UC Davis

UC Davis Previously Published Works

Title

Ten-year follow-up of eyes treated with stereotactic fractionated external beam radiation for neovascular age-related macular degeneration.

Permalink

https://escholarship.org/uc/item/1td8j8xg

Journal

Retina (Philadelphia, Pa.), 31(7)

ISSN

0275-004X

Authors

Trikha, Rupan
Morse, Lawrence S
Zawadzki, Robert J
et al.

Publication Date

2011-07-01

DOI

10.1097/iae.0b013e318203ee46

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

TEN-YEAR FOLLOW-UP OF EYES TREATED WITH STEREOTACTIC FRACTIONATED EXTERNAL BEAM RADIATION FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

RUPAN TRIKHA, MD, LAWRENCE S. MORSE, MD, PHD, ROBERT J. ZAWADZKI, PHD, JOHN S. WERNER, PHD, SUSANNA S. PARK, MD, PHD

Purpose: To determine the long-term effects of stereotactic fractionated external beam radiation on eyes treated for neovascular age-related macular degeneration.

Methods: A retrospective review of all eyes treated with stereotactic fractionated external beam radiation (20–40 Gy, 2-Gy fractions) between 1997 and 2000 was performed to identify eyes with ≥2-year follow-up for analysis. A subset was imaged prospectively using a high-resolution Fourier-domain optical coherence tomography.

Results: Among 94 eyes treated, 33 eyes (32 subjects) had ≥2-year follow-up information (mean follow-up, 6.2 years; range, 2–10 years). Final visual acuity ranged from 20/50 to no light perception. Final macular findings included central geographic atrophy (49%), disciform scar (30%), and active choroidal neovascular membrane (9%). Fourier-domain optical coherence tomography images of three eyes with geographic atrophy revealed photoreceptor layer loss within areas of geographic atrophy with intact retinal morphology in areas of radiation exposure outside geographic atrophy. Radiation retinopathy was suspected in 18% and confirmed by fluorescein angiography in 15%, ranging from mild to neovascular glaucoma/phthisis bulbi (2 eyes). Mean time from stereotactic fractionated external beam radiation to development of radiation retinopathy was 5.4 years (range, 1–10 years).

Conclusion: A moderate rate of delayed radiation retinopathy was noted in eyes with neovascular age-related macular degeneration treated with stereotactic fractionated external beam radiation. Geographic atrophy was a common finding.

RETINA 31:1303–1315, 2011

Age-related macular degeneration (AMD) is a leading cause of blindness in people aged >50 years. The recent development and use of intravitreal anti–vascular endothelial growth factor (anti-VEGF) therapy have provided a substantial improvement in visual outcome of patients with the neovascular form of the disease.[1,2] Intravitreal anti-VEGF therapy, however, is limited because of its short-term treatment effect and the need for continued re-treatment. Recently, a report of a pilot study showed a sustained treatment effect when intravitreal anti-VEGF therapy was combined with epiretinal brachytherapy applied during vitrectomy, leading to a renewed interest in the possible effect of radiotherapy in treating eyes with neovascular AMD (nAMD).[3]

Radiotherapy has been studied extensively as a primary treatment of nAMD before the advent of anti-VEGF therapy. The principle for the use of radiation in biologic tissue is based on its ability to induce free radicals and DNA damage. At variable

From the Department of Ophthalmology and Vision Science, University of California Davis Eye Center, Sacramento, California.

Supported in part by the National Eye Institute, Bethesda, MD (Grant Number 014743 to J.S.W.), and the Research to Prevent Blindness, New York, unrestricted departmental grant.

Presented in part as a paper at the annual meeting of the American Society of Retina Specialists, Maui, HI, October 2008, and as a poster at the annual meeting of the American Academy of Ophthalmology, Atlanta, GA, November 2008.

The authors have no financial/conflicting interests to disclose.

Reprint requests: Susanna S. Park, MD, PhD, University of California Davis Eye Center, 4860 Y Street, Suite 2400, Sacramento, CA 95817; e-mail: susanna.park@ucdmc.ucdavis.edu

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.

doses, nonproliferating tissue sustains minimal change from DNA damage, while metabolically active tissue suffers cell loss because of apoptosis or failure to regenerate.[4] The theoretical advantage of dose fractionation is well known and based on the different daily dose responses of normal and diseased tissues.[5] Normal cells are able to repair DNA injury, proliferate, and repopulate lost cells between dose fractions while diseased cells are not. Multiple clinical trials using radiotherapy as monotherapy for nAMD have been conducted and reported (Table 1).[6–24] Despite a wide range of doses of radiation and fractionation used, most clinical trials failed to show a significant visual benefit,[6–17] while a few showed a small but statistically significant visual benefit by 1 year to 2 years.[18–23] Although research on radiotherapy for nAMD was mostly abandoned with the introduction of anti-VEGF therapy, the recently published results of a pilot study combining anti-VEGF therapy with 24-Gy epiretinal brachytherapy delivered during vitrectomy as a single fraction have led to a large multicenter clinical trial investigating this combination therapy for nAMD (CABERNET trial). The pilot study showed that 75% of eyes treated with this combination therapy did not require any further treatment during the first year.[3] Visual acuity was comparable with the results reported with monthly anti-VEGF therapy.

Despite these encouraging short-term pilot data on combination of radiation with anti-VEGF therapy for nAMD, safety concerns remain regarding possible long-term toxicity in eyes after radiotherapy. Although the adverse effects of radiation after treatment for ocular and orbital tumors have been studied, limited data are available regarding long-term effects of radiation on eyes treated for nAMD.[25,26] Most clinical trials of nAMD did not report on significant ocular toxicity from radiation, but these studies had follow-up of 1 year to 2 years and used radiation doses <24 Gy.[6,9,11–13,19–22,24] A few studies reported radiation toxicity ranging from cataract to neovascular glaucoma after 12 Gy to 24 Gy of radiation even with short-term follow-up.[7,8,10,18,23] Because radiation toxicity can occur up to 15 years after treatment, long-term follow-up information is needed to better evaluate its incidence.[27,28] This study investigated the long-term effects of 20 Gy to 40 Gy, stereotactic, fractionated external beam radiation (St-EBR) in eyes with nAMD treated between 1997 and 2000.

Methods

A retrospective chart review was performed of subjects treated with St-EBR for the treatment of subfoveal choroidal neovascular membrane (CNVM) secondary to AMD. In the original study, St-EBR was used as monotherapy for subfoveal CNVM in a prospective Phase I trial conducted at the University of California Davis Medical Center from 1997 to 2000. The details of this treatment with 1-year follow-up data have been previously reported.[7] The protocol for this retrospective study of the long-term effect of St-EBR was reviewed and approved by the Office for Human Research Protections at the University of California Davis Medical Center.

Briefly, for delivery of St-EBR, each patient had a custom-made aquaplast mask to immobilize the head. Radiation was administered in a 3-beam stereotactic fashion focused on the foveal region, with a macular treatment volume of 5 mm in maximum diameter, which translates into a 19.6-mm^2 central macular area of treatment. The radiation beam produced a 4-mm margin of normal tissue exposure outside the treatment area, resulting in a 13 mm diameter of total radiation exposure. Based on expected radiation exposure using this method, the dose of radiation at the edge of the 5-mm zone of treatment is 50% of the treatment dose and drops substantially as one moves further peripherally. A 6-MV photon beam was delivered using the Varian 600C linear accelerator (Varian, Palo Alto, CA). Treatment fields included the ipsilateral inferior oblique, the contralateral superior oblique, and a vertex beam avoiding the contralateral eye. Radiation was administered with the patient fixating upward so that the horizontal beam would spare the lens.[7] Radiation doses ranged from 20 Gy to 40 Gy, given in 2-Gy daily fractions, with 40 Gy, the most common dose used in the original trial, being administered to 32 eyes (34%).

