR, 1 assigned to sham EBR, and 4 assigned to observation only. The percentage of scheduled visits that were completed in each

TABLE 3. Characteristics of AMDRT Patients at Baseline

Characteristic	New CNV				Recurrent CNV			
	EBR*		No EBR†		EBR		No EBR†	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Age (yrs.)								
60–69	7	(18.9)	6	(14.3)	0	(0.0)	0	(0.0)
70–79	17	(45.9)	20	(47.6)	2	(50.0)	2	(40.0)
>79	13	(35.1)	16	(38.1)	2	(50.0)	3	(60.0)
Mean	76.6		77.2		81		79.8	
Range	63–89		64–92		77–81		73–87	
Gender								
Female	21	(56.8)	27	(64.3)	1	(25.0)	2	(40.0)
Male	16	(43.2)	15	(35.7)	3	(75.0)	3	(60.0)
Race								
White	37	(100.0)	42	(100.0)	4	(100.0)	4	(80.0)
Non-white	0	(0.0)	0	(0.0)	0	(0.0)	1	(20.0)
Hypertension								
Normal	8	(21.6)	9	(21.4)	1	(25.0)	0	(0.0)
Suspect	2	(5.4)	2	(4.8)	1	(25.0)	0	(0.0)
Definite‡	19	(51.4)	24	(51.1)	2	(50.0)	5	(100.0)
Unknown	8	(21.6)	7	(16.6)	0	(0.0)	0	(0.0)

*EBR = External Beam Radiation Therapy.

†No EBR = Sham Treatment or Observation.

‡Definite = systolic pressure >160 or diastolic pressure >95 or on antihypertensive medication. Suspect = systolic pressure between 140 and 159 or diastolic pressure between 90 and 94.

treatment group is shown in Table 2. Among all missed visits, the most common reason for not completing the visit was patient refusal; other reasons were illness and transportation problems.

Within the New CNV arm, patient age ranged from 63 to 92 years with a mean age of 77 years (Table 3). Patients within the Recurrent CNV arm tended to be older, having a mean age of 80 years. Definite hypertension was present in more than half of all patient groups. Within the New CNV arm, approximately 13% of lesions were composed of ≥50% blood and there were fewer cases of predominantly classic CNV than occult CNV (Table 4). More than half of the lesions were >9 MPS disc area. Treatment groups within each arm were relatively well balanced with respect to the baseline characteristics noted above.

Within the New CNV arm, nearly half of the participants had initial visual acuity of 20/80 or better (Table 4). Visual acuity below 20/200 was more frequent in the EBR group than in the No EBR group.

Based on Reading Center review of baseline stereo photographs and fluorescein angiograms, 12 enrolled patients (13.8%) from five clinical centers were subsequently determined to be ineligible for AMDRT. Of these, 11 patients had new CNV lesions and one patient had a recurrent lesion. The most frequent reasons for ineligibility were fibrosis encompassing >50% of the lesion (n = 4), no

evidence of CNV (n = 3), lesion not subfoveal (n = 2), and photography issues that precluded an eligibility assessment (n = 2). Also, there were an additional three patients in the New CNV arm, two in the EBR group and one in the No EBR group, who had baseline visual acuity worse than the eligibility limit of 20/320. All patients, regardless of baseline eligibility, are included in the analysis.

There were five patients who were not managed according to their randomized assignment. Because of confusion at one center in transitioning from the randomization system used for an earlier study and the AMDRT, two patients assigned EBR received sham EBR, and two patients assigned sham EBR received EBR. These patients are included in the analysis in the group to which they were assigned by the AMDRT randomization. One other patient assigned EBR refused treatment and had no follow-up.

The median time elapsed between randomization and commencement of treatment for those participants who received either actual EBR treatment or sham treatment was 6 days with a range of 0 to 25 days. Field sizes employed ranged from 2.0 to 24.0 cm² (mean = 10.37 cm²).

