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Long-Term Outcome After Radiation Therapy for Subfoveal Choroidal Neovascularization Associated with Age-Related Macular Degeneration

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Purpose: The purpose of this study was to investigate the long-term effect of low-dose radiation therapy on subfoveal choroidal neovascularization associated with age-related macular degeneration.

Methods: The clinical course and visual outcome were compared retrospectively among two treated groups and a control group; 15 patients (15 eyes) received 10 Gy, another 15 patients (15 eyes) received 20 Gy. The control group consisted of 15 patients (15 eyes) without treatment. All patients were followed up for at least 18 months, and most were followed up for 3 years. The macula was irradiated with either 10 Gy in 5 fractions or with 20 Gy in 10 fractions after computed tomography (CT) simulation enabled real-time treatment planning from multiple CT slices.

Results: During the 3 years of follow-up, the lesions became better in 5 eyes, unchanged in 1, and worse in 9 with 10 Gy radiation; better in 7 eyes, unchanged in 1, and worse in 7 eyes with 20 Gy; and better in 1 eye and worse in 14 with no treatment. The difference between the groups treated with radiation and the control was statistically significant ($P < .05$). Visual acuity was also significantly better in the group receiving 20 Gy than in the control group up to 2 years after radiation ($P < .01$).

Conclusion: Radiation may extend the period of good visual function substantially by reducing subfoveal choroidal neovascularization activity. **Jpn J Ophthalmol 2000;44:530–537**
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Key Words: Age-related macular degeneration, choroidal neovascularization, radiation.

Introduction

Choroidal neovascularization (CNV) associated with age-related macular degeneration (AMD) is a major cause of severe visual loss among elderly people. It has been reported that at least 70% of eyes with subfoveal CNV in AMD patients have a visual acuity of 20/200 or worse after 21 months of follow-up.[1] So far, laser photocoagulation is the only established therapeutic strategy for treating subfoveal neovascular lesions. However, it is only applicable to those with well-demarcated CNV boundaries.[1–9] Since CNV in AMD patients generally contains an occult element that subsequently develops into recurrent CNV after laser treatment, only a limited number of patients benefit from this treatment.[9,10] Even if patients benefit from the laser treatment, they may have inevitably experienced a decrease in visual acuity immediately after photocoagulation. Thus, in order to retain better visual function, other methods of treatment have been explored, such as α-interferon injection,[11] surgi-

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cal removal of subretinal neovascular membranes,[12,13] and transplantation of fetal retinal pigment epithelium,[14] although none of these has yet been confirmed to be beneficial. Of the various alternatives, radiation therapy has attracted attention during the past several years because Chakravarthy et al[15] reported the beneficial effect of low doses of radiation on subretinal neovascular membranes associated with AMD. A number of reports have been made to support the idea that radiation improves or stabilizes CNV lesions.[16–19] However, there was also a report questioning the advantages of radiation.[20] Therefore, the effect of this therapy still remains controversial.

We began radiation therapy in 1994 in our clinic. The first patients were treated as a pilot group, and administered radiation in doses of either 10 Gy or 20 Gy. They have been followed up for 3 years. In this study, we report the long-term effect of radiation therapy in comparison with a historical control group with no treatment.

Materials and Methods

We reviewed the records of 30 patients with subfoveal CNV associated with AMD who were treated with radiation at Kyoto University Hospital between May 1994 and October 1995. The criteria for inclusion were symptoms of decreased vision associated with exudative AMD lesion extending through the foveal area (ie, serous detachment, subretinal hemorrhage, and hard exudate), and angiographic evidence of CNV involving the foveal avascular area. Patients had to be 50 years of age or older. When CNV had no classic element by fluorescent angiography, only lesions associated with subretinal fluid and hemorrhage were chosen for the treatment. Informed consent was obtained from all the patients prior to treatment. The patients in the control group were chosen from AMD patients who had been referred to our clinic in 1993 before we started radiation therapy. The patients who met the same eligibility criteria and were followed up for at least 36 months were chosen consecutively, and their fluorescein angiograms were evaluated as "the initial state at entry." One patient whose lesion was stable after therapy was excluded from this study because the observation period was less than a year. Baseline characteristics such as age, sex, initial status of the CNV, type of CNV (classic, occult, or combined), and initial visual acuity were not significantly different among the patients in the control and the treated groups (Table 1).