Because the 1-year data on treated eyes have been previously reported,[7] only patients with $\geq$2-year follow-up information were included in our current study. Paper and electronic medical records of all 89 subjects who enrolled in the original Phase I study were reviewed to identify subjects with follow-up clinical information of $\geq$2 years. Data collected included age, sex, ocular and medical history, dates of initial and follow-up eye examinations, best-corrected visual acuity (BCVA) by Snellen chart, and clinical eye examination findings at enrollment and follow-up visits. All available fluorescein angiograms (FA) obtained before and after St-EBR treatment were reviewed, with attention to CNVM type, size and location, macular morphology, and findings of retinal vasculopathy suggestive of radiation retinopathy.

In the initial prospective study and in this retrospective review, CNVM lesions were classified as classic if they were composed of at least 50%

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.

Table 1. Clinical Trials of Radiation Monotherapy for Exudative AMD

Study	Number of Eyes	Radiation	Total Radiation Dose	Fraction Dose
Yonemoto et al[24]	19 eyes	Proton beam*: 19 eyes: 7.3 Gy	7.3 Gy	7.3 Gy
Char et al[21]	27 eyes	EBR: 13 eyes: 7.5 Gy (single treatment); 14 eyes: observation	7.5 Gy	7.5 Gy
Spaide et al[13]	91 eyes	EBR: 91 eyes: 10 Gy; 119 retrospective eyes: control	10 Gy	2 Gy
Hart et al[11]	199 eyes	EBR: 99 eyes: 12 Gy; 100 eyes: observation	12 Gy	2 Gy
Flaxel et al[8]	48 eyes	Proton beam*: 24 eyes: 7.3 Gy (single dose); 24 eyes: 12.7 Gy (single dose)	7.3 and 12.7 Gy	7.3 and 12.7 Gy
Marcus et al[6]	83 eyes	EBR: 41 eyes: 14 Gy; 42 eyes: observation	14 Gy	2 Gy
Ciulla et al[9]	30 eyes	Proton beam*: 20 eyes: 14.6 Gy; 10 eyes: observation	14.6 Gy	7.3 Gy
RAD[12]	205 eyes	EBR: 101 eyes: 16 Gy; 104 eyes: sham radiation	16 Gy	2 Gy
Valmaggia et al[20]	161 eyes	EBR: 52 eyes: 1 Gy (0.25-Gy fx); 57 eyes: 8 Gy (2-Gy fx); 52 eyes: 16 Gy (4-Gy fx)	0.25, 8, 16 Gy	0.25, 2, 4 Gy
Churei et al[18]	36 eyes	EBR: 21 eyes: 20 Gy; 15 eyes: observation	20 Gy	2 Gy
Kobayashi and Kobayashi[22]	101 eyes	EBR: 51 eyes: 20 Gy; 50 eyes: observation	20 Gy	2 Gy
Marcus et al[10]	88 eyes	EBR: 41 eyes: 20 Gy; 22 eyes: sham radiation; 25 eyes: observation	20 Gy	4 Gy
Zambaraki et al[23]	166 eyes	Proton beam*: 83 eyes: 14.6 Gy (7.3-Gy fx); 83 eyes: 21.8 Gy (10.9-Gy fx)	14.6 and 21.8 Gy	7.3 and 10.9 Gy
Finger et al[17]	31 eyes	Palladium plaque brachytherapy 31 eyes: mean, 17.62 Gy (range, 12.5–24 Gy)	12.5–24 Gy	12.5–24 Gy
Bergink et al[19]	74 eyes	EBR: 37 eyes: 24 Gy; 37 eyes: observation	24 Gy	6 Gy
Prettenhofer et al[16]	80 eyes	EBR: 40 eyes: 14.4 Gy; 40 eyes: 25.2 Gy	14.4 and 25.2 Gy	1.8 Gy
Barak et al[7]	94 eyes	EBR: 22 eyes: 20 Gy; 10 eyes: 24 Gy; 11 eyes: 28 Gy; 11 eyes: 32 Gy; 8 eyes: 36 Gy; 32 eyes: 40 Gy	20–40 Gy	2 Gy

Study	Follow-up (Months)	Visual Results	Toxicity
Yonemoto et al[24]	11.6	No control for VA comparison	No confirmed radiation toxicity. 1 eye with vision loss of unknown causative agent
Char et al[21]	17	Statistical benefit in VA with treatment at average of 17 months	No radiation toxicity
Spaide et al[13]	12	No benefit in vision at 12 months	No radiation toxicity
Hart et al[11]	24	No benefit in VA at 24 months	No radiation toxicity
Flaxel et al[8]	12	More eyes with stabilization of VA with 12.7-Gy dose at 12 months	46% with radiation retinopathy at 12 months in 12.7-Gy group. No retinopathy in 7.3-Gy group
Marcus et al[6]	12	No difference in VA at 12 months	No radiation toxicity
Ciulla et al[9]	24	No benefit in VA compared with control at 24 months	No radiation toxicity
RAD[12]	12	No benefit in VA at 12 months	No radiation toxicity
Valmaggia et al[20]	18	Statistical benefit in VA with treatment between treatment dose groups (8 and 16 Gy) vs. control group (1 Gy) at 12 and 18 months	No radiation toxicity
Churei et al[18]	24	Statistical benefit in VA with treatment at 24 months	Radiation cataract in 1 eye at 8 months
Kobayashi and Kobayashi[22]	24	Statistical benefit in VA with treatment at 24 months	PSC progression 3 months after EBR
Marcus et al[10]	12	Statistical benefit in VA with treatment at 6 months. No statistical benefit at 12 months	1 eye with CWS and retinal nonperfusion adjacent to nerve at 12 months
Zambaraki et al[23]	12	Statistical benefit in VA with treatment using a higher dose (21.8 Gy) at 12 months	Radiation complication in 15.7% in 14.6-Gy group and 14.8% in 21.8-Gy group

(*continued on next page*)

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.

Table 1. (*continued*)

Study	Follow-up (Months)	Visual Results	Toxicity
Finger et al[17]	84	No control for VA comparison	No radiation toxicity
Bergink et al[19]	12	Statistical benefit in VA with treatment at 12 months	No radiation toxicity
Prettenhofer et al[16]	48	No difference in VA at 12 months	No radiation toxicity (up to 48 months)
Barak et al[7]	12	No VA benefit at 12 months	1 eye with NVG, sub- and preretinal hemorrhage at 14 months after 20 Gy

*Radiation dose from proton beam, given in cobalt gray equivalent, was divided by 1.1 to convert to gray.
VA, visual acuity; PSC, posterior subcapsular cataract; CWS, cotton wool spot; NVG, neovascular glaucoma; fx, fraction.

classic CNVM by FA. All other lesions were classified as nonclassic and included CNVM with minimally classic or occult lesions and predominantly hemorrhagic lesions. Final macular morphology was classified as geographic atrophy (GA), disciform scar, retinal pigment epithelial (RPE) atrophy, or active CNVM. Eyes were classified as having GA if the central macular region had loss of RPE and choriocapillaris as seen on clinical examination, fundus photography, or FA. Three eyes with active CNVM at the edge of large central area of GA were classified as having GA because the eye was atrophic centrally. Eyes were classified as having active CNVM if active leakage was noted on FA, new retinal hemorrhage or exudates were seen on fundoscopy, or new intra- or subretinal fluid was noted on examination or optical coherence tomography (OCT) in the absence of central GA. Disciform scar was ascribed to those eyes with subretinal fibrosis visible on fundus photography or clinical examination with or without subretinal fluid or macular edema.

