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Visual acuity and scar size in eyes with age-related subfoveal choroidal neovascular lesions, 30 months after radiation therapy

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Abstract. Purpose: In a study to determin the effectiveness of ionizing radiation on the deterioration of visual acuity (VA) due to choroidal neovascularisation (CNV) the affected eyes of 10 patients were treated with a total dose of 24 Gy (6 Gy fractions). A special lens-sparing technique was used to avoid cataract development. During 30 months of follow-up the visual acuity (VA) and scar size (SS) of the treated eyes and fellow eyes of all 10 patients were evaluated. *Results:* After 30 months of follow-up 5 eyes showed a stable VA and fluorescein angiogram (FA) appearance. Concerning 4 out of 5 eyes with progressive disease, the 4 eyes treated with radiation therapy had better VA and smaller SS as compared with the untreated fellow eyes with exudative AMD. *Conclusions:* The results suggest that 24 Gy either stabilizes or delays the deleterious effects of CNV on the visual acuity. Until now no late side effects have been observed.

Abbreviations: AMD – Age-related macular degeneration; CNV – Choroidal neovascularization; DD – Disc diameter; FA – fluorescein angiogram; SS – Scar size; VA – Visual acuity.

Introduction

The exudative form of age-related macular degeneration (AMD), with the development of choroidal neovascularisation (CNV), is a leading cause of blindness in western countries. The effect of laser photocoagulation for selected cases of subfoveal CNV is well known from the macular photocoagulation study (MPS) investigations [1-4]. The patient must accept an immediate and permanent decrease of VA after laser photocoagulation, but will have better VA using low-vision aids [1-3]. Only in case of a small CNV with a moderate or poor VA foveal ablation is recommended [4].

Other modalities of laserphotocoagulation including foveal sparing techniques are being proposed as alternative treatments but their definitive value

has not been proved [5]. Only a few patients with recent subfoveal CNV are suitable for laser therapy, because a large proportion (87%) of patients have an occult type of CNV at presentation [6]. Alternative forms of therapy for CNV are proposed, like submacular surgery, Interferon therapy, ICG-guided laser therapy and Thalidomide therapy but none of these new therapies seems to be valuable [7].

Patients with unilateral age-related exudative maculopathy developed neovascular membranes in the fellow eye in 31% of cases after 4 years of follow-up, and in general patients with exudative disease in one eye develop CNV in the fellow eye at a rate of about 10% per year [8]. The hypothesis that ionizing radiation may prevent endothelial cell proliferation and/or induce aberrant vessel obliteration and influences macrophages depended growth factors and/or regulatory genes, in case of CNV, is under investigation [7].

After the first report concerning the effect of radiation therapy on subfoveal CNV in 1992, several other reports were published [9-14]. We are now able to present the results after 30 months of follow-up concerning ten patients treated with radiation therapy with a total dose of 24 Gy (6 Gy fractions).

We decided to do a longer follow-up in this group of patients because initially they showed the best results after 12 months post-irradiation in our pilot study [11,13].

Materials and methods

This study was performed with permission of the institutional ethical committee for clinical experiments. The early results of this group of patients were previously published [11,13]. Ten patients with subfoveal CNV and recent decrease of VA were treated with a total dose of 24 Gy in 4 fractions of 6 Gy in the macular area. The time between two consecutive fractions was 1 week and the overall treatment time was 3 weeks. The dose was delivered by two 1 square cm 16 MV photon beams. The two photon beams diverge 30 degree from the eye axis and cross the eye axis in the macular area. By this technique the lens will receive less than 20% of the dose.

All patients underwent a complete ophthalmic examination of both eyes, including FA, before treatment and 3, 12, 18 and 30 months post-treatment. The early, mid and late venous phase of the pre- and post-treatment angiograms were analysed using an over-projection sheet for measuring the size of the membrane (in disc diameters = DD) and the leakage of fluorescein in the late phase. When there was an increase in size of the CNV in the early phase and/or an increase in late phase leakage the CNV membrane was considered to be progressive. When no change between the pre- and post-treatment angiograms was seen, the CNV was considered as stable. Any CNV with a

classic component but partial occult (including subretinal bloud and/or fluid or late undetermined leakage) was classified as occult type of CNV.

A decrease in VA was defined as a drop of 2 or more lines at the Snellen test. A stable VA was defined as an increase or decrease within 2 lines from initial best corrected VA. After 30 months of follow-up the VA and FA of the treated eyes and fellow eyes of all 10 patients were documented.

Results

The patients treated with a total dose of 24 Gy (6 Gy fractions) showed the following characteristics (Tables 1 and 2):

Patient 1: Male, 72 years. He presented with a classic type of CNV in the right eye and an initial VA of 0.3 (Figure 1A red free, Figure 1B early phase, Figure 1C late phase OD before treatment). After 30 months of followup the VA was 0.2 and the central SS was 1 DD (Figure 2A red free, Figure 2B early phase, Figure 2C late phase OD after treatment). His fellow left eye showed drusen and a VA of 1.0.

Patient 2: Female, 71 years. This patient initially had a VA af 0.2 and an occult type of CNV. After 30 months the VA dropped one line to 0.1 and the FA appearance of the CNV remained stable with a scar size of 2 DD. Her fellow eye with a scar of 2 DD had a VA of 0.4.

Patient 3: Female, 80 years. This patient showed a drop in VA from 0.08 to 1/60 within 3 months after radiation therapy for occult CNV. After 30 months of follow-up her VA in the study eye is 1/60 with a SS of 6 DD. Her fellow eye already had disciform scarring for more than one year without laser treatment at presentation, with a SS of 12 DD. After 30 months of follow-up the SS in the fellow eye stabilized and the VA remained 2/300.

Patient 4: Female, 74 years. This patient presented with a classic CNV (OD) and an initial VA of 0.25 (Figure 3A red free, Figure 3B early phase, Figure 3C late phase OD before treatment). A drop in VA occurred after 18 months post-radiation treatment and she ended up with a VA of 0.1 and a SS of 2 DD after 30 months (Figure 4A red free, Figure 4B early phase, Figure 4C late phase OD after treatment). The fellow left eye showed untreated disciform scarring present for more than one year at presentation (Figure 5A red free, Figure 5B late phase OS) and with a stable SS of 6 DD and a VA of 2/60 after 30 months of follow-up (Figure 6A red free, Figure 6B late phase OS).