• **EFFECT OF TREATMENT ON VISUAL ACUITY:** At three months, the proportion of eyes with a 3 or more line loss

TABLE 4. Characteristics of Eyes at Baseline

Characteristic	New CNV				Recurrent CNV			
	EBR		No EBR		EBR		No EBR	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Lesion ≥ 50% blood	5	(13.9)	5	(17.1)	1	(25.0)	2	(40.0)
Total	36*		41		4		5	
CNV Lesion Type								
Predominately Classic	4	(11.8)	7	(18.4)	3	(75.0)	0	(0.0)
Minimally Classic	23	(67.6)	21	(55.3)	1	(25.0)	4	(100.0)
Occult Only	7	(20.6)	10	(26.3)	0	(0.0)	0	(0.0)
Total	34*		38*		4		4*	
Size of total lesion (MPS disc areas)								
<4	11	(33.3)	13	(32.5)	2	(50.0)	1	(25.0)
>4-<9	6	(18.2)	4	(10.0)	1	(25.0)	2	(25.0)
>9	16	(48.5)	23	(57.5)	1	(25.0)	2	(50.0)
Total	33*		40*		4		5	
Visual Acuity								
20/50 or better	7	(18.9)	5	(11.9)	1	(25.0)	0	(0.0)
20/64-20/80	10	(27.0)	15	(35.7)	2	(50.0)	1	(20.0)
20/100-20/200	13	(35.9)	20	(47.6)	1	(25.0)	2	(40.0)
20/250 or worse	7	(18.9)	2	(4.8)	0	(0.0)	2	(40.0)
Total	37		42		4		5	
Phakic	15	(40.5)	22	(52.3)	1	(25.0)	2	(40.0)
Total	37		42		4		5	

*Total may not equal number of eyes in each group. Fundus features and photography issues may preclude graders from making some assessments.

in visual acuity from baseline was 17% for the EBR group and 37% for the No EBR group in the New CNV arm (Table 5; $P = .08$; χ^2 test). No patients in the Recurrent CNV arm lost 3 or more lines. At six months, the proportion with a 3-line loss in visual acuity from baseline in the New CNV arm had increased to 25% in the EBR group and 48% in the No EBR group and within the Recurrent CNV arm, one of three patients in the EBR group and two of four patients in the No EBR group had a 3-line loss ($P = .05$; stratified χ^2 test). By 12 months, the proportion with a 3-line loss from baseline visual acuity was the same (43%) for both treatment groups in the New CNV arm. Among the Recurrent CNV patients, the proportion with a 3-line loss from baseline visual acuity was one of three in the EBR group and three of three in the No EBR group ($P = .61$; stratified χ^2 test). Adjustment through regression analysis for imbalances in baseline visual acuity between patients in the EBR and No EBR groups resulted in slightly higher P -values ($P = .11$ at three months, $P = .06$ at six months). Similar increases in P values resulted from excluding patients with baseline visual acuities < 20/320 ($P = .11$ at 3 months, $P = .09$ at 6 months). Additionally, when the two patients who were assigned to EBR but managed as No EBR, and the two patients who were assigned to No EBR but managed as EBR were included in data analysis according to their management group (rather than their assigned group), the

results at three months were unchanged and the treatment difference at six months was slightly smaller ($P = .14$).

Because visual acuity assessments may be affected by patients' knowledge of their treatment status, we investigated whether the observed effect of EBR on visual acuity was different in centers that employed sham EBR than the observed effects in centers that did not. When treatment effect was defined as the difference between EBR and no EBR groups in the proportion with a 3-line loss, the treatment effect was less in the centers that used sham EBR at some, but not all visits. A repeated measures regression model did not show a difference in treatment effect between the centers that did and did not use sham EBR ($P = .70$).

• **CNV LESION APPEARANCE AT 12 MONTHS IN THE NEW CNV ARM:** At 12 months, patients in the EBR group were more likely to have smaller lesions than patients in the No EBR group (Table 6; $P = .05$). Patients in the EBR group were also less likely to have an increase from baseline in fibrosis than patients in the No EBR group (40% vs 83%; $P = .002$) and were less likely to have scarring from arcade to arcade (4% vs 42%; $P = .0004$).