Before radiation therapy, treatment planning was done using a computed tomography (CT) simulator, which enabled real-time treatment planning from multiple CT slices.[21] This system consists of a CT scanner, a multiple-image monitor, a 3-dimensional treatment-planning computer, and a laser beam projector. The clinical target volume included the macula and optic disc. The target volume and other critical structures including the ipsilateral lens and contralateral eye were demarcated manually. Then the center of the target volume, which is usually the "reference dose point," was automatically determined by this planning system. The dose distribution curves were superimposed on each CT slice, and the treatment field was demonstrated in the beam's-eye-view for observing the relationship between the target volume and other critical structures (Figure 1). The patient was immobilized with a custom-made plastic shell during the simulation and the radiation treat-

Table 1. Baseline Characteristics of Patients

	10 Gy	20 Gy	Control
Age (mean)	70	69	71
Male/female	10/5	11/4	10/5
CNV type			
Classic	5	3	4
Combined	7	6	8
Occult	3	6	3
CNV size			
1 disc area >	4	4	5
1 disc area ≤3.5 disc area >	7	8	7
3.5 disc area ≤	4	3	3

CNV: choroidal neovascularization.

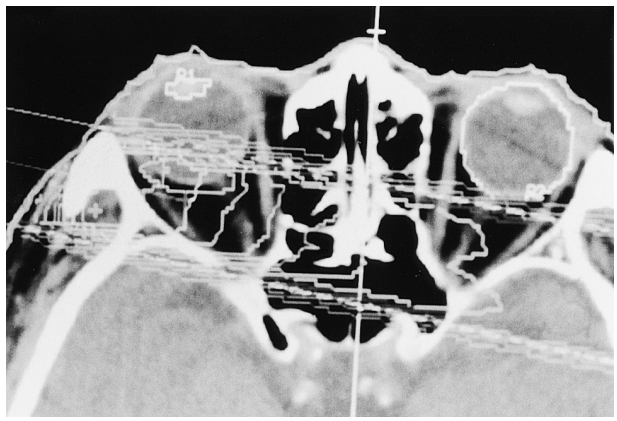

Figure 1. Computed tomography scan of choroidal neovascularization patient before radiation. (**A**) 3-Dimensional simulating system was used to determine treatment planning. Patients were irradiated with a single lateral 6 MV photon beam, angled 10° posteriorly. Field size averaged 3.0 × 2.5 cm and clinical target volume was usually irradiated with more than 95% of reference dose.

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ment, and all patients were irradiated with a single lateral 6 MV-photon beam angled 10° posteriorly. The field size averaged 3.0 × 2.5 cm and the clinical target volume was usually irradiated with more than 95% of the reference dose. The ipsilateral lens was irradiated with less than 10% of the total reference dose. The first 15 eyes received a dose of 10 Gy in 5 fractions over 1 week, and the last 15 eyes were treated with 20 Gy in 10 fractions over 2 weeks.

Follow-up visits were scheduled at 1 month, 3 months, and at least every 3 months thereafter. At each scheduled follow-up visit, the best corrected visual acuity was measured, ophthalmoscopic and biomicroscopic examinations were performed and fundi were photographed in color. In addition, fluorescein angiography was performed at least every 6 months. The size of CNV was determined by fluorescein angiograms and also by indocyanine green angiograms when the CNV contained occult elements; the size was referred to as disk area. The changes in CNV size and activity were judged by two specialized doctors in a masked manner, using the photographs of fluorescein angiography. The changes were scored as follows: much better as 2, better as 1, unchanged as 0, worse as −1 and far worse as −2. The lesion was similarly scored from the description in the patients' charts and color photographs. For the overall judgment, a score change greater than ±2 was considered significant. If the size of CNV became larger than its initial state at any time, the case was evaluated as "worse," even if the lesion was dry at the last visit.

Visual acuity was expressed as minimum angle of resolution (MAR) and a doubling or more of MAR was regarded as "worse." Conversely, if the MAR decreased one half or less, the vision was judged as "better."