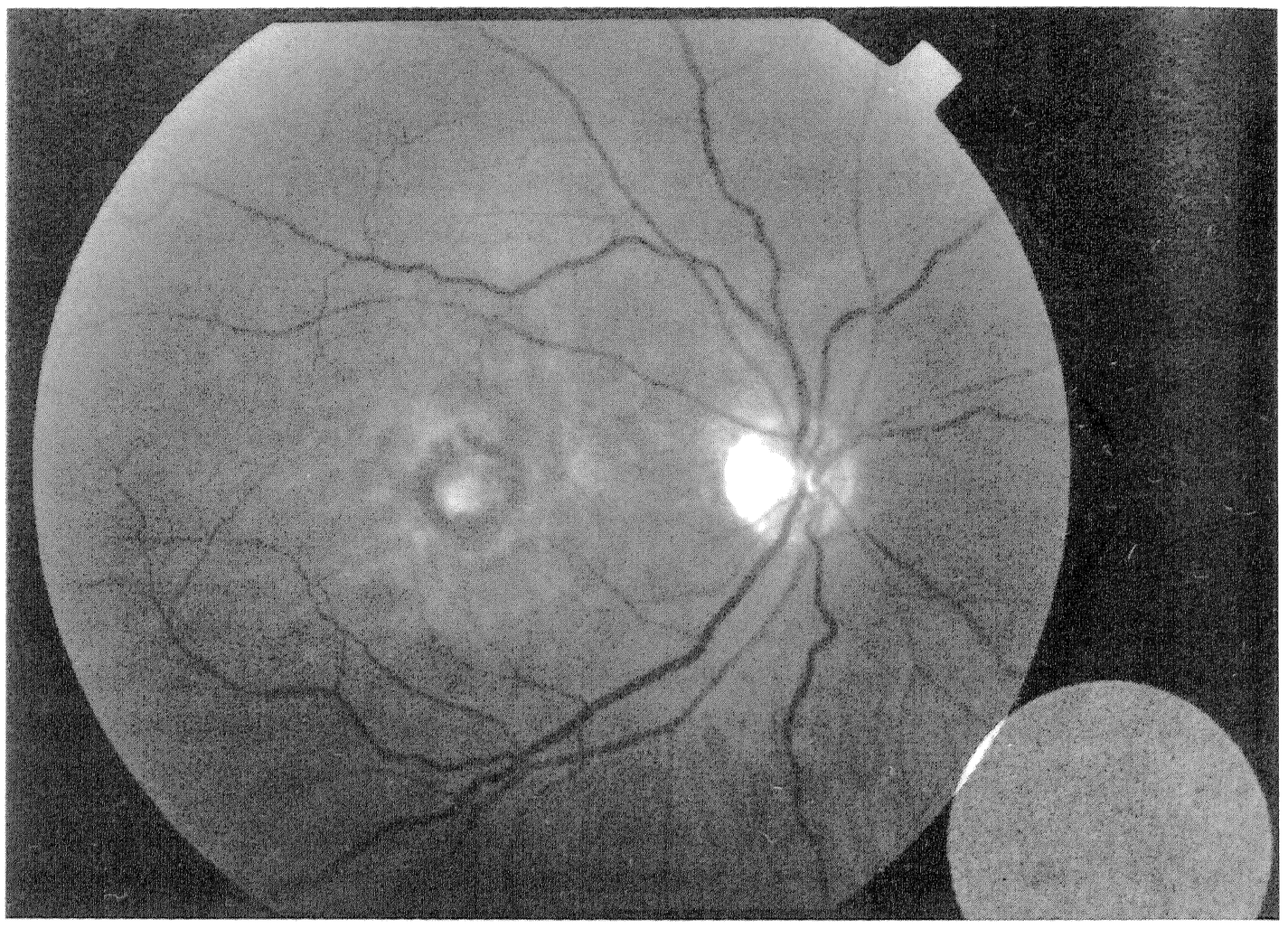

Figure 1. Patient 1 with a classic type of CNV of the right eye and a VA of 0.3 at presentation before radiation treatment. *Figure 1A.* Red free picture of the FA.

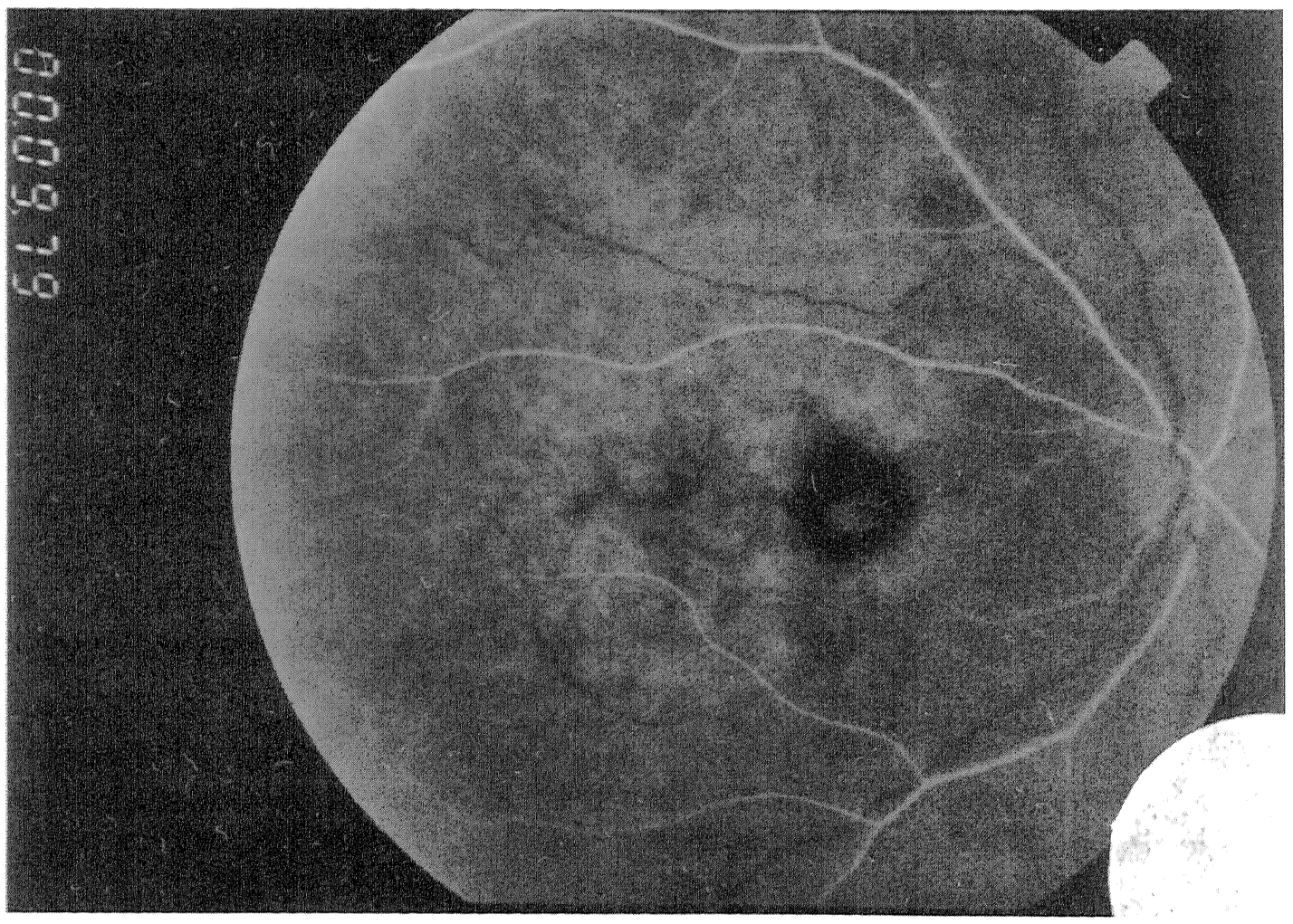

Figure 1B. Early phase of the FA.

