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Radiation Therapy for Small Choroidal Neovascularization in Age-related Macular Degeneration

Hideaki Matsuhashi,* Yasuko Noda,*
Daisuke Takahashi* and Yasushi Mariya†

*Departments of *Ophthalmology; †Radiology,*
Hirosaki University School of Medicine, Hirosaki, Japan

Purpose: To evaluate the effects of radiation therapy on age-related macular degeneration with subfoveal or juxtafoveal choroidal neovascularization ≤1 disc area.

Methods: Fourteen patients (14 eyes) received a total radiation dose of 10–20 Gy in 5–10 fractions. The mean follow-up time was 22 months. Ten patients (10 eyes) in a control group were followed up for an average of 16 months without treatment.

Results: At a 12-month posttreatment examination, funduscopic and angiographic findings showed improvement in 7 eyes (50%), no change in 1 eye (7%), and deterioration in 6 eyes (43%) among the treated patients. The same findings demonstrated improvement in 1 eye (10%), no change in 2 eyes (20%), and deterioration in 7 eyes (70%) among the control patients. This difference was determined to be statistically significant between the two groups by the Mann–Whitney *U*-test. Visual acuity had improved in 4 eyes (29%), was unchanged in 6 eyes (43%), and had declined in 4 eyes (29%), among the treated patients. Among the control patients, visual acuity had improved in none of the eyes (0%), was unchanged in 6 eyes (60%), and had declined in 4 eyes (40%). The difference in visual acuity between the two groups was not statistically significant.

Conclusions: Radiation therapy inhibited small choroidal neovascularization, as seen by funduscopy and angiography, but its effectiveness in improving visual prognosis was not always evident. **Jpn J Ophthalmol 2000;44:653–660**

Key Words: Age-related macular degeneration, choroidal neovascularization, radiation therapy.

Introduction

Subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) carries a poor visual prognosis,[1,2] and its treatment is currently one of the most debated subjects in ophthalmology. The efficacy of laser photocoagulation of well-demarcated CNV has been confirmed by clinical trials conducted by the Macular Photocoagulation Study Group.[3–5] However, most patients with exudative maculopathy have poorly defined, or so-called occult CNV, and are not eligible for laser treatment.[6] Although the recent development of indocyanine green (ICG) videoangiography has increased treatment eligibility, approximately two thirds of all occult CNV cases are still untreatable.[7] Furthermore, even if they meet the criteria of the Macular Photocoagulation Study Group, eyes with subfoveal CNV inevitably demonstrate an immediate decrease in central visual acuity after laser application. Therefore, investigation of alternative therapeutic approaches with potentially less damage to the neurosensory retina is now warranted.

Surgical excision of subfoveal CNV is reportedly effective in selected cases, especially with type 2 neovascular membrane, which often occurs in presumed ocular histoplasmosis syndrome. However, this treatment does not appear to be beneficial in eyes with type 1 neovascular membrane in AMD,

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Correspondence and reprint requests to: Hideaki MATSUHASHI, MD, Department of Ophthalmology, Hirosaki University School of Medicine, 5 Zaifucho, Hirosaki-shi, Aomori-ken 036-8562, Japan

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because removal of the neovascular membrane usually causes an apparent defect in the retinal pigment epithelium.[8–10]

Chakravarthy et al[11] and Bergink et al[12] reported independently on the beneficial effect of low-dose radiation on subfoveal CNV. Their methods were based on the hypothesis that closure of aberrant vessels may be induced by radiation with doses lower than those that would damage normal retinal and choroidal structures. It was thought that proliferating vascular endothelial cells had a higher radiosensitivity than nondividing endothelial cells.[13] This method does not require a complete delineation of CNV on angiography, and thus we could apply it to eyes with occult CNV. Besides, radiation may be applied to eyes with relatively good vision, because it does not cause the immediate decline in visual acuity (VA) as noted after photocoagulation. However, the efficacy and safety of radiotherapy have not been fully documented through follow-up after short-term studies.[14–19] In fact, some negative results have been reported recently[20] with this treatment. In a previous report, we stated that radiotherapy should be indicated in eyes with relatively good vision or with small CNV.[15] In this study, we describe the clinical courses of patients with AMD and small CNV after external beam radiation.