• **ADVERSE EFFECTS:** Adverse events were infrequent. By 12 months, one treated patient developed multiple

TABLE 5. Change in Visual Acuity By Visit, Treatment Assignment

FV03	New CNV				Recurrent CNV				P-Value*
	EBR		No EBR		EBR		No EBR		
	N = 29	%	N = 35	%	N = 3	%	N = 4	%	
Change in Visual Acuity (lines)									
≥1 increase	6	21%	10	28%	0	0%	0	0%	P = 0.08
<1 change	15	52%	7	20%	2	67%	2	50%	
1–2 decrease	3	10%	5	15%	1	33%	2	50%	
3–5 decrease	5	17%	7	20%	0	0%	0	0%	
≥6 decrease	0	0%	6	17%	0	0%	0	0%	
Confidence Interval†	20% (–2%, +39%)				—				

FV06	New CNV				Recurrent CNV				P-Value*
	EBR		No EBR		EBR		No EBR		
	N = 32	%	N = 31	%	N = 3	%	N = 4	%	
Change in Visual acuity (lines)									
≥1 increase	5	16%	7	23%	1	33%	0	0%	P = 0.05
<1 change	13	41%	4	13%	1	33%	0	0%	
1–2 decrease	6	19%	5	16%	0	0%	2	50%	
3–5 decrease	6	19%	7	23%	1	33%	2	50%	
≥6 decrease	2	6%	8	26%	0	0%	0	0%	
Confidence Interval†	23% (0%, +44%)				—				

FV12	New CNV				Recurrent CNV				P-Value*
	EBR		No EBR		EBR		No EBR		
	N = 28	%	N = 28	%	N = 3	%	N = 3	%	
Change in Visual acuity (lines)									
≥1 increase	7	25%	5	18%	1	33%	0	0%	P = 0.61
<1 change	5	18%	5	18%	0	0%	0	0%	
1–2 decrease	4	14%	6	21%	1	33%	0	0%	
3–5 decrease	8	29%	7	25%	1	33%	2	67%	
≥6 decrease	4	14%	5	18%	0	0%	1	33%	
Confidence Interval†	0% (–43%, +43%)				—				

*From Exact Test.

†Calculated with confidence interval analysis software based on methods by Newcombe and Altman.³²

cotton wool spots and retinal nonperfusion adjacent to the disc, possibly indicating radiation retinopathy. Visual acuity in this eye was 20/80 at baseline and 20/80 at 12 months. There were five deaths among AMDRT patients: four of which occurred among patients who did not receive EBR. Cataract surgery was performed on two patients, one in each treatment group. Six patients reported ocular dryness; four had not received EBR and two had received EBR.

• **OTHER (NON-STUDY) TREATMENTS:** Six patients underwent other nonstudy ocular procedures before 12 months. Two radiated patients who were enrolled before FDA approval of verteporfin therapy underwent PDT with verteporfin and one radiated patient had laser photocoagulation. Among nonradiated patients, one patient each underwent submacular surgery, transpupillary thermotherapy (TTT) and acupuncture.

DISCUSSION

AMONG AMDRT PATIENTS, THERE WAS A TREND TOWARD a modest and short-lived beneficial effect of radiotherapy compared to observation. At six months follow-up, 26% of radiated and 50% of eyes not radiated demonstrated a loss of ≥3 visual acuity lines (Table 5, $P = .04$; stratified χ^2 test). However, this early beneficial trend faded by 12 months follow-up, as 43% of radiated and 50% of observed eyes demonstrated loss of ≥3 visual acuity lines ($P = .61$). Radiotherapy was associated with smaller lesion size and far less fibrosis and scarring (Table 6). Short-term radiation-induced complications were infrequent at this dose, with only one radiated eye demonstrating multiple cotton wool spots and possible radiation retinopathy.