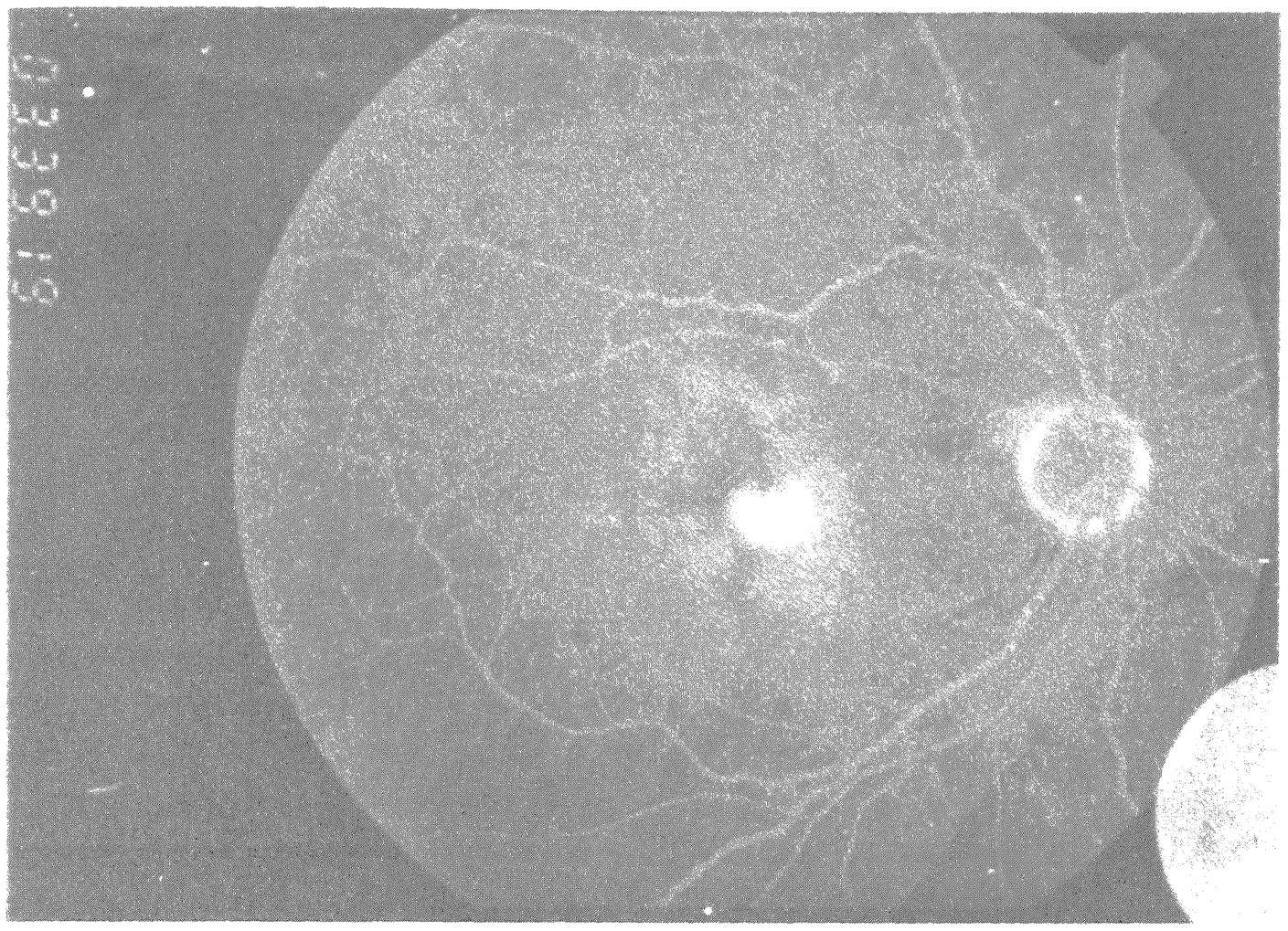

Figure 1C. Late phase of the FA.

Patient 5: Female, 83 years. The left eye with a classic CNV and an initial VA of 0.2 showed a stable angiogram with a SS of 2 DD after 30 months. The VA decreased to 0.125 after 30 months post-treatment. The fellow eye has a VA of 0.8 and drusen in the macular area.

Patient 6: Male, 72 years. This patient presented with a classic CNV with an initial VA of 0.2. A decrease in VA to 0.1 after 6 months and to 1/60 after 12 months post-treatment occurred. The SS of 1 DD at presentation enlarged to 4 DD at 30 months of follow-up. The fellow right eye still has a VA of 0.8 and has some pigmetary changes in the macular area.

Patient 7: Male, 85 years. Between 12 and 18 months after treatment for occult CNV, the VA declined from 0.16 to 2/60 and after 30 months the VA is 2/60 with a SS of 5 DD. The fellow eye with a VA of 1/60 had disciform scarring, without previous laser treatment, at presentation with a SS of 6 DD.

Patient 8: Male 76 years. The left eye with classic CNV and an initial VA of 0.5 showed a decrease in VA to 0.2 after 12 months and to 0.08 after 30 months of follow-up with an increase in SS from 1 DD to 3 DD. The fellow eye with

Figure 2. Patient 1 with a classic CNV of the right eye and a VA of 0.2, 30 months after radiation treatment. The late phase (Figure 2C) shows a central SS of 1 DD and the late phase leakage is less compared with the pre-treatment angiogram (Figure 1C) *Figure 2A*. Red free picture of the FA.

a VA of 1/60 and a scar size of 4 DD at presentation remained stable during 30 months of follow-up. This eye was not treated with laserphotocoagulation.

Patient 9: Male 77 years. The right eye presented with a classic CNV and a VA of 0.16. At the end of the follow-up period the VA increased to 0.25 and the FA remained stable. The fellow eye with some drusen had a stable VA of 0.8.

Patient 10: Female 73 years. This patient with a classic CNV had a stable VA of 0.3 during the follow-up period, with a SS size of 1 DD. The fellow eye with a VA of 0.8 did not show any change.

Conclusions

Thirty months after radiotherapy, with a total dose of 24 Gy, 5 out of 10 patients have a stable VA without progression of the CNV on FA (Table 1). Patient 1, 5, 9 and 10 presented with a classic CNV, while patient 2 had an