Materials and Methods

The principal eligibility criteria for subjects in this study were: (1) age >50 years, (2) subfoveal or juxtafoveal CNV ≤1 disc area, (3) CNV with exudative changes, (4) condition untreatable by laser photocoagulation because of poorly defined CNV or VA of 0.2 or better, or the patient had refused laser treatment, and (5) signed informed consent. Exclusion criteria were: (1) atrophic or cicatricial lesions; (2) retinal circulatory disturbance, including diabetic retinopathy, retinal vein occlusion, or hypertensive retinopathy; (3) other macular diseases or optic atrophy.

For more than 4 years beginning in January 1994, we treated 14 patients (14 eyes) (10 men and 4 women) ranging in age from 53 to 80 years (mean = 66 years). The mean follow-up period was 22 months (range, 12–36 months). Radiotherapy was performed in a manner similar to that reported by Chakravarthy et al,[11] using a 10 MV x-ray beam. In the simulation, using computed tomography, the 90% isodose curves encompassed the posterior pole through a single lateral port. Twelve patients received a total radiation dose of 14 Gy, delivered in 7 fractions of 2 Gy each over 9–11 days. One patient received a total dose of 20 Gy in 10 fractions. The last patient received a dose of 10 Gy in 5 fractions, and the treatment was stopped because he was infected with epidemic keratoconjunctivitis. Best-corrected VA was measured and fundus appearance evaluated by color photography. The findings by fluorescein angiography (FAG) were assessed before treatment, at 3 and 6 months after treatment, and at 6-month intervals thereafter. Indocyanine green videoangiography of the posterior fundus, slit-lamp photography of the lens, and central visual field testing (using Humphrey Field Analyzer, program 30-2) were performed before treatment and 12 months after treatment.

As a control, we studied 10 patients (9 men and 1 woman; 10 eyes) ranging in age from 55 to 83 years (mean = 68 years) who met the same criteria as the treated group. These patients had refused either radiation or laser treatment and had been observed without any treatment for more than 12 months since 1993. Their VA was assessed and evaluated by fundus photography, FAG, and ICG videoangiography. The mean follow-up time was 18 months (range, 12–36 months).

Funduscopic findings were classified into five stages: (1) vascularized drusen, (2) serous retinal detachment, (3) retinal pigment epithelial detachment, (4) subretinal hemorrhage, and (5) disciform lesion. This classification was in accordance with the criteria[21] published by the research committee on chorioretinal degeneration supported by the Ministry of Health and Welfare of Japan. According to the Macular Photocoagulation Study Group guidelines,[3–5] two basic patterns of CNV, classic and occult, were identified by FAG. The size and the location of CNV were determined by FAG and ICG videoangiography based on the classification by Guyer et al.[7]

Results

Findings of each patient at baseline and during the subsequent clinical course are summarized in Tables 1 and 2. Changes in funduscopic and angiographic findings from baseline to the 12-month follow-up examination were divided into five classes: Class 1: regression of CNV (Figure 1), Class 2: decrease of exudative changes, Class 3: unchanged, Class 4: increase of exudative changes, and Class 5: enlargement of CNV (Figure 2). Once deterioration was confirmed and surgical treatment was applied, a patient sometimes dropped out of the study. In patients who dropped out before the 12-month follow-up, the findings just prior to leaving were used for analysis.