Fluorescein angiography images were viewed on the digitial ophthalmic imaging system (OIS) system, and the photodynamic therapy–measuring tool was used to manually outline the CNVM and areas of GA. Lesion area and greatest linear dimension (GLD) were determined using this tool and used in our analysis.

Fundus photograph and FA images were analyzed independently by three retinal specialists (R.T., L.S.M., and S.S.P.) for the detection of microvascular changes consistent with radiation retinopathy. The diagnosis of radiation retinopathy was assigned to eyes with any of the following findings agreed on by the three reviewers: retinal microaneurysms with or without retinal hemorrhages, cotton wool spots, retinal neovascularization, or retinal capillary dropout. In the one patient diagnosed with diabetes mellitus after EBR, the diagnosis of radiation retinopathy was made based on fundus photography and FA comparison with the contralateral untreated eye that showed no signs of retinopathy.

A subset of subjects who could be contacted were imaged prospectively with a high-resolution Fourier-domain optical coherence tomography developed at the University of California Davis, with an axial resolution of 4 μm to 4.5 μm and a transverse resolution of 10 μm to 15 μm. Before imaging, written informed consent was obtained. The imaging portion of the study was performed according to a separate protocol approved by the Office for Human Research Protections at the University of California Davis Medical Center and in accordance with the tenets of the Declaration of Helsinki.

Fourier-domain optical coherence tomography analysis included a reconstruction of the macula to obtain precise correlation between the OCT image and its location in the macula. The instrument used a superluminescent diode as a light source (model D855; 855 nm at 75-mm bandwidth; Superlum Diodes, Ltd, Moscow, Russia). A raster series of 100 B-scans (1,000 A-scans/frame and 9 frames/second) imaged over a 6-mm $\times$ 6-mm area of the macula were acquired with 11-second acquisition time for a macular volume. The individual B-scans were registered using custom software to minimize fine axial motion artifacts and to create a two-dimensional image of the macula. This reconstructed C-scan image of the macula was overlaid on a color fundus photograph using retinal vessels, optic nerve, and the macular lesion as landmarks.[29,30] Individual OCT images from the desired macular region were then analyzed.

Statistical analysis was performed using a chi-square test for comparison of proportions and a two-tailed Student's *t*-test for comparison of means. Linear regression analysis was performed to correlate initial CNVM area and final area of GA. A P value of <0.05 was considered to be statistically significant. Mean

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.

visual acuity was determined by conversion to logarithm of the minimum angle of resolution.

Results

Among 94 eyes from 89 subjects treated with St-EBR from October 1997 to April 2000, ≥2-year follow-up data were available for 33 eyes (35.1%) from 32 subjects. The 32 subjects with ≥2-year follow-up data had similar baseline age, BCVA, and distribution of CNVM lesion type when compared with the total 89 subjects enrolled in the original clinical trial (Table 2). However, the subgroup with ≥2-year follow-up had a smaller average CNVM lesion size than the total group and included a slightly higher proportion of women.

Tables 2 and 3 provide the baseline characteristics and follow-up data of 33 eyes of 32 subjects with ≥2 years of follow-up after St-EBR treatment. Mean follow-up after St-EBR among the 32 subjects analyzed in this study was 6.2 years, ranging from 2 years to 10 years. The mean age at last follow-up examination was 82.9 years, ranging from 70 years to 95 years. Baseline BCVA ranged from 20/32 to count fingers, with a mean of 20/125. Baseline mean CNVM size was 7.54 ± 5.26 mm^2, ranging from 0.9 mm^2 to 24.9 mm^2. Choroidal neovascular membrane type for this study group was classified as classic for 9 eyes (27%), nonclassic for 21 eyes (64%), and unknown for 3 eyes (9%).

Radiation treatment dose in the ≥2-year follow-up subgroup ranged from 20 Gy to 40 Gy as follows: 20 Gy to 3 eyes (9%), 24 Gy to 2 eyes (6%), 28 Gy to 4 eyes (12%), 32 Gy to 2 eyes (6%), 36 Gy to 3 eyes (9%), and 40 Gy to 19 eyes (58%). The percentage of eyes receiving 40 Gy of radiation in the total treated group was 34, lower than that in the ≥2-year follow-up subgroup, while the percentage of eyes receiving 20 Gy in the total treated group was 23, higher than that in the follow-up subgroup. The distribution for the remaining radiation doses was comparable between the total treated group and the follow-up subgroup.

The analysis of BCVA is limited to a comparison of the last BCVA in the medical record with the pretreatment BCVA because of nonstandard measurements and variable events after treatment. As shown in Table 3, the mean baseline BCVA was 20/125, ranging from 20/25 to count fingers. Final BCVA ranged from 20/50 to no light perception, with a mean of 20/300 after excluding 5 patients with BCVA of hand motion or worse (no logarithm of the minimum angle of resolution equivalent for calculation).

As summarized in Table 4, the macular findings at last follow-up visit among the 33 eyes with ≥2-year follow-up were as follows: central GA in 16 eyes (49%), disciform macular scar in 10 eyes (30%), active CNVM in 3 eyes (9%), and mild RPE atrophy in 2 eyes (6%). Two remaining eyes (6%) developed phthisis bulbi secondary to neovascular glaucoma with no fundus view. Mean radiation doses for eyes with different macular morphologies at final follow-up visit were similar and as follows: 35.25 Gy (range, 20–40 Gy) for GA, 35.30 Gy (range, 20–40 Gy) for disciform scar, 33.3 Gy (range, 20–40 Gy) for active CNVM, and 34.0 Gy (28 and 40 Gy) for phthisis and RPE atrophy.

Pretreatment FA was available for 30 of 33 eyes. Postradiation FA was available for all 33 eyes with mean angiographic follow-up of 4.5 years, ranging from 8 months to 10 years. Pretreatment FA demonstrated

Table 2. Baseline Characteristics of All Eyes Treated with St-EBR for nAMD from 1997 to 2000, with Subclass of Eyes with ≥2 Years of Follow-up Information

	All Subjects[7]	Patients with ≥2-Year Follow-up
Treated eyes/subjects	94/89	33/32
Mean age at baseline, years (range)	76.2 years (55–91 years)	76.8 years (61–90 years)
% Female	51	61
Baseline BCVA range, mean logMAR	20/25–20/400 (0.82)	20/25 to CF (0.8)
Mean pretreatment CNVM size* (range)	9.74 mm^2 (range not available)	7.54* mm^2 (0.9–24.9 mm^2)
CNVM type*: classic/nonclassic, %	21/79	27/64*
Radiation Dose, Gy	Number of Eyes (%)	Number of Eyes (%)
20	22 (23)	3 (9)
24	10 (11)	2 (6)
28	11 (12)	4 (12)
32	11 (12)	2 (6)
36	8 (8)	3 (9)
40	32 (34)	19 (58)

*Choroidal neovascular membrane type and size were unknown for 3 of 33 eyes that did not have an initial FA available at the time of this study.

CF, count fingers; classic CNVM, >50% classic CNVM; nonclassic CNVM, minimally classic, occult, or hemorrhagic lesion.

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.