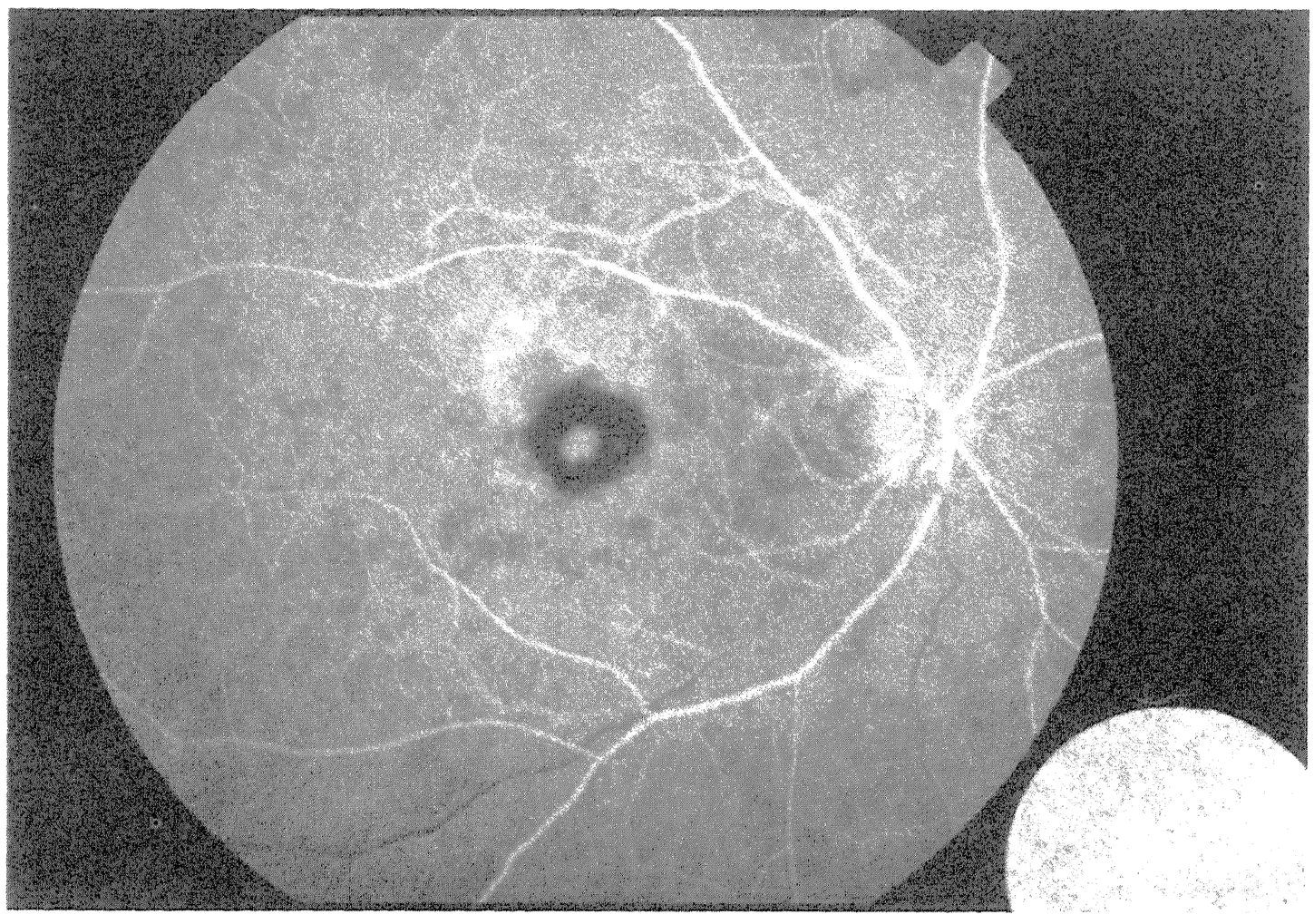

Figure 2B. Early phase of the FA.

Figure 2C. Late phase of the FA.

Figure 3. Patient 4 with a classic type of CNV of type right eye and a VA of 0.25 at presentation before radiation treatment. *Figure 3A*. Red free picture of the FA.

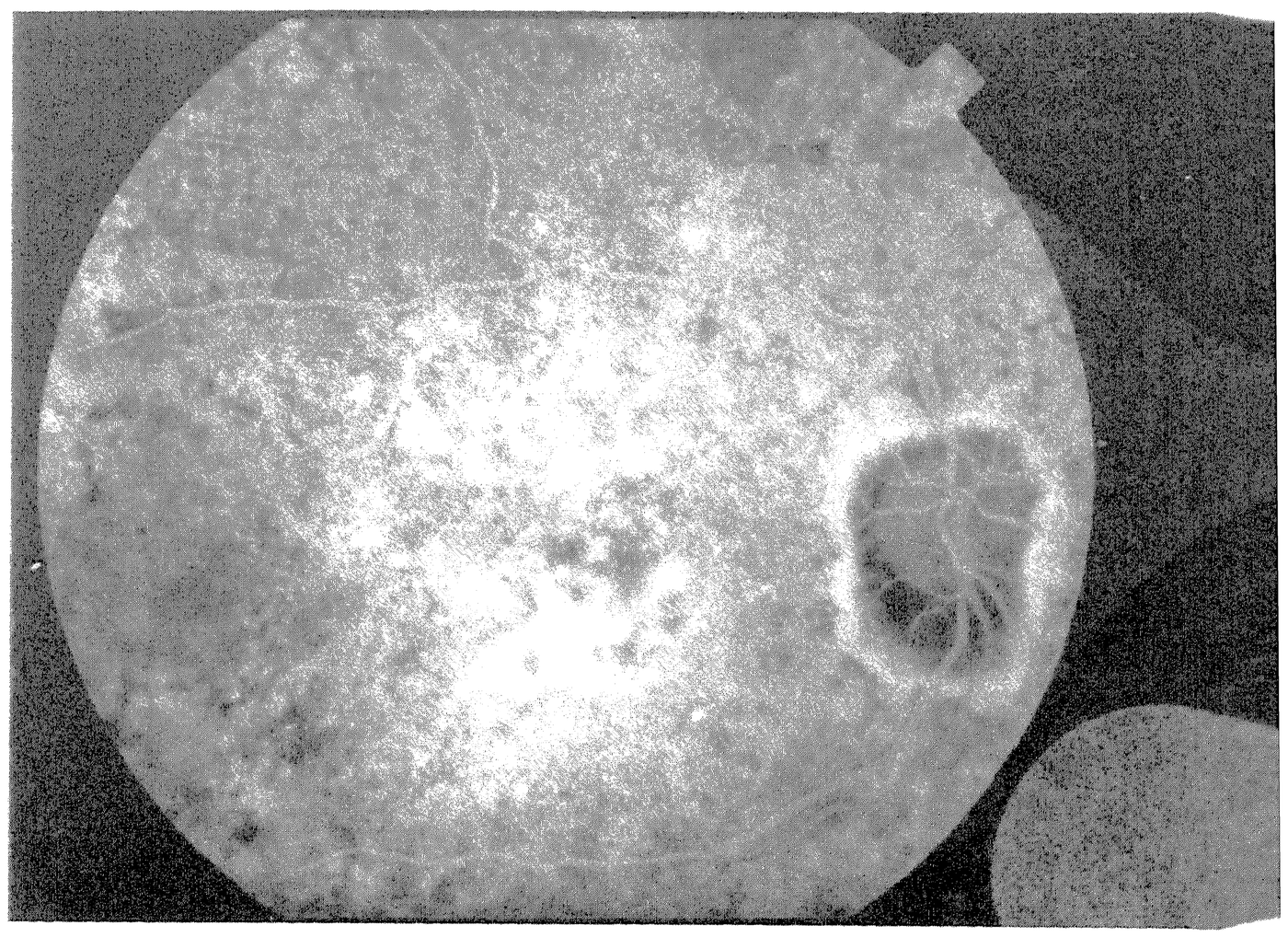

Figure 3B. Early phase of the FA with well-demarcated hyperfluorescence.