Table 1. Clinical Course of Treated Patients

Case No.	Age (yr)	Sex	Stage*	CNV Location†	CNV Type‡	ICG Findings§	Visual Acuity			12-Month Angiographic Results (class)¶	Last Follow-up (mo)
							Initial	12 Month	Final		
1	64	Male	SRD	Subfoveal	O	FS	0.1	0.05	0.01	4	36
2	62	Male	SRD	Juxtafoveal	O	Multiple FSs	0.08	0.8	1.2	1	39
3	74	Female	SRD	Subfoveal	O	Multiple FSs	0.05	0.05	0.05	4	12
4	71	Male	SRD	Juxtafoveal	C	Relatively large FS	0.3	–	0.05	5	10
5	66	Male	SRD	Subfoveal	O	Multiple FSs	0.3	0.3	0.6	1	36
6	62	Male	SRD	Subfoveal	O	FS	0.6	0.6	0.6	2	36
7	69	Male	SH	Subfoveal	O	Negative	0.09	0.2	0.2	2	36
8	60	Male	PED	Subfoveal	O	Multiple FSs	0.3	0.1	0.08	4	24
9	80	Male	SRD	Subfoveal	O	Multiple FSs	0.07	0.1	0.04	2	24
10	53	Female	SH	Juxtafoveal	O	FS	0.5	1.0	1.0	2	12
11	61	Male	SRD	Subfoveal	O	FS	0.8	0.2	0.2	3	12
12	66	Male	SRD	Subfoveal	O + C	Multiple FSs	0.01	0.02	0.02	1	12
13	68	Female	DL	Subfoveal	O + C	Relatively large FS	0.06	–	0.08	5	7
14	54	Female	SRD	Subfoveal	C	Relatively large FS	0.3	0.2	0.2	5	12

*SRD: Serous retinal detachment, PED: pigment epithelial detachment, SH: subretinal hemorrhage, DL: disciform lesion.
†CNV: Choroidal neovascularization.
‡O: Occult (ill-defined) CNV, C: classic (well-defined) CNV.
§ICG, Indocyanine green; FS (focal spot): hyperfluorescence no greater than 1 disc area in size by ICG.
¶See text for description of classification.

In the treated group, 7 eyes (50%) had improved, including 3 eyes in Class 1 and 4 eyes in Class 2; 1 eye (7%) was unchanged, and 6 eyes (43%) worsened, including 3 eyes in Class 4 and 3 eyes in Class 5. In the control group, 1 eye (10%) of Class 2 had improved, 2 eyes (20%) of Class 3 were unchanged, and 7 eyes (70%) had deteriorated, including 1 eye of Class 4 and 6 eyes of Class 5. The differences between the two groups were statistically significant ($P = .05$) by the nonparametric Mann–Whitney *U*-test (Table 3).

Among the treated patients, 2 dropped out less than 11 months after radiation, and 2 dropped out soon after the 12-month follow-up examination. Among patients with eyes that had been classified Class 4 at 12 months, 1 patient dropped out after 24 months and 1 left after 36 months of follow-up. Of the 7 cases whose fundus had improved by 12 months, 4 cases maintained a favorable status through the following 2 years. Among the control patients, 4 eyes received laser treatment after the 12-

Table 2. Clinical Course of Control Patients

Case No.	Age (yr)	Sex	Stage*	CNV Location†	CNV Type‡	ICG Findings§	Visual Acuity			12-Month Angiographic Results (class)¶	Last Follow-up (mo)
							Initial	12-Month	Final		
101	56	Male	SRD	Subfoveal	O	FS	0.2	0.3	0.2	4	36
102	74	Female	DL	Subfoveal	C	FS	0.2	0.2	0.2	5	12
103	70	Male	SH	Subfoveal	O	Multiple FSs	0.04	c.f.	c.f.	5	11
104	71	Male	SH	Subfoveal	O	Not applied	0.3	0.1	0.1	3	16
105	74	Female	SRD	Subfoveal	O	Negative	0.4	0.2	0.09	5	24
106	55	Male	SH	Subfoveal	C	FS	0.09	0.03	0.03	5	12
107	58	Male	SH	Subfoveal	O	Negative	0.6	0.4	0.4	5	12
108	59	Male	SRD	Subfoveal	O + C	FS	0.2	0.2	0.6	2	30
109	66	Male	VD	Subfoveal	O	FS	0.08	0.1	0.1	3	14
110	84	Male	SRD	Subfoveal	O	FS	0.04	0.03	0.03	5	15

*SRD: Serous retinal detachment, VD: vascularized drusen, SH: subretinal hemorrhage, DL: disciform lesion.
†CNV, Choroidal neovascularization.
‡O: Occult (ill-defined) CNV, C: classic (well-defined) CNV.
§ICG: Indocyanine green, FS (focal spot): hyperfluorescence no greater than 1 disc area in size by ICG.
¶See text for description of classification.