The strengths of our study include the multicenter, randomized, and controlled format with a centralized coordinating center and photographic reading center. The weaknesses of our pilot study include a relatively small number of enrolled

TABLE 6. Status of Lesions at 12 Months*

	EBR [†]		No EBR [‡]		
	n = 25	%	n = 24	%	
Lesion size, Disc Area					
≤6	10	40%	4	17%	<i>P</i> = 0.05
>6 and ≤12	11	44%	12	50%	
>12	4	16%	8	33%	
Fibrosis Compared to Baseline					
More	10	40%	20	83%	<i>P</i> = 0.002
Same or Less	15	60%	4	17%	
Scarring					
None or can't grade	14	56%	4	16%	<i>P</i> = 0.0004
Atrophic or localized	10	40%	10	42%	
Arcade to Arcade	1	4%	10	42%	
*Patients with New CNV Only (Too few patients with recurrent CNV).					
†EBR = External Beam Radiation.					
‡No EBR = Sham treatment or observation.					

patients, 14% ineligible patients, the five patients who were treated not in accordance with their randomized assignment, patients who underwent other nonstudy ocular procedures, and inadequate patient follow-up after one year. There were 22 patients who were lost to follow-up by 12 months, 9 (22%) of the treated patients and 13 (29%) of the patients who were not treated (Table 2). The limited follow-up is inadequate to fully assess long-term complications, such as radiation retinopathy or optic neuropathy, and we did not formally test for radiation keratopathy by fluorescein staining or Schirmer's testing. However, examinations with slit lamp biomicroscopy of the cornea and conjunctiva did not reveal any abnormalities. Additionally, radiation-treated patients did not report a greater incidence of subjective dry eye symptoms. Although there was no observed difference in the proportion with 3-line loss in visual acuity between treatment groups at 12 months in the New CNV study, the confidence interval for the difference includes values up to 43%.

Information from eight other randomized radiotherapy trials²²⁻²⁹ and from nonrandomized studies using proton beam radiation¹⁹⁻²¹ indicates that radiotherapy may have a palliative effect. Table 7 summarizes the visual acuity results from these randomized trials. Five of the eight randomized studies used standard 2 Gy fractions with varying results. The RAD Study Group²⁷ and Marcus and associates²⁸ demonstrated that external beam radiation using 2 Gy fractions to a total dose of 16 and 14 Gy, respectively, was not beneficial. Similarly Hart and associates²⁹ found no benefit using 2 Gy fractions to a total dose of 12 Gy. While no benefit was observed for the primary outcome parameter, distance visual acuity, Hart and associates²⁹ reported a radiotherapy benefit for secondary outcome parameters such as near visual acuity and contrast sensitivity. Valmaggia and associates²⁵ observed a benefi-

cial effect using 2 Gy fractions to total doses of 8 and 16 Gy. Eyes with better initial distance visual acuity or with classic CNV were found to benefit more from treatment. None of these studies demonstrated any radiotherapy impact on CNV size or fluorescein angiography outcomes. However, standard 2 Gy fractions to a total dose of 20 Gy resulted in visual acuity and fluorescein angiographic benefit for eyes with smaller CNV and better visual acuity.²⁶ While it is probable that low dose radiotherapy using standard 2 Gy fractions is an inadequate primary treatment for subfoveal CNV, these five trials²⁵⁻²⁹ indicate a possible palliative effect. Additionally, it is pertinent that an angiographic benefit was observed using the highest total dose (10 fractions of 2 Gy = 20 Gy).²⁶ Our total dose of 20 Gy using a higher nonstandard fraction size of 4 Gy has a greater radiobiologic effect than a total dose of 20 Gy using 2 Gy fractions.

It is also significant that two randomized trials using external beam radiation with higher nonstandard fractions (4 fractions of 6 Gy²² and 1 fraction of 7.5 Gy²³) showed a statistically significant beneficial effect on visual acuity. The strongest evidence for the benefit of radiotherapy exists in data from trials investigating proton beam radiation. Nonrandomized data from Flaxel and associates²⁰ and Yonemoto and associates^{19,21} show some evidence of a radiation dose response (1 fraction of 8 Gy compared with 1 fraction of 14 Gy). Mean visual acuity in eyes receiving a single 14 Gy fraction was unchanged at two years follow-up.²¹ Radiation retinopathy was detected in 11 of 27 eyes treated with 14 Gy but this was not associated with severe visual loss.²⁰ Proton beam studies using a single fraction of 8 to 16 Gy have shown a substantial increase in radiobiologic effect as well as an increased likelihood for radiation-induced