Table 3. Summary of Subjects with ≥2-Year Follow-up After St-EBR for nAMD

Patient Number	Gender	Age at Treatment (Years)	Pretreatment BCVA	Total Radiation	F/u Period (Years)	Last BCVA
1	M	68.75	20/200	40	7.25	20/200
2	F	83.75	20/40	40	5	20/40
3	F	69.75	20/50	36	9	20/200
4	F	80	20/400	20	6	CF
5	M	89	20/120	40	2	20/500
6	F	66.25	20/32	40	8.5	20/400
7	F	77.5	20/100	40	5	CF
8	F	77.25	20/70	20	3.5	20/320
9	M	73.5	20/40	40	2	20/32
10	F	82	20/200	40	2	20/400
11	M	76.5	20/200	28	9	20/400
12	M	70.5	20/400	20	3.8	20/80
13	F	80.5	20/200	24	6.75	20/400
14	F	89.75	20/150	40	2.5	CF
15	M	72	20/80	32	9.5	20/400
16	M	70	20/400	36	9	20/200
17	M	72	20/125	40	6.75	20/200
18	M	85.3	20/160	40	6	20/200
19	F	81.5	20/60	32	8.75	20/50
20	M	70.5	20/150	40	2.5	20/200
21	F	69.5	20/80	40	2	20/100
22	M	77.5	20/25	28	9.33	NLP
23	F	75	20/70	36	7.25	20/300
24	F	73	20/200	40	5	CF
25	F	61.25	20/80	40	8.5	NLP
26	M	77.75	20/800	40	8.5	20/400
27	M	81	CF	40	10	LP
28	F	72.75	20/200	28	7	CF 2 feet
29	F	90	20/400	40	5	LP
30	F	79	20/50	40	6	HM
31	F	90	20/400	24	5	20/400
32	F	73.18	20/60	40	8	20/400
33	F	77.5	20/400	28	7	20/200
Mean	F/M: 20/13	76.8	—	34.9	6.2	—

Patient Number	Final Status	CNVM Type	Pre-TX CNVM Area (mm^2)	Post-EBR GA Area (mm^2)	Time to GA (Years)	Time to Radiation Retinopathy (Years)
1	GA	Nonclassic	9.20	63.80	7.25	7.25
2	RPE atrophy	Nonclassic	8.60	—	—	—
3	GA	Classic	15.10	41.40	3	—
4	Disciform scar	NA	—	—	—	—
5	Disciform scar	Nonclassic	8.86	—	—	—
6	GA	Nonclassic	5.10	9.50	8.5	—
7	Disciform scar	NA	—	—	—	—
8	GA	Nonclassic	5.08	16.78	1.5	—
9	Active CNVM	Classic	1.98	—	—	—
10	Disciform scar	Nonclassic	6.26	—	—	—
11	RPE atrophy	Classic	3.16	—	—	—
12	Active CNVM	Nonclassic	12.36	—	—	—
13	Disciform scar	Nonclassic	4.30	—	—	—
14	GA	Nonclassic	11.81	11.08	0.25	—
15	GA	Classic	1.80	33.30	9	—
16	GA	Nonclassic	10.10	76.40	0.5	—
17	GA	Nonclassic	6.70	18.70	0.75	—
18	GA	Nonclassic	8.10	8.40	2.25	—
19	GA	Nonclassic	2.40	29.60	4.75	—

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.

Table 3. (*continued*)

Patient Number	Final Status	CNVM Type	Pre-TX CNVM Area (mm^2)	Post-EBR GA Area (mm^2)	Time to GA (Years)	Time to Radiation Retinopathy (Years)
20	GA	Classic	13.75	12.20	1.25	—
21	Active CNVM	Nonclassic	12.79	—	—	—
22	Phthisis and NVG	Nonclassic	24.90	—	—	6
23	GA	NA	—	—	7	—
24	Disciform scar	Nonclassic	4.61	—	—	—
25	Phthisis and NVG from EBR	Nonclassic	14.00	—	—	1
26	GA	Classic	8.60	21.10	8.5	—
27	Disciform scar	Classic	1.90	—	—	10
28	Disciform scar	Nonclassic	8.70	—	—	—
29	Disciform scar	Classic	3.10	—	—	—
30	Disciform scar	Nonclassic	4.30	—	—	—
31	GA	Classic	5.00	7.80	2.65	—
32	GA	Nonclassic	2.70	3.10	4	1
33	GA	Nonclassic	0.90	1.00	2.65	7
Mean	—	—	7.54	23.61	4.0	5.4

VA, visual acuity; F/u period, time from radiation to last follow-up; pre-TX, before EBR; NVG, neovascular glaucoma; time to GA, time from EBR to the initial finding of GA on fundus imaging or clinical examination; time to radiation retinopathy, time from EBR to the first evidence of radiation retinopathy; M, male; F, female; nonclassic, CNVM with minimally classic or no classic leakage pattern; NLP, no light perception; LP, light perception; CF, count fingers; classic, CNVM with >50% classic leakage pattern; NA, FA not available for classification; HM, hand motions.

nonclassic CNVM in 21 eyes (64%) and classic CNVM in 9 of 33 eyes (27%). There was no significant difference in the incidence of GA ($P = 0.20$, chi-square) or disciform scar ($P = 0.16$, chi-square) among treated eyes with classic CNVM when compared with those with nonclassic CNVM.

Because the area of GA often corresponded to that of CNVM before treatment (Figure 1), the pretreatment and posttreatment FAs were compared for eyes that developed GA. Both pretreatment and posttreatment FAs were available for 15 of 16 eyes that developed GA. Mean radiation dose among all 16 eyes was 35.25 Gy, ranging from 20 Gy to 40 Gy. The mean initial CNVM size for the 15 eyes with available FA was 7.1 ± 4.4 mm^2, with a mean GLD of 2.8 ± 1.0 mm. The mean size of GA on the most recent FA among these 15 eyes was 23.6 ± 22.1 mm^2, with a GLD of 4.9 ± 2.5 mm. The difference between the initial size of CNVM and the final area of GA was statistically significant ($P = 0.008$, *t*-test) but small (mean GLD difference of 2.1 mm). Eleven of the 15 eyes (73%) had GLD of GA that was <3 mm larger than that of the original CNVM. The mean difference in size of the original CNVM and the final area of GA among these 11 eyes was 1.1 mm, a small increase in calculated GLD over 5.3 years. Linear regression analysis revealed a statistically significant correlation between the initial CNVM area and the final GA area for these 11 patients ($r = 0.69$, $P < 0.05$). The 4 remaining eyes (27%) showed >4-mm increase in GLD between the initial CNVM size and the final area of GA over an average follow-up of 8.8 years. In all four cases, a recurrent or new CNVM was seen on FA within the area that subsequently developed GA. There was no difference in the dose of radiation administered to these 4 eyes with progressively enlarging CNVM and GA when compared with those where size of GA was similar to the initial CNVM (mean 35.3 Gy, *t*-test, $P = 0.95$). The time from radiation to first development of GA by clinical examination, FA, or fundus photography ranged from 3 months to 9 years, with a mean of 4.0 years. Five of 16 eyes (33.3%) developed first evidence of GA within 2 years of St-EBR.

When the area of GA was compared with the radiation treatment zone (diameter 5 mm and area 19.6 mm^2), 7 of 15 eyes (47%) of the 15 eyes with posttreatment FA had an area of GA significantly smaller than the radiation treatment zone and 33% of eyes had an area of GA much larger than the radiation zone. Three eyes (20%) had an area of GA similar in size and location to the central target radiation zone, but all 3 eyes had an initial CNVM size that was close to the size and location of the radiation treatment zone.

Radiation retinopathy as defined in our study was diagnosed in 6 eyes (18%) based on fundus photography and/or FA (5 of these eyes had FA findings that supported this diagnosis). The average time from St-EBR to development of radiation retinopathy for all 6 eyes was 5.4 years, ranging from

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.