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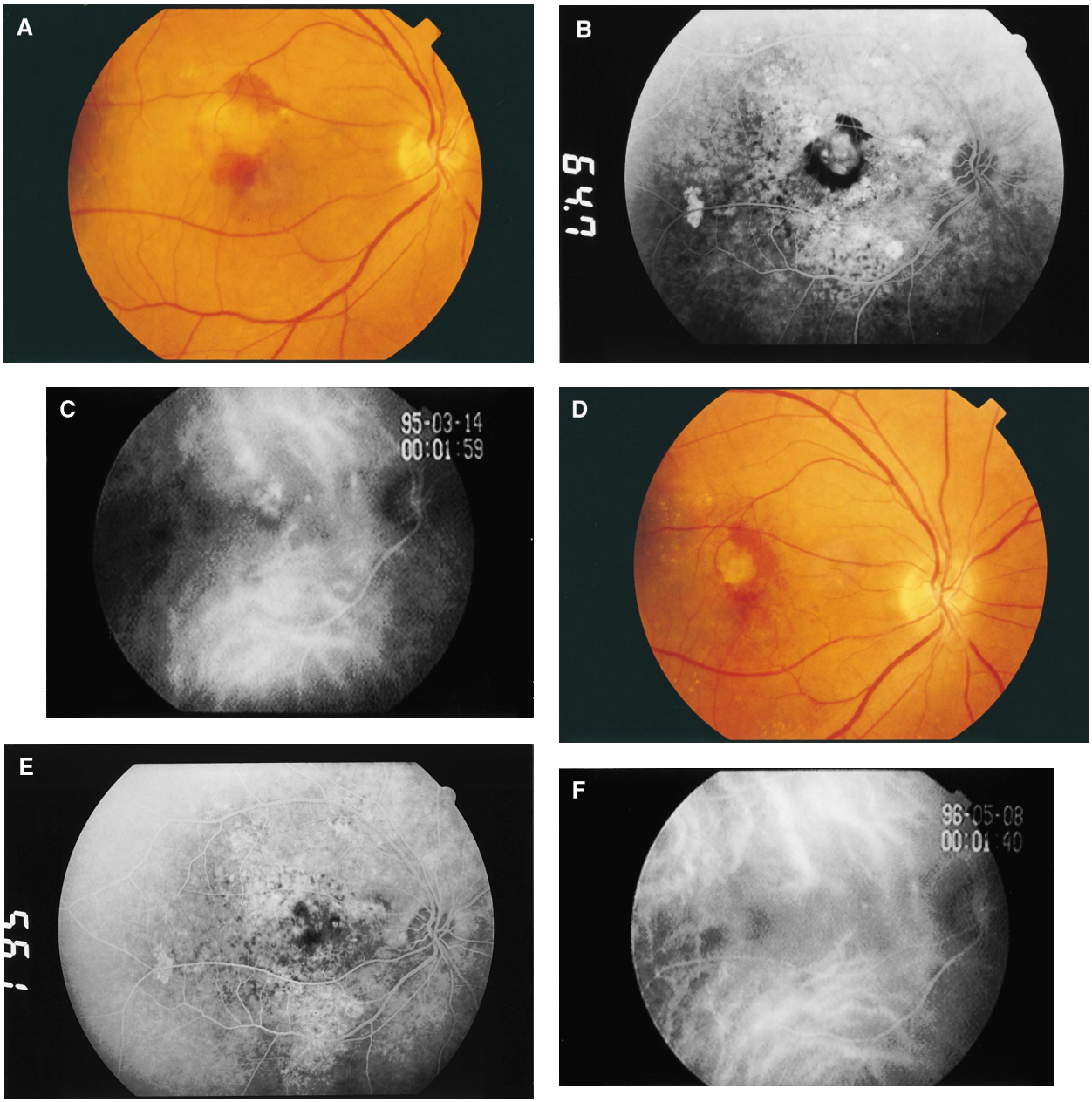

Figure 1. (**A**) Case 5 had visual acuity of 0.3 before radiation. Elevation of retinal pigment epithelium with contiguous hemorrhage was noted in macula. Serous retinal detachment and drusen were noted to surround lesion. (**B**) Fluorescein angiography (FAG) reveals a subfoveal choroidal neovascularization (CNV) with fluorescence blocked by blood and surrounding speckled hyperfluorescence. (**C**) Indocyanine green angiography shows multiple focal spots that corresponded to CNV. (**D**) Twelve months after radiation, subretinal hemorrhage and fluid have resorbed. Visual acuity is stable at 0.3. (**E**) FAG shows significant regression of CNV. (**F**) ICG also shows decreased number of focal spots.

month examination, 2 deteriorated eyes were untreatable, and 1 patient dropped out after 36 months of follow-up.