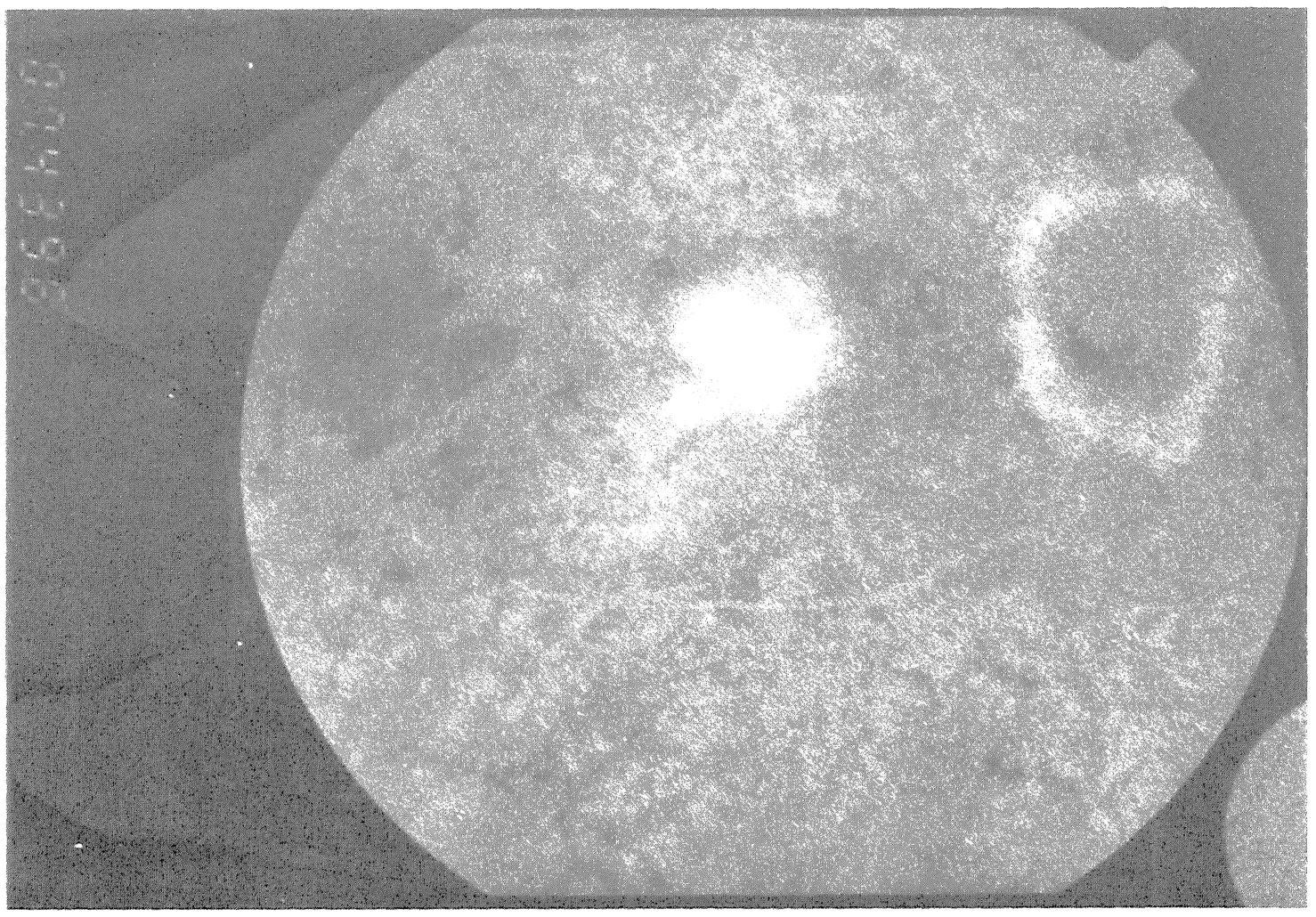

Figure 3C. Late phase of the FA with leakage.

Table 1. Patients (n=5) with stable visual acuity (VA) and scar size (SS) on fluorescein angiography 30 months after radiation therapy with a total dose of 24 Gy (6 Gy fractions) compared with the untreated fellow eye

	Study eye		Fellow eye	
Patient No	VA	SS	VA	SS
1.	0.2	1 DD	1.0	drusen
2.	0.1	2 DD	0.4	2 DD
5.	0.125	2 DD	0.8	drusen
9.	0.25	2 DD	0.8	drusen
10.	0.3	1 DD	0.8	drusen

occult CNV. The VA initially was better than 0.1 and remained stable in all cases at 30 months after radiotherapy.

The other 5 patients had progressive disease with a decrease in VA and an increase in SS despite radiation therapy (Table 2). Patient 3, 6 and 7 ended up with a VA of finger counting at 1 or 2 meter, while patient 4 and 6 had a VA of 0.1 and 0.08 respectively after 30 months.