Table 4. Visual Acuity and Macular Morphology at Last Follow-up Among Eyes with nAMD Treated with St-EBR and with at least 2-Year Follow-up Information

Mean baseline BCVA (range)	20/125 (20/25 to CF)	
Mean final BCVA (range)	20/300* (20/50 to NLP)	
Final Macular Morphology	Number of Eyes (%)	Mean Radiation Dose (Gy)
GA**	16 (49)	35.25
Disciform scar**	10 (30)	35.30
Active CNVM	3 (9)	33.33
RPE atrophy	2 (6)	34.00
Phthisis	2 (6)	34.00

*Mean final BCVA excluded five eyes with hand motion or worse vision for which there is no logMAR equivalent.
**No statistical significant difference in radiation dose between eyes that developed GA and disciform scar.
CF, counting fingers; NLP, no light perception; logMAR, logarithm of the minimum angle of resolution.

1 year to 10 years (Tables 3 and 5). Visually insignificant retinopathy characterized by a few microaneurysms and retinal hemorrhages was seen in 2 eyes (Patients 32 and 33) after receiving 40 Gy and 28 Gy, respectively (Figure 2, A and B). The remaining 4 eyes had potentially visually significant retinopathy with vision ranging from 20/200 to no light perception. Among these eyes, 2 eyes (Patients 1 and 27) developed advanced macular ischemia overlying a disciform scar 7.25 years and 10 years after 40 Gy of St-EBR, respectively (Figure 2, C and D). The remaining 2 eyes (Patients 22 and 25) developed neovascular glaucoma and phthisis bulbi. Subject 25 had undiagnosed diabetes mellitus at the time of radiation and developed neovascular glaucoma >5 years after 40 Gy St-EBR. Fluorescein angiogram obtained 1 year after radiation demonstrated microaneurysms consistent with retinopathy in the treated eye and not in the contralateral eye. Corresponding fundus photographs showed diffuse cotton wool spots and retinal hemorrhages in the treated eye and no retinopathy in the contralateral eye. Subject 22 presented suddenly with neovascular glaucoma 6 years after 28 Gy St-EBR without previous evidence of retinal vascular disease despite close clinical monitoring. Because there was no view of the fundus because of vitreous hemorrhage, it is unclear whether the neovascular glaucoma was from radiation toxicity or a vascular occlusion that developed between visits.

Among the 33 eyes with long-term follow-up information, 6 eyes received additional therapy for exudative AMD, either before or after St-EBR. Two eyes (Patients 9 and 14) received thermal laser before St-EBR for juxtafoveal CNVM. Two other eyes (Patients 16 and 23) were receiving intravitreal anti-VEGF therapy at last follow-up for active CNVM at the edge of central GA. Both eyes had received 36 Gy St-EBR and were included in our subset of eyes with GA because of the presence of large central GA (see Methods). Two eyes (Patients 19 and 30) received photodynamic therapy after St-EBR, with one eye developing GA and the other developing a disciform scar at last follow-up.

To obtain detailed morphologic information of eyes that developed GA after St-EBR, 3 eyes (Patients 11, 16, and 17) from 2 subjects with central GA or RPE atrophy who could be contacted were imaged prospectively using a high-resolution Fourier-domain optical coherence tomography developed at our institution. Fundus image reconstruction was performed to accurately identify the area of OCT imaging because foveal fixation was not present in all three eyes. Loss of photoreceptor layer inner segment–outer segment junction was present in areas of GA or RPE atrophy (Figure 3). Areas of retina within the target radiation treatment zone but outside the area of GA or RPE atrophy were unremarkable with an intact photoreceptor layer inner segment–outer segment junction in most cases. The inner retinal layers appeared to be intact over most areas of GA or RPE atrophy and within the radiation treatment zone, with only few small areas demonstrating diffuse retinal atrophy. In one of the eyes with RPE atrophy on fundus photography, a hyperreflective sub-RPE lesion was seen on Fourier-domain optical coherence tomography and believed to represent a small area of fibrosis from a regressed CNVM. The remaining two eyes of one subject revealed diffuse atrophy of the outer retina and RPE, without any sub-RPE hyperreflective lesion.

Discussion

This study provides the longest follow-up information to date of eyes with nAMD treated with radiation.

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.

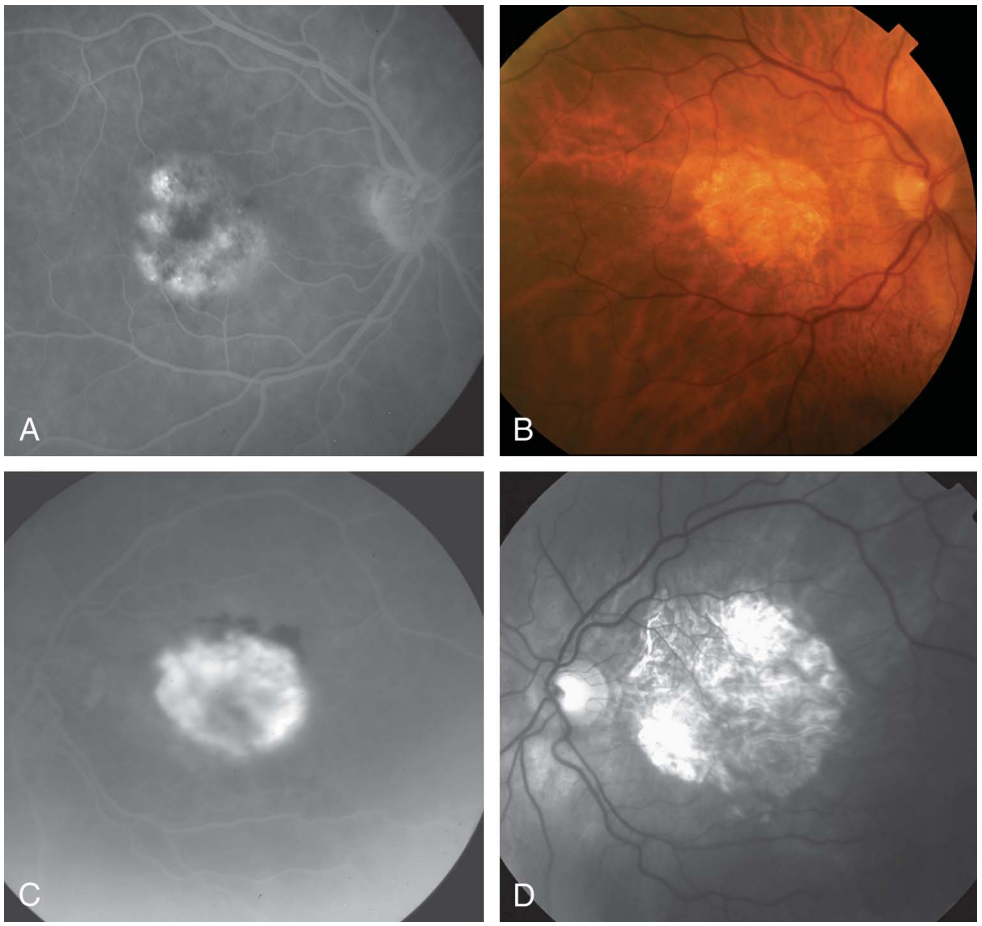

Fig. 1. Fluorescein angiogram at baseline and fundus photograph at last follow-up of two eyes that developed central GA after St-EBR. **A**. Venous-phase FA of the right eye of Patient 6 showing subfoveal CNVM at baseline with BCVA of 20/32. **B**. Fundus photograph of the same eye 8.5 years after 40 Gy St-EBR shows an area of central GA that resembles the size and location of the CNVM seen at baseline. **C**. Late-phase FA of the left eye of Patient 26 shows a classic subfoveal CNVM with BCVA of 20/800. **D**. Red-free fundus photograph of the same eye 8.5 years after 40 Gy St-EBR shows an area of central GA slightly larger than the CNVM noted at baseline. No radiation retinopathy is noted in either eye.