TABLE 7. Other Randomized Clinical Trials of Radiation Therapy For CNV

Study	Dose	Visual Acuity Results	P value
Bergink et al (1998)	Observation	52% vs 32% 3 line loss	0.03
	vs		
	6Gy × 4 = 24Gy	41% vs 9% 6 line loss	0.002
Char et al (1999)	Observation	5.5 mean lines lost	0.046
	vs		
	7.5 Gy × 1 = 7.5Gy	1.9 mean lines lost	
RAD Study Group (1999)	Sham	3.7 mean lines lost	0.528
	vs		
	2Gy × 8 = 16Gy	3.5 mean lines lost	
Kobayashi et al (2000)	Observation	+0.562 mean logMAR change	0.0001
	vs		
	2Gy × 10 = 20Gy	+0.226 mean logMAR change	
Marcus et al (2001)	Sham	3.9 mean lines lost	0.35
	vs		
	2Gy × 7 = 14Gy	4.14 mean lines lost	
Valmaggia et al (2002)	1Gy × 1 = 1Gy	3.23 mean lines lost	
	2Gy × 4 = 8Gy	1.73 mean lines lost	0.011
	2Gy × 8 = 16Gy	1.93 mean lines lost	0.050
Hart et al (2002)	Observation	71% vs 61% 3 line loss	0.08
	vs		
	2Gy × 6 = 12Gy	44% vs 37% 6 line loss	0.29
Ciulla et al (2002)	Sham	0.61 logMAR	None given
	vs		
	8Gy × 2 = 16Gy	0.61 logMAR	

complications. Doses in this range have an approximate radiobiologic equivalence to over 50 Gy using standard 2 Gy fractions. Harding and coworkers presented data (AAO Meeting, Orlando, Florida, October 2002) from a randomized, controlled trial comparing proton beam radiation (4 fractions of 4.5 Gy) to observation. A statistically significant mean visual acuity benefit was found at one year but only a beneficial trend existed at two years follow-up. Additionally, Ciulla and associates²⁴ found a trend toward visual acuity stabilization using 2 fractions of 8 Gy (proton beam radiation) compared to observation. Finally, the impressive reduction in fibrosis that occurred in radiated eyes has also been observed by Hart and coworkers.⁹ Unfortunately this pilot study did not include an evaluation of contrast sensitivity that may have been preserved in radiation-treated eyes with less fibrosis. Thus, our data along with the information summarized above lend support for further investigation into defining if radiotherapy has a role in exudative AMD.

Enrollment was halted because of a low enrollment rate and thus, our data are weakened as a result of low patient recruitment and inadequate follow-up rate past one year. Low recruitment in radiotherapy trials²⁴ is not unique in the United States especially after approval of photodynamic therapy with verteporfin as a therapy for predominantly classic CNV in AMD. Additionally, oph-

thalmologists are often reticent to refer patients or participate in trials where non-ophthalmologists provide the experimental therapy. The coordination of activities between Ophthalmology and Radiation Oncology Departments can be challenging, especially where such relationships do not pre-exist, and sham EBR treatment is difficult for many to implement. With an increased interest in and investigation of retinal pharmacotherapy for exudative AMD, further large-scale assessment of radiotherapy in the United States will remain challenging.

The results of the AMDRT suggest no reason to pursue this dose (5 fractions of 4 Gy) of radiotherapy as a primary therapy for subfoveal CNV secondary to AMD. However, the short-lived but statistically significant visual acuity benefit observed at six months along with a very strong reduction of fibrosis in radiated eyes indicate that radiotherapy should not be excluded from further investigation in exudative AMD. As numerous treatments are being investigated as adjuncts to photodynamic or other experimental therapies, the results of the AMDRT and other radiotherapy studies using similar doses and fraction sizes should not preclude further investigation of similar doses as part of multimodality therapy. Evidence also suggests that a therapeutic window may still exist for radiotherapy as a primary or adjunctive treatment at higher fraction sizes than that used in the AMDRT.

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APPENDIX The AMD and Radiotherapy (AMDRT) Study Group

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