For statistical analysis of visual prognosis, we converted the decimal VA into the logarithm of the minimal angle of resolution (Log_{MAR}), and we defined an improvement in VA as a decrease of 0.3 Log_{MAR} units or more and a decline of VA as a gain of 0.3 Log_{MAR} units or more. In the treated patients, the VA had improved in 4 eyes (29%), was unchanged in 6 eyes (43%), and had declined in 4 eyes (29%) from baseline to the 12-month follow-up ex-

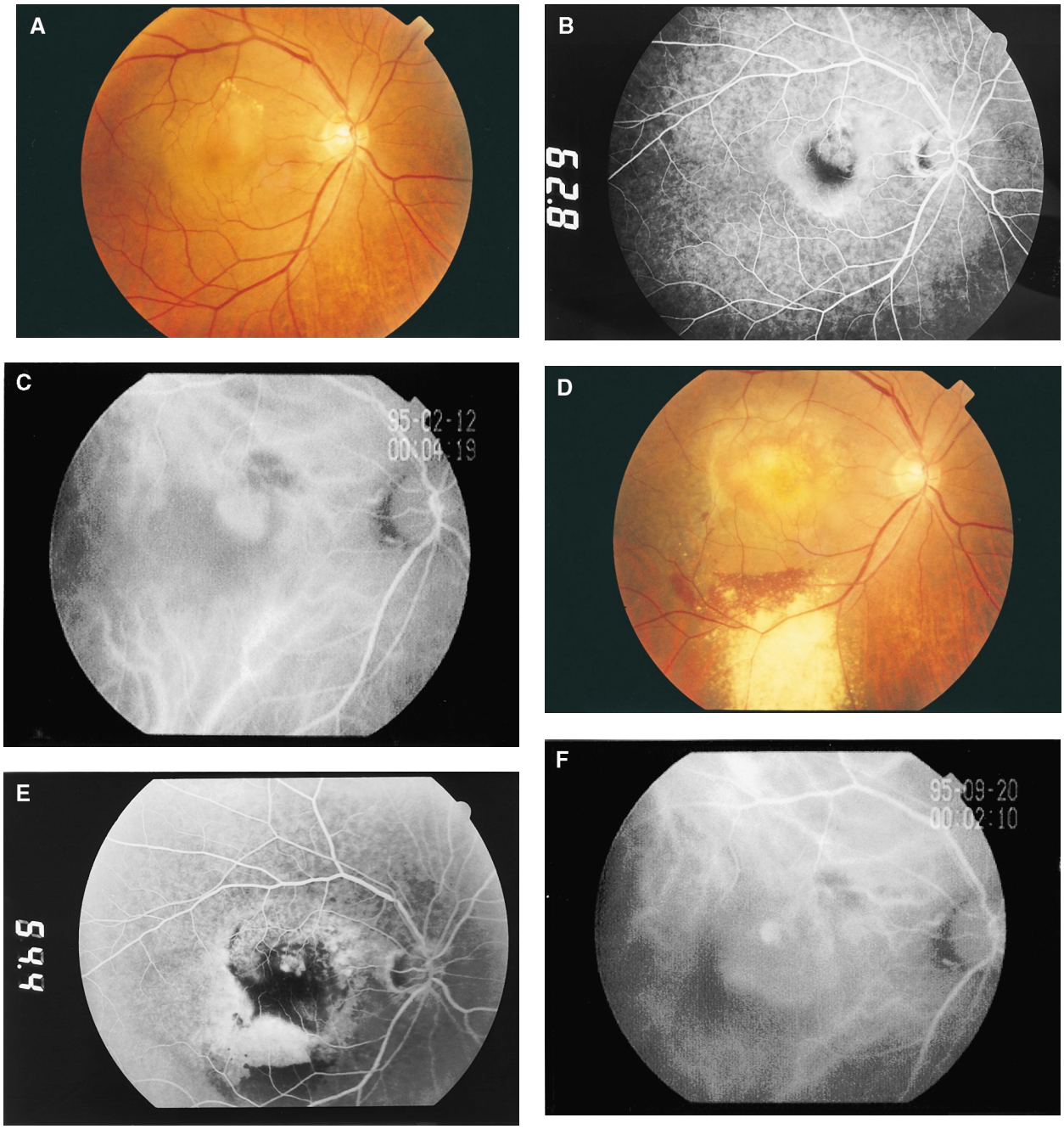

Figure 2. (**A**) Case 4 had visual acuity of 0.3 and elevation of retinal pigment epithelium with subretinal fluid in macula. (**B**) Fluorescein angiography (FAG) reveals well-defined juxtafoveal choroidal neovascularization (CNV) surrounded by hyperfluorescence that corresponds to serous retinal detachment. (**C**) Indocyanine angiography, in early phase, shows intense hyperfluorescence nearly 1 disc area in size. (**D**) Nine months after radiation, patient has visual acuity of 0.04 and large discoid lesion accompanied by intense exudative change. (**E**) FAG shows CNV, about 6 disc areas in size, with poorly demarcated boundaries. (**F**) At 7 months after radiation, ICG shows focal spot overlying large plaque of hyperfluoresence.

amination. In the control group, none of the eyes had improved, 5 eyes (50%) were unchanged, and 5 eyes (50%) had declined in VA. No significant difference was found between the two groups (Table 4).

Reliable data from central visual field testing were obtained in 10 eyes from the treated group before and 12 months after radiation. Six eyes had improved, 2 eyes had remained stable, and 2 eyes had

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Table 3. Funduscopic and Angiographic Results at 12-Month Follow-up

Clinical Findings*	No. of Treated Eyes	%	No. of Control Eyes	%
Regression of CNV	3	21	0	0
Decrease of exudative change	4	29	1	6
Stable	1	7	2	13
Increase of exudative change	3	21	1	19
Enlargement of CNV	3	21	6	63
			$P = .05^{\dagger}$	

CNV: Choroidal neovascularization.
†*P* value, nonparametric Mann–Whitney *U*-test.

deteriorated. In each patient, visual field results correlated with other clinical findings.

None of the treated patients developed radiation cataract or keratoconjunctivitis. Two eyes (cases 1 and 3) developed small retinal hemorrhages outside the macular region; however, the hemorrhages spontaneously resolved during the follow-up period.

Discussion