Retinal vascular changes suspicious for radiation retinopathy developed as late as 10 years after St-EBR, and visually significant complications such as neovascular glaucoma and macular ischemia developed in a few eyes despite vigorous dose fractionation and stereotactic delivery of radiation. The most common visually significant finding in our study was central GA, present in 49% of eyes. This latter finding was unexpected, and given its high incidence, we attempted to further characterize the GA to determine whether it resulted from a direct toxic effect of radiation on the RPE, choriocapillaris, or retina.

Most retinal damage from radiation is believed to result from retinal vascular endothelial cell loss, leading to retinopathy characterized by retinal hemorrhages, telangiectasias, edema, microaneurysm formation, and neovascularization.[4] However, direct damage to the outer retina and RPE by ionizing radiation has been reported in animal and human studies, and radiation-induced choroidal damage has been described.[31–35] In our study population, the size of GA tended to correlate with that of the CNVM rather than that of radiation treatment. The mean difference in size of the original CNVM and the final area of GA in 11 eyes with GA and no recurrent CNVM was 1.1-mm increase in calculated GLD over 5.3 years, a growth that can be attributed to the natural time course of expansion of GA because of AMD as previously reported.[36] In addition, Fourier-domain optical coherence tomography images of three eyes with GA or RPE atrophy showed a relatively intact retinal morphology in the radiation treatment zone outside the area of atrophy, similar to the finding reported for GA associated with nonexudative AMD.[37,38]

Although these findings do not rule out the possible direct toxic effect of radiation on the choriocapillaris and RPE, they support the hypothesis that GA may have resulted from progression of degenerative changes in the retina and RPE from AMD. In fact, a recent analysis of patients treated with monthly ranibizumab injection that developed severe vision loss at Year 1 in the MARINA[2] and ANCHOR[39] trials found that the likely cause of vision loss was enlargement of GA. Furthermore, a retrospective review of patients treated with ranibizumab for nAMD for more than 5 years found >50% incidence of GA and >40%

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.

Table 5. Characteristics of Eyes That Developed Radiation Retinopathy After St-EBR for nAMD

Patient	Radiation (Gy)	Pre-TX VA	Final Vision	Medical HX	Final Result
1	40	20/200	20/200	HTN	Macular ischemia, MAs
22	28	20/25	NLP	HTN	NVG and phthisis
25	40	20/80	NLP	Diabetes	Macular ischemia, CWS with later NVG and phthisis
27	40	CF	LP	HTN	Diffuse posterior pole ischemia
32	40	20/60	20/400	Hypothyroid	Few CWS, MAs, heme
33	28	20/400	20/200	HTN	Few MA's

Pre-TX VA, visual acuity before EBR; medical HX, medical history; HTN, hypertension; MAs, microaneurysms; NLP, no light perception; NVG, neovascular glaucoma; CF, count fingers; LP, light perception; CWS, cotton wool spots; heme, retinal hemorrhages.

incidence of persistent subretinal fibrosis by OCT. One mechanism that we propose for these observations is that the GA may be a result of ischemia to the overlying RPE and retina from a barrier effect by the CNVM or subretinal fibrosis causing reduced oxygen diffusion to the outer retina. This theory would explain the close correlation between the area of GA and the area of the original CNVM seen in most eyes with GA in our study.

The present study also demonstrated a moderate rate (18%) of presumed radiation retinopathy over a mean follow-up period of more than 6 years despite vigorous fractionation and stereotactic delivery of EBR. Although the findings of retinal hemorrhages, retinal microaneurysms, macular ischemia, and neovascular glaucoma are not specific for radiation retinopathy, the six eyes with these findings were presumed to have radiation retinopathy based on the criteria described in the Methods and absence of other identifiable causes of retinal vasculopathy. Most of the cases of radiation retinopathy developed in eyes receiving higher doses of radiation (4 of the 6 eyes received 40 Gy). The two manifestations of visually significant radiation retinopathy observed in our study were neovascular glaucoma (two eyes) and macular ischemia (two eyes), both of which have been reported previously.[4,40] The development of neovascular glaucoma after 40 Gy radiation in 1 patient who was diagnosed with diabetes mellitus after enrollment and treatment is not surprising. However, the development of neovascular glaucoma in another patient with underlying hypertension, after receiving 28 Gy EBR, was concerning. No definitive diagnosis of radiation retinopathy was possible in this latter subject because there was no fundus view. Thus, an occult retinal vascular occlusion or some other process leading to ocular ischemia could not be excluded.

Typically, radiation retinopathy is associated with doses >45 Gy[4,25–27] but has been reported after doses as low as 14 Gy given in a single fraction in the treatment of nAMD.[8] Most studies using radiotherapy for nAMD using fractionated radiation of doses <24 Gy have not found evidence of radiation retinopathy, but follow-up for nearly all these studies is ≤ 2 years.[6,9,11–13,19–22,24] Because the development of radiation retinopathy can range from 6 months to 15 years, it is likely that a higher rate of retinopathy might be seen with longer follow-up.[40] Barak et al[7] in the 1-year follow-up of the original cohort of 89 subjects in this study reported only a single case of vitreous hemorrhage and neovascular glaucoma 14 months after 20 Gy EBR given in 2-Gy daily fractions, a finding that was suspected to be a result of radiation toxicity.

The longest follow-up study thus far was by Finger et al[17] who reported on a mean 33-month (range, 3–84 months) follow-up data of 31 eyes after brachytherapy for nAMD. They found no incidence of radiation retinopathy after receiving a mean of 17.62 Gy (range, 12.4–24 Gy) in a single dose. In our study, 18% of eyes had radiation retinopathy with a mean time from St-EBR to development of radiation retinopathy being 5.4 years (range, 1–10 years). Although the higher incidence of radiation retinopathy in our study may be attributed to the higher doses of radiation and longer follow-up, 2 eyes in our study developed radiation retinopathy after 28 Gy of St-EBR, a dose not significantly higher than that used in other studies for nAMD. It is important to note that total volume of tissue irradiated may have been higher with EBR even with stereotactic delivery when compared with brachytherapy with ^{103}Pd used by Finger et al because of higher lateral spread of radiation.[17,24,41,42] This could explain the higher incidence of radiation toxicity in our study in comparison with that reported by Finger et al.[17] Significant differences in the mode of radiation delivery, target size, and radiation dose curves make a direct comparison between brachytherapy and St-EBR very difficult.

Our results highlight the importance of longer follow-up to evaluate the safety of radiotherapy in treating eyes with nAMD. Clear weaknesses of our study are that only a portion of the original cohort was

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.