Mann-Whitney *U*-test was used to evaluate the results. Probability levels $<.05$ were considered statistically significant.

Results

Anatomical Changes After Radiation Therapy

Data on the treated and the control patients are listed in Tables 2–4. Eleven eyes (73%) from each treated group responding once to the therapy scored +1 or more. These changes were consistently observed within 6 months after treatment. For the patients with no beneficial response (4 eyes in each group) throughout the posttreatment period, the treatment was indicated as "ineffective" (Table 2). "Worse" or "other treatment" means the lesion responded once to the therapy but finally became worse than the initial state, in some cases requiring other treatment. "Unchanged" means the lesion responded once to the therapy but the final score was ±1 or 0 after deteriorating. "Better" means a score of +2 or 3, and "dry" means a score of 4 with no serous fluid and no CNV leakage on fluorecsein angiography. Since 4 eyes that dropped out at 18 months had already worsened, these eyes were counted as 'worse' to decrease the bias, and the rest were counted as "better" because the eyes had already been "dry" at the 18-month visit.

With no treatment, only 1/15 eyes (7%) spontaneously regressed within 1 year. Even though 7 eyes in

Table 2. Data on Patients Treated with 10 Gy Radiotherapy

Case	Sex	Age (y)	CNV Type	CNV*	Follow-up (mo)	Initial VA (MAR)	Last VA (MAR)	Last Status
1	F	65	Classic	B	18	5	11.1	dry
2	M	67	Combined	B	36	3.3	10	dry
3	M	60	Classic	B	36	25	10	dry
4	F	65	Combined	C	36	33.3	12.5	dry
5	F	74	Combined	A	36	6.67	2	unchanged
6	M	75	Classic	C	36	16.7	16.7	unchanged
7	F	77	Occult	A	36	1.67	25	worse
8	M	74	Occult	C	36	2.5	1000	worse
9	M	58	Combined	A	36	2	25	other treatment
10	M	72	Classic	A	36	2	10	other treatment
11	M	60	Classic	B	18	3.3	33.3	other treatment
12	M	72	Combined	B	36	2.5	5	ineffective
13	F	77	Occult	B	36	50	1000	ineffective
14	M	73	Combined	B	18	2	25	ineffective
15	M	82	Combined	C	18	14.3	33.3	ineffective

CNV: choroidal neovascularization; VA: visual angle; MAR: minimum angle of resolution.
*CNV size was classified as A: <1 disc area; B: ≥1 to <3.5 disc area; C: ≥3.5 disc area.

Table 3. Data on Patients Treated with 20 Gy Radiotherapy

Case	Sex	Age (y)	CNV Type	CNV*	Follow-up (mo)	Initial VA (MAR)	Last VA (MAR)	Last Status
1	M	67	Occult	B	36	6.67	3.33	dry
2	M	72	Combined	A	36	10	2.5	dry
3	M	65	Classic	A	36	1.25	1.00	dry
4	M	58	Occult	C	36	2.50	3.33	dry
5	M	71	Occult	B	36	2.50	2.50	better
6	M	70	Combined	C	36	1.43	2.00	better
7	F	72	Occult	C	36	3.33	16.67	better
8	M	68	Occult	B	36	6.67	33.33	unchanged
9	M	77	Classic	A	36	5.00	33.33	other treatment
10	F	66	Occult	B	36	3.30	20.00	other treatment
11	F	68	Combined	B	36	3.33	50	other treatment
12	F	78	Combined	B	36	16.70	50.00	ineffective
13	M	81	Classic	A	18	3.30	100.00	ineffective
14	M	61	Combined	B	36	1.25	50.00	ineffective
15	M	65	Combined	B	36	5.00	50.00	ineffective

CNV: choroidal neovascularization; VA: visual angle; MAR: minimum angle of resolution.
*CNV size was classified as A: <1 disc area; B: ≥1 to <3.5 disc area; C: ≥3.5 disc area.

the nontreated control group were dry after 3 years, 6 of them continuously worsened after the initial entry and ended up with larger subretinal fibrous scar tissue (visible as tissue staining on angiogram) than the initial size of the CNV. The remaining 8 eyes in the control group were all highly active at 36 months, presenting massive exudate with the lesions extending to larger than a 5-disc area. As an overall evaluation, the resulting disease status was considered "worse" if the score declined to −2 or lower during the follow-up period even if the fundus was almost "dry" after 36 months.