Chakravarthy et al[11] previously reported that regression of CNV had been noted in 77% of 19 patients, and VA had been maintained or improved in 63% of those patients 12 months after radiation doses of 10–15 Gy were given in 5 fractions. Bergink et al[12] reported that after radiation doses of 12, 18, or 24 Gy in 6-Gy fractions were performed on three groups of 10 patients each, VA had been stable in 70% of the patients and angiographic appearance had been stable in 60% of the patients after a mean follow-up period of 10 months. No regression of CNV had been noted. Finger et al[14] recently reported that angiographic appearance had been stable in 71% of 81 patients and VA had been stable or had improved two or more lines in 64% of patients after a mean follow-up period of 9 months after radiation doses of 12–15 Gy with an external beam or with palladium 103. Conversely, Spaide et al[20] reported that 10 Gy of external beam radiation had no beneficial effect on VA improvement of three or more lines in 2.4% of patients. In fact, VA had declined three or more lines in 49.4% of the 85 patients after a 1-year follow-up.

In the present study, the funduscopic and angiographic appearances had improved in 50% of the 14 treated patients and had deteriorated in 43% by the 12-month follow- up, while in 70% of the 10 control patients had deteriorated. A statistically significant difference was noted between the two groups. However, VA was stable in most of the patients, and no statistically significant difference in VA could be found between the two groups. In some patients, VA had remained stable or declined while the fundus status had improved. These results suggested that radiation therapy has an inhibitory effect on the progression of CNV; however, its efficacy for visual prognosis was not confirmed. Even if some therapies are effective in inhibiting the growth of CNV, good VA may not be preserved for a long period in eyes with large discoid lesions occupying the central macula, because of the inevitable degeneration of the outer retina, which is separated from normal choroidal circulation by the underlying fibrovascular membrane. On the other hand, in eyes with small CNV accompanied by serous retinal detachment or serous pigment epithelial detachment, VA may be preserved or improved if these exudative changes are resorbed and the parafoveal retinal structure is maintained. Therefore, we anticipate that the efficacy of radiation therapy will be confirmed by a randomized controlled trial of a large number of patients with small