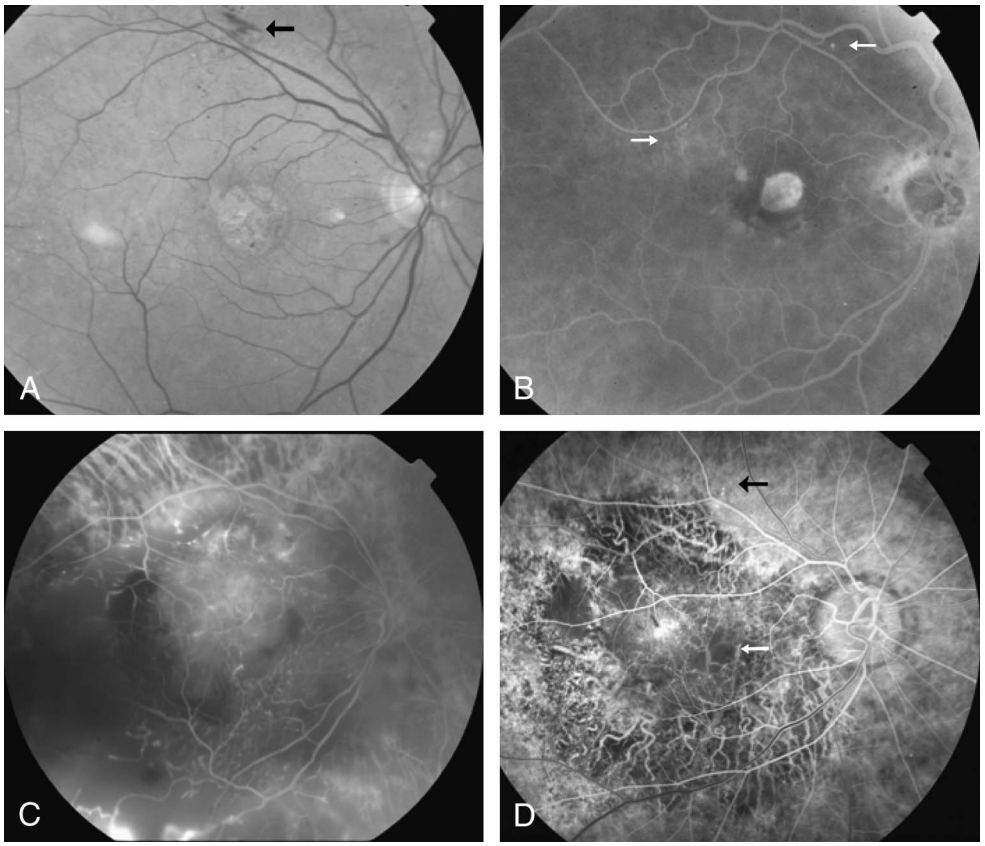

Fig. 2. Fundus photograph and FA showing radiation retinopathy after St-EBR. **A**. Red-free fundus photograph of Patient 32 showing central GA with flame-shaped retinal hemorrhages and microaneurysms along the superotemporal arcade (black arrow). **B**. Mid-phase FA of Patient 33 showing small central GA and subtle areas of retinal telangiectasias and scattered microaneurysms in the macula and along the superior temporal arcade (white arrows). **C**. Venous-phase FA of Patient 33 showing blocked fluorescence from subretinal hemorrhage with overlying large area of retinal capillary nonperfusion, especially prominent along the inferior temporal arcade. **D**. Mid-phase FA of Patient 1 showing a large area of choriocapillaris loss corresponding to a large area of GA seen on fundus photograph with overlying large area of retinal capillary nonperfusion (white arrow). A cluster of microaneurysms also are seen outside the macular region (black arrow).

available for long-term follow-up information and that baseline FA was not available for review for all the subjects. In addition, this was a retrospective study with nonstandard follow-up assessment, and additional therapies for nAMD were used in some study eyes. Nonetheless, the finding of a high rate of GA is noteworthy. Although it may represent the natural course of the disease, GA and the associated poor vision reinforce the belief that radiotherapy may not be suitable as a monotherapy for nAMD. The high rate of radiation toxicity noted in our study may be a consequence of a higher radiation dose and possibly a higher volume of tissue exposed as may be expected from EBR. The evolution of radiotherapy to use devices delivering radiation to small tissue volumes might help mitigate some of these toxic effects.

In summary, this retrospective study is the longest follow-up study to date on long-term effects of radiation on eyes with nAMD. Although the dose of radiation used in this study is somewhat higher than

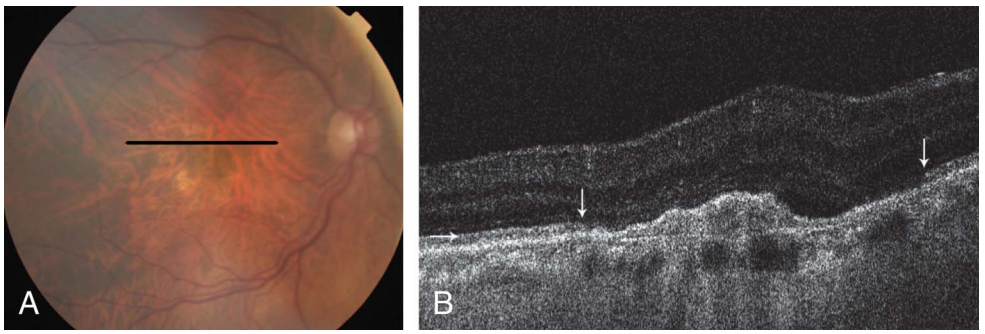

Fig. 3. Fundus photography and a high-resolution Fourier-domain optical coherence tomography (Fd-OCT) images of the right eye of Patient 11 showing a focal area of photoreceptor loss over an area of RPE atrophy 9 years after 28 Gy St-EBR for nAMD. **A**. Fundus photograph showing focal RPE atrophy. The black line delineates the location of the Fd-OCT B-scan image shown in **B**. Horizontal Fd-OCT B-scan image through the area of RPE atrophy showing focal loss of photoreceptor layer inner segment–outer segment junction in an area corresponding to that of RPE atrophy (between vertical arrows). Subretinal hyperreflective lesion also is seen in the area of atrophy, which likely represents subretinal fibrosis. The photoreceptor layer inner segment–outer segment junction (horizontal arrow) is intact outside the region of RPE atrophy exposed to full dose of radiation.

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.

that used in other clinical trials, the study results give some insight into the potential long-term effects of radiation on eyes with nAMD. A moderate rate of delayed radiation retinopathy was noted despite a high fractionation and stereotactic delivery. Thus, patients at risk for retinal vasculopathy, such as those with diabetes mellitus or undergoing chemotherapy, should avoid this therapy even when retinopathy is absent. In addition, a surprisingly high rate of GA was noted in our study population. Although the high incidence of GA likely represents the natural course of AMD after regression of CNVM, further studies are needed to evaluate a potential direct toxic effect of radiation. The answer to this question may become clearer as long-term results of current clinical trials using radiotherapy combined with anti-VEGF therapy for the treatment of nAMD become available. These study subjects should be monitored closely in the long term for possible radiation-related toxic effects that may adversely affect long-term visual outcome.

Key words: age-related macular degeneration, exudative age-related macular degeneration, geographic atrophy, neovascular age-related macular degeneration, radiation, radiation retinopathy.