Eventually, in the group receiving 10 Gy, the lesions were evaluated as "better" in 4 eyes, "unchanged" in 2, and "worse" in 9 (including those receiving other treatments and the "ineffective" cases) (Table 2). With those receiving 20 Gy, 7 eyes were "better," 1 was "unchanged," and 7 were "worse." With no treatment, 1 eye was "better" and 14 eyes were "worse." The differences among these three groups were statistically significant (Kruskal-Wallis rank test, $P < .05$).

Visual Prognosis

Visual changes in the treated and nontreated patients are summarized in Figure 2. Here, "better" or "worse" indicates becoming half or double in the visual angle (MAR). The changes were compared at

Table 4. Data on Control Patients

Case	Sex	Age (y)	CNV Type	CNV*	Follow-up (mo)	Initial VA (MAR)	Last VA (MAR)	Last Status
1	61	M	Classic	A	36	10.00	10	dry
2	79	M	Combined	B	36	12.50	1000	worse
3	69	M	Classic	A	36	3.33	20	worse
4	57	F	Classic	A	36	10.00	10	worse
5	77	M	Occult	C	36	3.33	33.3	worse
6	64	F	Combined	B	36	3.33	14.3	worse
7	70	M	Combined	B	36	6.67	25	worse
8	77	M	Combined	B	36	1.25	12.5	worse
9	74	F	Combined	B	36	2.00	14.3	worse
10	70	M	Classic	A	36	5.00	16.7	worse
11	79	M	Combined	B	36	20.00	50	worse
12	71	M	Combined	C	36	10.00	11.1	worse
13	72	M	Occult	C	36	5.00	33.3	worse
14	72	F	Occult	B	36	1.67	16.7	worse
15	64	F	Combined	A	36	3.33	6.67	worse

CNV: choroidal neovascularization; VA: visual angle; MAR: minimum angle of resolution.
*CNV size was classified as A: <1 disc area, B: ≥1 to <3.5 disc area, and C: ≥3.5 disc area.

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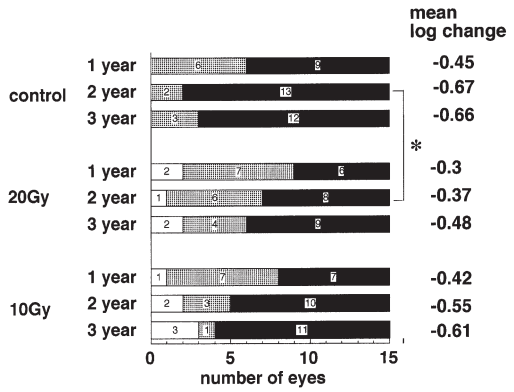

Figure 2. Visual changes during follow-up. Visual acuity changes were judged as "better" if minimum angle of resolution (MAR) became half or less, and "worse" if MAR became doubled or more. Open bars: better; hatched bars: stable; solid bars: worse. Asterisk indicates significant difference at $P < .01$ (Mann-Whitney U-test).

12, 24, and 36 months after treatment. Four eyes that dropped out at 18 months had an extensive decrease in vision (below 20/400) and were included as "worse" at 24 and 36 months as well to decrease the statistical bias. Mean log change in visual acuity was always in the order of control > 10 Gy > 20 Gy at each time point. When visual changes were classified into three groups of "better," "stable," and "worse," the difference between the patients treated with 20 Gy and the control was statistically significant at 24 months ($P < .01$). Then, we studied the distribution of eyes in different groups of visual acuity (Figure 3). The eyes were grouped into three grades according to the best corrected visual acuities: 20/40 or better, 20/200 or better and less than 20/40, and <20/200. There was no statistically significant difference between the group treated with 10 Gy and the control,