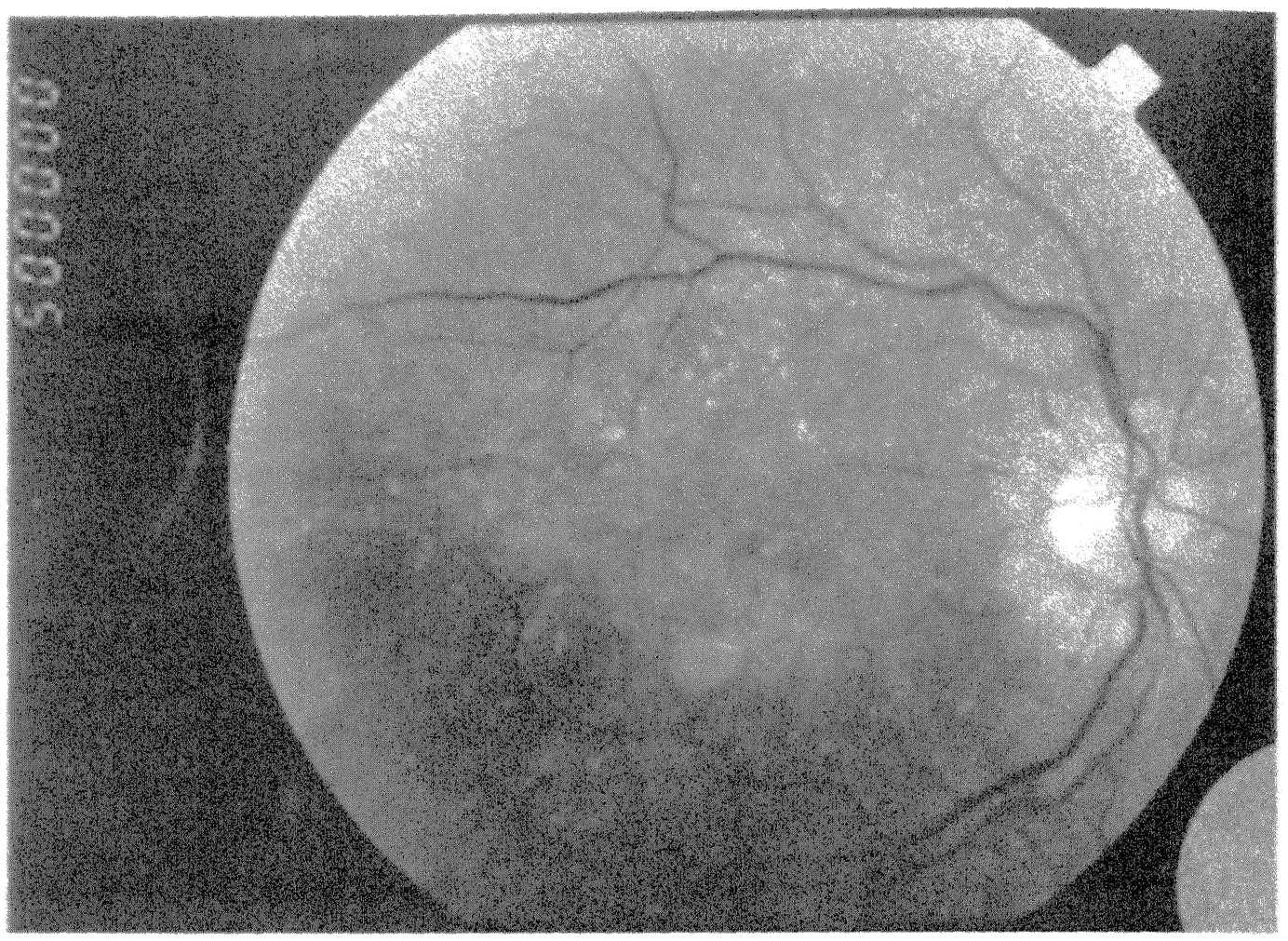

Figure 4. Patient 4 with a classic type of CNV of the right eye and a VA of 0.1, 30 months after radiation therapy. The late phase (Figure 4C) shows a central SS of 2 DD. *Figure 4A.* Red free picture of the FA.

Table 2. Patients (n=5) with deterioration of visual acuity (VA) and scar size (SS) on fluorescein angiography 30 months after radiation therapy with a total dose of 24 Gy (6 Gy fractions) compared with the untreated fellow eye

	Study eye		Fellow eye	
Patient No	VA	SS	VA	SS
3.	1/60	6 DD	2/300	12 DD
4.	0.1	2 DD	3/60	6 DD
6.	1/60	4 DD	0.8	drusen
7.	2/60	5 DD	1/60	6 DD
8.	0/08	3 DD	1/60	4 DD

Four (patient 3, 4, 7, 8) of the the 5 patients with progressive disease, had untreated disciform scarring in the fellow eye at presentation. The 4 eyes treated with radiation therapy had better VA and smaller SS compared with the untreated fellow eyes after 30 months of follow-up (Table 2). Until now we

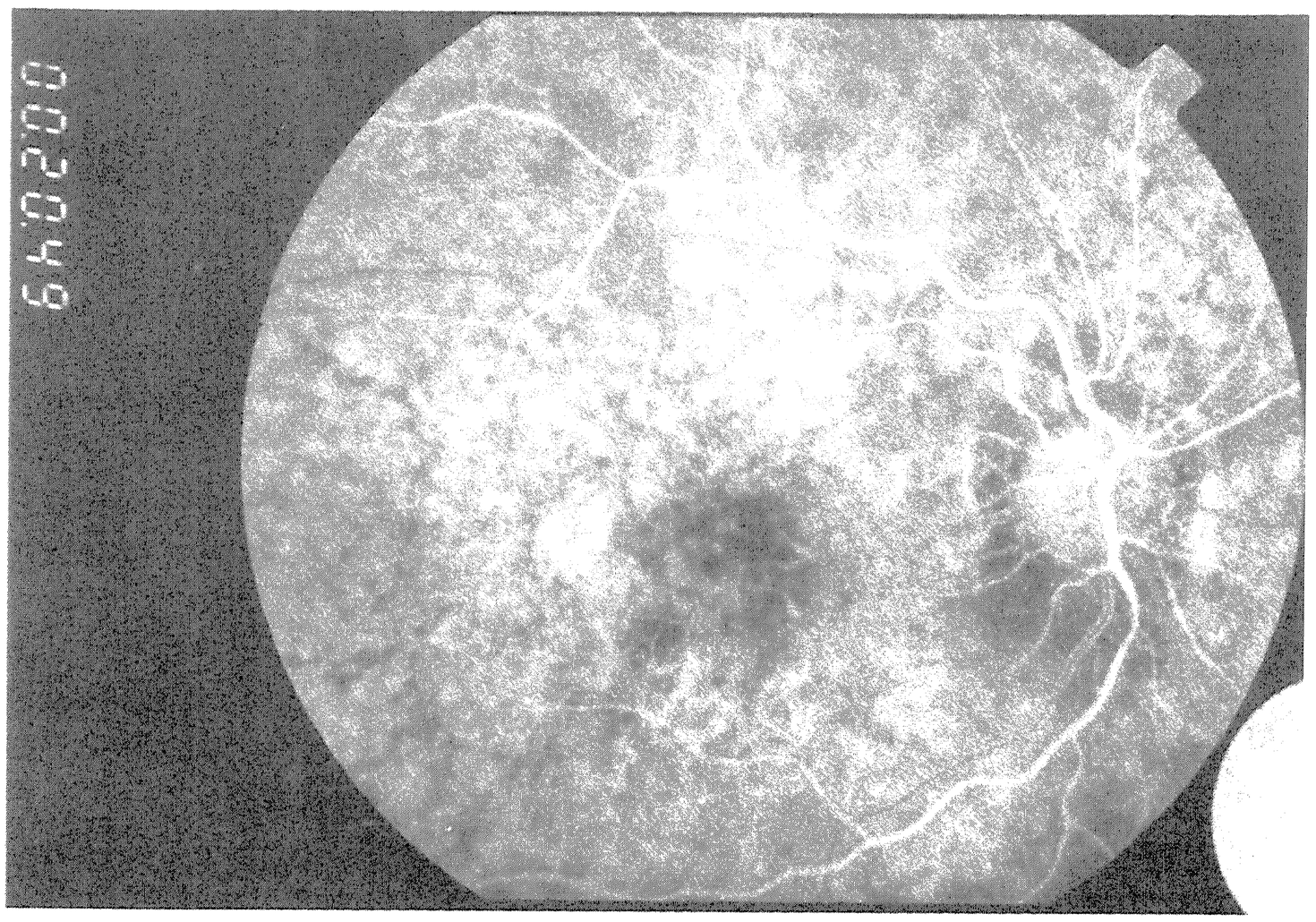

Figure 4B. Early phase of the FA.