Table 4. Change in Visual Acuity from Baseline to 12-Month Follow-up

Visual Acuity*	No. of Treated Eyes	%	No. of Control Eyes	%
Improved (≤ -0.3 Log_{MAR})	4	29	0	0
Stable (-0.3 Log_{MAR}–0.3 Log_{MAR})	6	43	6	60
Declined (≥ 0.3 Log_{MAR})	4	29	4	40
			$P = .22^{\dagger}$	

*Log_{MAR}: Logarithm of the minimum angle of resolution.
†*P* value, nonparametric Mann–Whitney *U*-test.

subfoveal CNV, and relatively good initial VA, who are not eligible for laser or surgical treatment.

In the report by Spaide et al,[20] which found no efficacy in this method, the eligibility criteria regarding the size of the CNV were broad, <12 disc areas, although the mean initial VA was relatively good (20/80). The figures for the two cases that showed deterioration in their report, demonstrated a CNV >1 disc area by ICG before treatment. In our study, 3 cases that had a CNV of nearly 1 disc area, as confirmed by ICG, before treatment, had an enlarged CNV by 12 months after radiation. The poor clinical results in the report by Spaide et al[20] might be related to the small amount of total radiation (10 Gy). Mandai et al[19] recently reported treatment with a radiation dose of 10 Gy or 20 Gy on two groups of 10 patients each. The number of patients who maintained their VA was significantly larger in the latter group after a follow-up period of more than 18 months.

One problem with radiation therapy is its unpredictability. The CNV can be immediately eliminated with laser photocoagulation, yet persistent or recurrent CNV is frequently observed after treatment.[3] On the other hand, in the present study, it took about 6 to 12 months after radiation to confirm the fundus changes in each patient. Also we could find no predictive feature for the fundus response after radiation, although patients with relatively large CNV demonstrated by ICG tended to have poor visual prognosis.

Another problem with radiation is the side effects. Retinopathy has been noted to develop after external beam radiation with doses of 30 to 35 Gy or more.[22,24] In this study, however, small retinal hemorrhages were observed outside the macula of 2 eyes, although it has not yet been determined whether these changes were caused by radiation retinopathy. Subclinical retinal change may be induced with radiation doses lower than we expected. Some clinical and histopathologic studies revealed that radiation retinopathy appeared to be secondary to vascular damage and was characterized by capillary closure.[22,24] Therefore, ischemic retinal diseases, such as diabetic retinopathy, hypertensive retinopathy, and retinal vein occlusion, are contraindications for radiation therapy in AMD. Also, we would not recommend it for patients with uncontrolled diabetes, uncontrolled hypertension, or other systemic disease causing retinal ischemia.

In conclusion, low-dose external beam radiation achieved an inhibitory effect on small CNV in patients with AMD, and produced no serious side effects, including an immediate decline in VA, which often occurs after laser or surgical treatment. However, its efficacy for long-term visual prognosis has not been determined. A randomized controlled study of a large number of patients is needed to evaluate how beneficial this method actually is for patients.