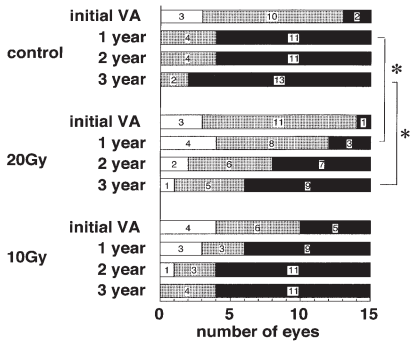

Figure 3. Distribution of visual acuity during follow-up. Open bars: ≥20/40; hatched bars: ≥20/200; solid bars: >20/200. Asterisk indicates significant difference at $P < .01$ (Mann-Whitney U-test).

but the difference was significant between the patients treated with 20 Gy and the control at 12 and 36 months ($P < .01$).

Case Reports

The clinical courses of two treated cases are presented. A 74-year-old woman with AMD had a highly exudative CNV involving the fovea, which caused a massive exudate extending down to the outside of the arcade (case 5 in Table 2, Figures 4 A,B). The angiogram showed classic CNV with its margin masked by a subretinal hemorrhage. The patient was treated with 10 Gy irradiation and the lesion resolved quickly after the therapy. Only a slight serous detachment was observed at 12 months posttreatment with no apparent late leakage on the angiogram (Figure 4C, score of 2; and Figure 4D, score of 1). The serous detachment persisted for several months and at 20 months after treatment, serous detachment and exudate increased (Figure 4E, score of −2; and Figure 4F, score of 1). Fluorescein angiography showed that there was an increased activity of the occult element of CNV, but no further worsening was observed by fundus examination for the next 4 months. Her visual acuity was maintained at 20/40 during the follow-up.

In Figure 5, the clinical course of a 68-year-old woman with a combined type of CNV is shown (case 11, Table 3). The size of CNV was estimated to be approximately 1.5 disc in area. One year after receiving 20 Gy, leakage from the lesion was reduced on late phase angiogram (score of 1); subretinal serous fluid had almost disappeared (score of 1). The lesion remained almost dry until her 2-year follow-up visit when she presented with recurrent subretinal CNV with subretinal hemorrhage. This time the CNV was considered a classic type, which was larger than a 2-disc area. Since her visual acuity dropped to 20/400, subretinal CNV removal was performed and now the fundus remains dry.

Discussion

We have demonstrated the long-term effect of two different doses of radiation therapy. The doses we used in this study were considered safe based on previous studies.[22–25] So far, no patients have experienced side effects from this therapy. Also in our institute, a regimen of 20 Gy in 10 fractions over 2 weeks has long been used in the treatment of Graves' ophthalmopathy without major complications related to the irradiation.[24] Reviewing the patients in our study, we found that approximately