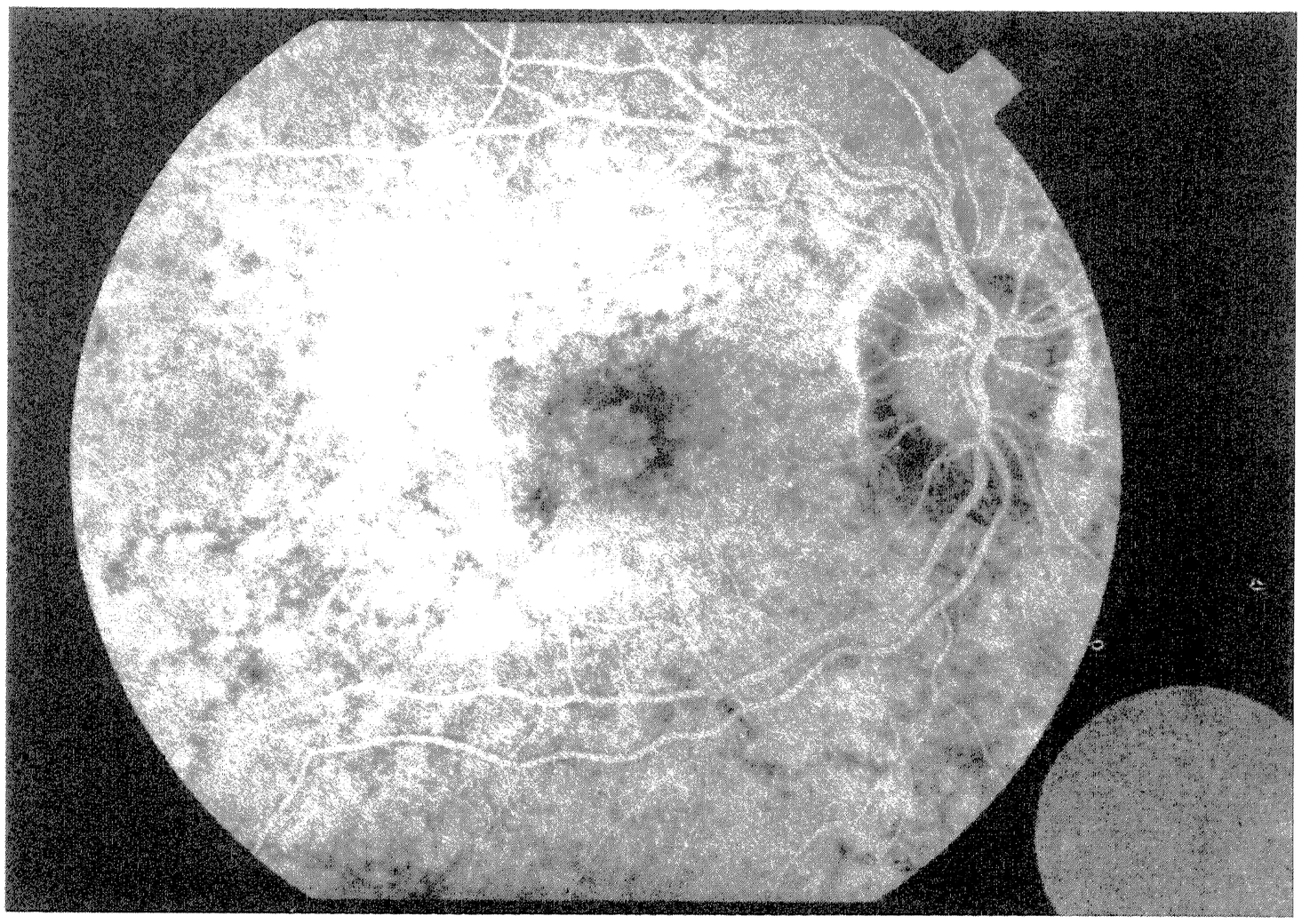

Figure 4C. Late phase of the FA.

Figure 5. Patient 4 with a disciform lesion of the untreated left eye at presentation. *Figure 5A.* Red free picture of the FA.

did not see any severe side-effects of this radiation therapy such as radiation retinopathy or dry eyes. Slight changes in lensopacification, however, can not be ruled out.

Discussion

In exudative AMD new capillaries proliferate under the retinal pigment epithelium and/or between the retinal pigment epithelium and the retina after they have broken through Bruch's membrane. They leak blood, lipoproteins and subretinal fluid in the active phase. Over a period of months fibrous tissue appaers with the development of a fibrovascular disciform scar, with secondary destruction of the overlying photoreceptors and the remaining retinal pigment epithelium. According to Bird there are no well formulated concepts concerning the mechanism by which neovascularisation is induced. Maybe macrophages cause vasoproliferation by producing growth factors [15]. Finger et al. concluded after reviewing the literature that possibly radiotherapy indirectly effect genes resulting in growth arrest and / or apoptosis [14]. The Belfast study group postulated that radiotherapy acts to minimise size and intensity of the disciform response, through arresting the proliferation