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References

1. Bressler NM, Frost LA, Bressler SB, Bressler SB, Murphy RP, Fine SL. Natural course of poorly defined choroidal neovascularization associated with macular degeneration. Arch Ophthalmol 1988;106:1537–42.
2. Singermann LJ, Stockfish JH. Natural history of subfoveal pigment epithelial detachments associated with subfoveal or unidentifiable choroidal neovascularization complicating age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 1989;227:501–7.
3. Macular Photocoagulation Study Group. Argon laser photocoagulation for senile macular degeneration. Results of a randomized clinical trial. Arch Ophthalmol 1982;100:912–8.
4. Macular Photocoagulation Study Group. Subfoveal neovascular lesions in age-related macular degeneration. Guidelines for evaluation and treatment in the Macular Photocoagulation Study. Arch Ophthalmol 1991;109:1242–57.
5. Macular Photocoagulation Study Group. Visual outcome after laser photocoagulation for subfoveal choroidal neovascularization secondary to age-related macular degeneration. Arch Ophthalmol 1994;112:480–8.
6. Freund KB, Yannuzzi LA, Sorenson JA. Age-related macular degeneration and choroidal neovascularization. Am J Ophthalmol 1993;115:786–91.
7. Guyer DR, Yannuzzi LA, Slakter JS, Sorenson JA, Hope-Ross M, Orlock DR. Digital indocyanine green videoangiography of occult choroidal neovascularization. Ophthalmology 1994;101:1727–37.
8. Gass JDM. Biomicroscopic and histopathologic considerations regarding the feasibility of surgical excision of subfoveal neovascular membranes. Am J Ophthalmol 1994;118:285–98.
9. Thomas MA, Dickinson JD, Melberg NS, Ibanez HE, Dhaliwal RS. Visual results after surgical removal of subfoveal choroidal neovascular membrane. Ophthalmology 1994;101:1384–96.
10. Ormerod LD, Puklin JE, Frank RN. Long-term outcomes after the surgical removal of advanced subfoveal neovascular membranes in age-related macular degeneration. Ophthalmology 1994;101:1201–12.
11. Chakravarthy U, Houston RF, Archer DB. Treatment of age-related subfoveal neovascular membranes by teletherapy: a pilot study. Br J Ophthalmol 1993;77:265–73.
12. Bergink GJ, Deutman AF, van den Broek JFCM, van Daal WAJ, van der Maazen RWM. Radiation therapy for subfoveal choroidal neovascular membranes in age-related macular degeneration: a pilot study. Graefes Arch Clin Exp Ophthalmol 1994;232:591–8.

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13. De Gowin RL, Lewis LJ, Hoak JC, Mueller AL, Gibson DP. Radiosensitivity of human endothelial cells in culture. J Lab Clin Med 1974;84:42–8.

14. Finger PT, Berson A, Sherr D, Riley R, Balkin RA, Bothworth LJ. Radiation therapy for subretinal neovascularization. Ophthalmology 1996;103:878–89.

15. Matsuhashi H, Takahashi D, Noda Y, et al. Low-dose radiation therapy for choroidal neovascularization in age-related macular degeneration. Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 1996;100:803–9.

16. Harino S, Ohshima Y, Tsujikawa K, et al. Treatment of age-related subfoveal choroidal neovascularization by low-dose external radiation: a preliminary study. Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 1997;101:341–8.

17. Hollick EJ, Goble RR, Knowles PJ, Ramsey MC, Deutsch G, Casswell AG. Radiotherapy treatment of age-related subfoveal neovascular membranes in patients with good vision. Eye 1996;10:609–16.

18. Bergink GJ, Hoyng CB, van der Maazen RWM, Deutman AF, van Daal WAJ. Visual acuity and scar size in eyes with age-related subfoveal choroidal neovascular lesions, 30 months after radiation therapy. Doc Ophthalmol 1996;92:61–75.

19. Mandai M, Takahashi M, Miyamoto H, et al. Longterm effects of radiation treatment for age-related macular degeneration. Rinsho Ganka (Jpn J Clin Ophthalmol) 1998;52:567–71.

20. Spaide RF, Guyer DR, McCormick B, et al. External beam radiation therapy for choroidal neovascularization. Ophthalmology 105:24–30, 1998.

21. Matsui M, Uyama M, Yuzawa M. Guideline of senile disciform macular degeneration. Research Committee on chorioretinal degenerations. The Ministry of Health and Welfare of Japan, Chiyoda-ku, Tokyo, Japan, 1992.

22. Brown GC, Shields JA, Sanborn G, Augsberger JJ, Savino PJ, Schatz NJ. Radiation retinopathy. Ophthalmology 1982;89: 1494–501.

23. Maguire AM, Schachat AP. Radiation retinopathy. In: Ryan SJ, Ogden TE, Hinton D, Schachat AP, eds. Retina. St. Louis: CV Mosby, 1994:1509–14.

24. Archer DB, Amoaku WMK, Gardiner TA. Radiation retinopathy—clinical, histopathological, ultrastructural and experimental correlations. Eye 1991;5:239–51.