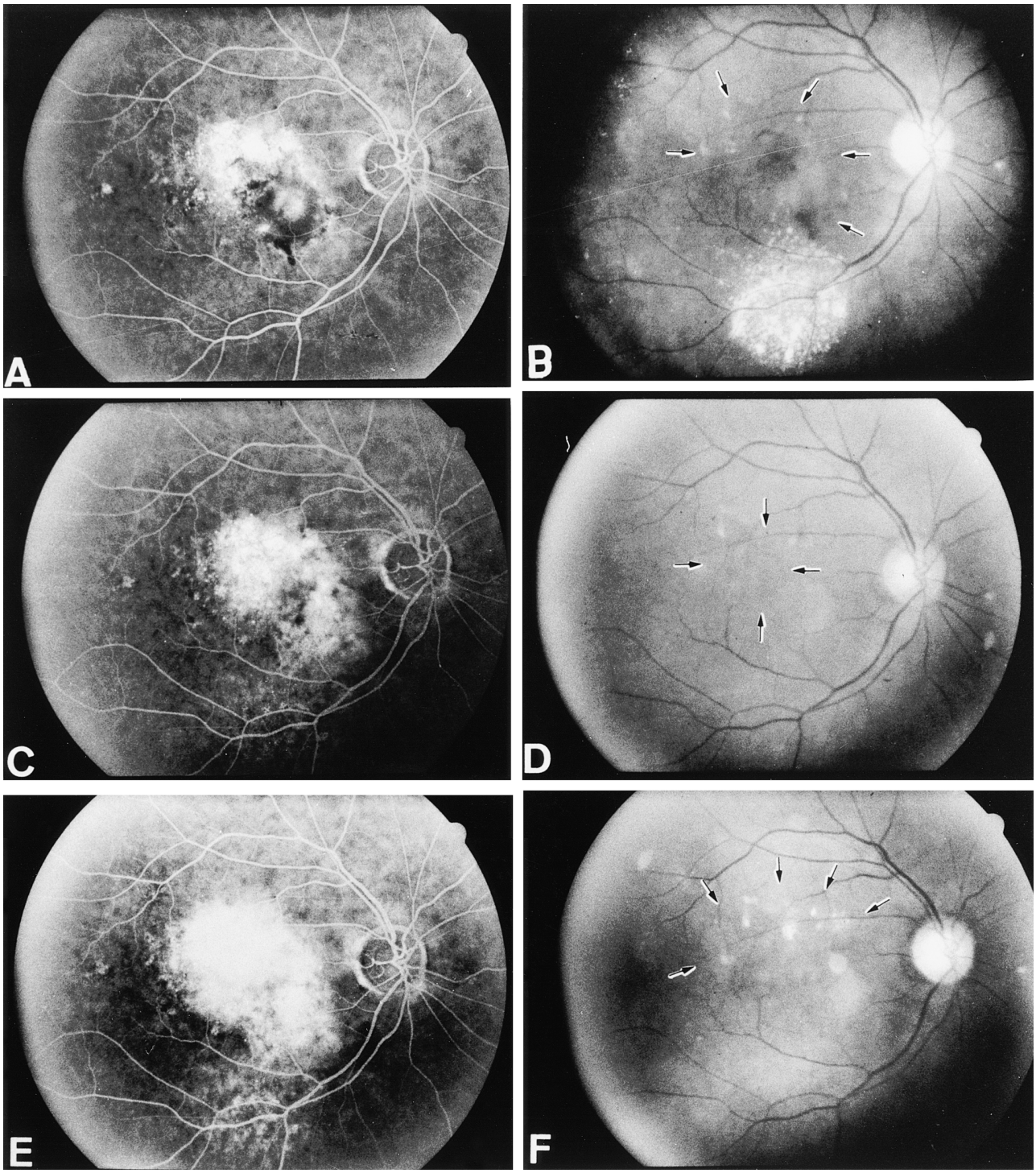

Figure 4. Clinical course of 74-year-old woman with age-related macular degeneration (AMD). (**A**) Late phase fluorescein angiography of patient before treatment. (**B**) Fundus photograph of patient before treatment. Highly exudative lesion including whole macular area is visible. Best corrected visual acuity before treatment was −0.8 as indicated by log visual acuity relative to 20/20. (**C**) Fluorescein angiogram of patient 12 months after 10 Gy irradiation. There was no active leakage in late phase of angiography. (**D**) Fundus photograph of patient at 12 months after treatment. Lesion began to improve after therapy, and there was only slight serous detachment at macula (marked by arrows). (**E**) Fluorescein angiography of patient 24 months after treatment. Enhanced leakage was observed from choroidal neovascularization of occult nature. (**F**) Fundus photograph of patient at 24 months after treatment. There was increase in area of serous detachment associated with exudation (marked by arrows).