References

1. Gragoudas ES, Adamis AP, Cunningham ET Jr, et al; VEGF inhibition study in ocular neovascularization clinical trial group. Pegaptanib for neovascularization age-related macular degeneration. N Engl J Med 2004;351:2805–2816.
2. Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–1431.
3. Avila MP, Farah ME, Santos A, et al. Twelve-month short-term safety and visual-acuity results from a multicenter prospective study of epiretinal strontium-90 brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration. Br J Ophthalmol 2009;93:305–309.
4. Archambeau JO, Mao XW, Yonemoto LT, et al. What is the role of radiation in the treatment of subfoveal membranes: review of radiobiologic, pathologic, and other considerations to initiate a multimodality discussion. Int J Radiat Oncol Biol Phys 1998;40:1125–1136.
5. Monroe AT, Bhandare N, Morris CG, Mendenhali WM. Preventing radiation retinopathy with hyperfractionation. Int J Radiat Oncol Biol Phys 2005;61:856–864.
6. Marcus DM, Sheils WC, Johnson MH, et al. External beam irradiation of subfoveal choroidal neovascularization complicating age-related macular degeneration. Arch Ophthalmol 2001;119:171–180.
7. Barak A, Hauser D, Yipp P, et al. A phase I trial of stereotactic external beam radiation for subfoveal choroidal neovascular membranes in age-related macular degeneration. Br J Radiol 2005;78:827–831.
8. Flaxel CJ, Friedrichsen EJ, Smith JO, et al. Proton beam irradiation of subfoveal choroidal neovascularization in age-related macular degeneration. Eye 2000;14:155–164.
9. Ciulla TA, Danis RP, Klein SB, et al. Proton therapy for exudative age-related macular degeneration: a randomized, sham-controlled clinical trial. Am J Ophthalmol 2002;134: 905–906.
10. Marcus DM, Peskin E, AMDRT Research Group. The age-related macular degeneration radiotherapy trial (AMDRT): one year results from a pilot study. Am J Ophthalmol 2004;138: 818–828.
11. Hart PM, Chakravarthy U, Mackenzie G, et al. Visual outcomes in the subfoveal radiotherapy study: a randomized controlled trial of teletherapy for age-related macular degeneration. Arch Ophthalmol 2002;120:1029–1038.
12. Radiation Therapy for Age-Related Macular Degeneration (RAD) Group. A prospective, randomized, double-masked trial on radiation therapy for neovascular age-related macular degeneration (RAD Study). Ophthalmology 1999;106: 2239–2247.
13. Spaide RF, Guyer DR, McMormic B, et al. External beam radiation therapy for choroidal neovascularization. Ophthalmology 1998;105:24–30.
14. Chakravarthy U, Mackenzie G. External beam radiotherapy in exudative age-related macular degeneration: a pooled analysis of phase I data. Br J Radiol 2000;73:305–313.
15. Sivagnanavel V, Evans JR, Ockrim Z, Chong V. Radiotherapy for neovascular age-related macular degeneration. Cochrane Database Syst Rev 2004; 18: CD004004.
16. Prettenhofer U, Haas A, Mayer R, et al. Long-term results after external radiotherapy for age-related macular degeneration. Strahlenther Onkol 2004;180:91–95.
17. Finger PT, Gelman YP, Berson AM, Szechter A. Palladium-103 plaque radiation therapy for macular degeneration: results of a 7 year study. Br J Ophthalmol 2003;87:1497–1503.
18. Churei H, Ohkubo K, Nakajo M, et al. External-beam radiation therapy for age-related macular degeneration: two years' follow-up at a total dose of 20 Gy in 10 fractions. Radiat Med 2004;22:398–404.
19. Bergink GJ, Hoyng CB, Van der Maazen RW, et al. A randomized controlled trial of efficacy of radiation therapy in the control of subfoveal neovascularization in age-related macular degeneration: radiation versus observation. Graefes Arch Clin Exp Ophthalmol 1998;236:321–325.
20. Valmaggia C, Ries G, Ballinari P. Radiotherapy for subfoveal choroidal neovascularization in age-related macular degeneration: a randomized clinical trial. Am J Ophthalmol 2002;133:521–529.
21. Char DH, Irvine AI, Posner MD, et al. Randomized trial of radiation for age-related macular degeneration. Am J Ophthalmol 1999;127:574–578.
22. Kobayashi H, Kobayashi K. Age-related macular degeneration: long-term results of radiotherapy for subfoveal neovascular membranes. Am J Ophthalmol 2000;130:617–635.
23. Zambarakji HJ, Lane AM, Ezra E, et al. Proton beam irradiation for neovascular age-related macular degeneration. Ophthalmology 2006;113:2012–2019.
24. Yonemoto LT, Slater JD, Friedrichsen EJ, et al. Treatment of subfoveal choroidal neovascularization in age-related macular degeneration: treatment techniques and preliminary results. Int J Radiat Oncol Biol Phys 1996;36:867–871.
25. Parsons JT, Bova FJ, Fitzgerald CR, Mendenhall WM, Million RR. Radiation retinopathy after external-beam radiation: analysis of time-dose factors. Int J Radiat Oncol Biol Phys 1994;30:765–773.

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.

26. Takeda A, Shigematsu N, Suzuki S, et al. Late retinal complications of radiation therapy for nasal and paranasal malignancies: relationship between irradiated-dose area and severity. Int J Radiat Oncol Biol Phys 1999;44:599–605.
27. Flaxel CJ. Use of radiation in the treatment of age-related macular degeneration. Ophthalmol Clin North Am 2002;15: 437–444.
28. Guyer DR, Mukai S, Egan KM, et al. Radiation maculopathy following proton beam irradiation for choroidal melanoma. Ophthalmology 1992;99:1278–1285.
29. Smith AJ, Telander DG, Zawadzki RJ, et al. High-resolution Fourier-domain optical coherence tomography and microperimetric findings after macular-off retinal detachment repair. Ophthalmology 2008;115:1923–1929.
30. Stopa M, Bower BA, Davies E, et al. Correlation of pathologic features in spectral domain optical coherence tomography with conventional retinal studies. Retina 2008;28:298–308.
31. Takahashi K, Kishi S, Muraoka K, et al. Radiation choroidopathy with remodeling of the choroidal venous system. Am J Ophthalmol 1998;125:367–373.
32. Amoaku WM, Lafaut B, Sallet G, De Laey JJ. Radiation choroidal vasculopathy: an indocyanine green angiography study. Eye 1995;9:738–744.
33. Egbert PR, Fajardo LF, Donaldson SS, et al. Posterior ocular abnormalities after irradiation for retinoblastoma: a histopathological study. Br J Ophthalmol 1980;64:660–665.
34. Williams GR, Lett JT. Damage to the photoreceptor cells of the rabbit retina from 56 Fe ions: effect of age at exposure. Adv Space Res 1996;18:55–58.
35. Lett JT, Williams GR. Effects of linear energy transfer on the formation and fate of radiation damage to the photoreceptor cell complement of the rabbit retina: implications for the projected manned mission to mars. In: Swenberg CE, ed. Biological effects and physics of solar and galactic cosmic radiation, Part A. New York, Plenum Press, 177–184 (1993).
36. Klein R, Meuer SM, Knudtson MD, Klein BE. The epidemiology of progression of pure geographic atrophy: the Beaver Dam Eye Study. Am J Ophthalmol 2008;146:692–699.
37. Wolf-Schnurrbusch UEK, Enzmann V, Brinkmann CK, Wolf S. Morphologic changes in patients with geographic atrophy assessed with a novel spectral OCT-SLO combination. Invest Ophthalmol Vis Sci 2008;49:3095–3099.
38. Fleckenstein M, Issa PC, Helb H, et al. High-resolution spectral domain-OCT imaging in geographic atrophy associated with age-related macular degeneration. Invest Ophthalmol Vis Sci 2008;49:4137–4144.
39. Brown DM, Michels M, Kaiser PK, et al; ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular are-related macular degeneration: two-year results of the ANCHOR study. Ophthalmology 2009;116:57–65.
40. Brown GD, Shields JA, Sanborn G, et al. Radiation retinopathy. Ophthalmology 1982;89:1494–1501.
41. Finger PT, Berson A, Ng T, et al. Ophthalmic plaque radiation therapy for age-related macular degeneration association with subretinal neovascularization. Am J Ophthalmol 1999;127:170–177.
42. Berson A, Finger PT, Chakravarthy U. Radiation therapy for age-related macular degeneration. Semin Radiat Oncol 1999;9: 155–162.

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.