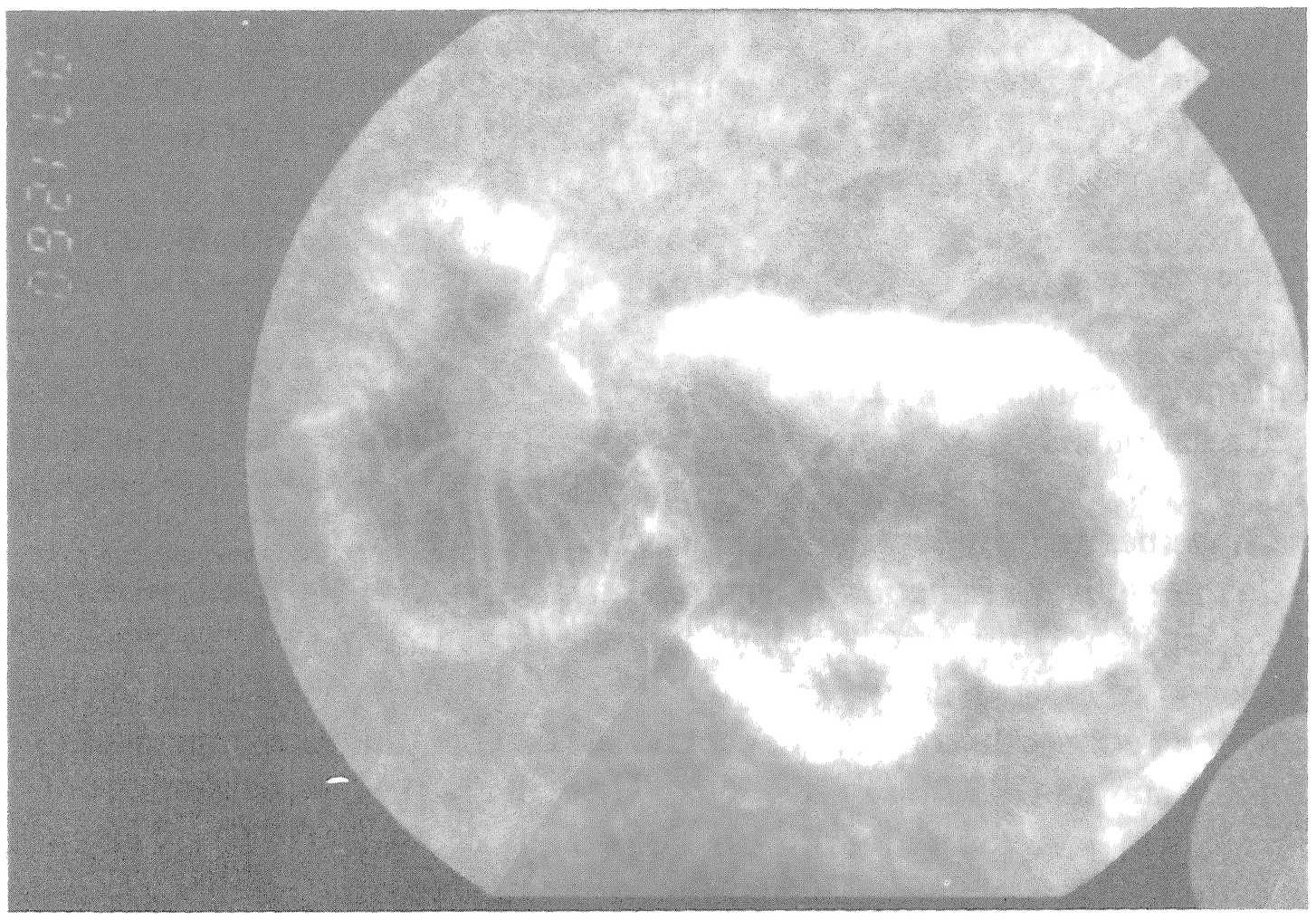

Figure 5B. Late phase of the FA. Late phase of the FA of the untreated left eye with disciform scarring and a stable SS of 6 DD after 30 months of follow-up. There is clearly a difference in scar size between the treated right eye (Figure 4C) of patient 4 and the untreated left eye (Figure 5B). Although the patient had slight myopic correction in both eyes (S-2.0), she also had age-related peripapillary atrophy.

of endothelial cells resulting in mitotic cell death and through its attenuating effects on the inflammatory response resulting in a reduced disciform scar [12]. Their results concerning radiotherapy for exudative AMD are encouraging, because the VA was significantly better and the SS was smaller in 11 eyes treated with radiotherapy, compared with the untreated fellow eyes with disciform scarring after a mean follow-up of 28 months [12].

After reviewing the literature they concluded that concordance in scar size between the eyes of untreated patients was found to be highest when the duration of the disease was at least 12 months in the second eye to be affected. This implies that the appearance of the fibrovascular disciform scar does not change substantially after 12 months from initial presentation [12].

The natural course of the visual acuity in patients with classic or occult CNV is known from many studies [1-4]. The VA of eyes with untreated subfoveal CNV with an initial VA of 0.1 or better, will decrease to 0.08 or worse in 44% of eyes after 3 months of follow-up and in 80.5% of eyes after 24 months of follow-up.

When compared to the natural course of the disease (80.5% of eyes deteriorate to a VA of 0.08 or worse within 24 months) radiation therapy with a dose of 24 Gy seems to have a beneficial effect on the VA (3 of 10 eyes had a VA of 0.08 or worse within 30 months).

Although 5 eyes showed progresssive disease after radiation therapy, we noticed in 4 of them a better VA and smaller SS after 30 months, when compared with the untreated fellow eyes with exudative AMD. These results confirm the results of the Belfast study group [12].

Radiation may have some negative side effects on the eye when doses are given beyond tolerance levels. The lens is a relatively radiosensitive structure and opacification will develop when doses exceed 6 - 12 Gy.

In this study the radiation was applied in such a way that the lens was more or less spared. Until now there are no indications that there is an increased incidence of cataract in the treated eyes. More severe side effects such as radiation retinopathy or radiation optic neuropathy are rare after doses of 46.5 Gy and 55 Gy (2.0 Gy fractions) respectively [16]. Four fractions of 6 Gy, given in 3 weeks, is more or less biologically equivalent to 50 Gy given in 25 daily fractions of 2 Gy. The incidence of radiation damage after 24 Gy (6 Gy fractions) is expected to be very low and quite safe [16,17]. As expected no cases of radiation retinopathy are observed until now.

In conclusion, after a substantial period of follow-up (30 months), 7 of 10 patients treated with a total dose of 24 Gy (6 Gy fractions) in the macular area, maintained a VA of 0.08 or better while, concerning the natural course data, 20% was expected.

This data, including the reduction in scar area after radiation treatment, suggest a beneficial effect of radiation therapy in subfoveal exudative age-related disease.

The overall conclusion during the meeting of the American Academy of Ophthalmology in October 1995 was that there is a strong theoretical basis for this therapy but that a definite answer has to come from long-term prospective randomized controlled trials. In several centers over the world, including in the Netherlands, these trials are under way.

References

1. 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: 1242–1257.
2. Macular Photocoagulation Study Group. Laser phutocoagulation of subfoveal neovascular lesions in age-related macular degeneration. Arch Ophthalmol 1991; 109: 1220–1231.
3. Macular Photocoagulation Study Group. Laser phutocoagulation of subfoveal neovascular lesions of age-related macular degeneration. Updated findings from two clinical trials. Arch Ophthalmol 1993; 111: 1200–1209.

4. Macular Photocoagulation Study Group. Visual outcome after laser photocoagulation for subfoveal choroidal neovascularisation secondary to age-related macular degeneration. The influence of initial lesion size and initial visual acuity. Arch Ophthalmol 1994; 112: 480–488.
5. Orth DH, Rosculet JP, Butros SD. Foveal sparing photocoagulation for exudative age-related macular degeneration. Retina 1994; 2: 153–159.
6. Freund KB, Yannuzzi LA, Sorenson JA. Age-related macular degeneration and choroidal neovascularisation. Am J Ophthalmol 1993; 115: 786–791.
7. Guyer DR. Experimental therapies for exudative age-related macular degeneration. The American Academy of Ophthalmology 1995; section III; 58–68.
8. Baun O, Vinding T, Krogh E. Natural course in fellow eyes of patients with unilateral 'age-related exudative maculopathy. Acta Ophthalmol 1993; 71: 398–401.
9. Bergink GJ, Deutman AF, van Daal WAJ. Radiation therapy for subfoveal choroidal neovascular membranes in age-related macular degeneration: a pilot study. Int Ophthalmol 1992; 16 (Suppl): 16.
10. Chakravarthy U, Houston RF, Archer DB. Treatmtant of age-related subfoveal neovascular membranes by teletherapy, a pilot study. Br J Ophthalmol 1993; 77: 265–273.
11. 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. Graefe's Arch Clin Exp Ophthalmol 1994; 232: 591–598.
12. Hart PM, Archer DB, Chakravarthy U. Asymmetry of disciform scarring in bilateral disease when one eye is treated with radiotherapy. Br J Ophthalmol 1995; 79: 562–568.
13. Bergink GJ, Deutman AF, van den Broek JFCM, van Daal WAJ, van der Maazen RWM. Radiation therapy for age-related subfoveal choroidal neovascular membranes, a pilot study. Doc Ophthalmol 1995; 90: 67–74.
14. Finger PT, Berson A, Sherr D, Riley R, Balkin RA, Bosworth JL. Radiation therapy for subretinal neovascularization. Ophthalmology 1996; 103: 878–889.
15. Bird AC. Choroidal neovascularisation in age-related macular disease. Br J Ophthalmol 1993; 77: 614–615.
16. Gordon KB, Char DH, Sagerman RH. Late effects of radiation on the eye and ocular adnexa. Int J Radiation Oncolgy Biol Phys 1995; 31: 1123–1139.
17. Archer DB, Responses of retinal and choroidal vessels to ionising radiation. Doyne lecture. Eye 1993; 7: 1–13.

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