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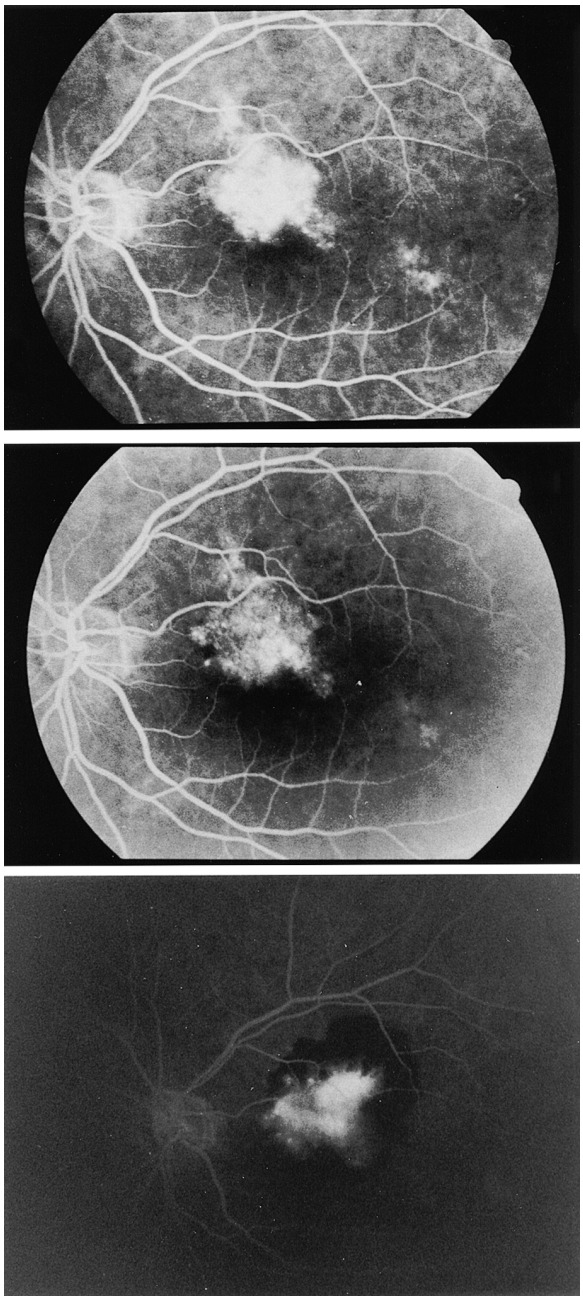

Figure 5. Clinical course of 68-year-old woman with age-related macular degeneration. Top: Late phase fluorescein angiogram of patient before treatment. Choroidal neovascularization (CNV) contained both classic and occult element. Patient received 20 Gy in 10 fractions. Middle: Late phase fluorescein angiogram of CNV 1 year after treatment. Leakage was much reduced and fundus was almost dry. Bottom: 2 years after treatment. Classic CNV developed with subretinal hemorrhage and visual acuity was 20/400.

70% of the patients responded initially to the therapy, scoring 1 or more The proportion of eyes that subsequently became scarred was not statistically significant. However, approximately 50% of the eyes that responded initially relapsed, which is typically described in case reports. These regressing eyes were observed any time after 8 months of treatment. Interestingly, the lesion usually remained in the "better" status than when treatment began until approximately 2 years afterwards. The case shown in Figure 4 is an example of how these patients usually retained fair visual acuity for an extended period. However, 2 years after the treatment and thereafter, a marked deterioration, such as is shown in Figure 5, was observed in a number of eyes. This implies that radiation might alter some physiological function of the endothelium for approximately 2 years after the treatment, stabilizing CNV growth by some yet unknown mechanism.

In the anatomical evaluation, both the 10 and 20 Gy radiation doses had a statistically significant effect, but only the group treated with 20 Gy had a significantly better visual prognosis for 2 years. Radiation therapy is not likely to cause a complete resolution of the lesion, but only reduces CNV activity for a limited period. This fact is also reflected in the visual prognosis that showed how the distribution of the eyes gradually shifted toward "worse" with time, even in the treated groups. Yet the significantly better visual prognosis up to 3 years after the treatment among patients treated with 20 Gy than among those with no treatment suggests that the effect of radiation therapy may extend the period of better visual function. In addition, considering the nature of radiation, another possible benefit of this therapy is that it may increase the success rate of other therapies, such as laser photocoagulation and surgery. The smaller CNV resulting from radiation may minimize the area that has to be photocoagulated or removed even if some residual neovascularization remains, and a lesion stabilized by radiation may mean a lower rate of recurrence. Recently, Spaide et al[20] questioned the effect of this therapy on the neovascularization seen with AMD. Since the effect of radiation is rather moderate and the clinical course after the treatment is long, a solid randomized trial is needed for a fair comparison between the clinical courses of patients treated with radiation therapy and controls. A randomized trial using 20 Gy radiation therapy is now being undertaken in a multicenter study in Japan. In a few years, we hope to be able to determine the effect and the adequate application of this therapy in the treatment of AMD and its associated complications.

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