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Radiation therapy for age-related subfoveal choroidal neovascular membranes

A pilot study

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Abstract. In this pilot study the effect of radiation therapy on subfoveal CNV membranes associated with age-related macular degeneration was evaluated. Four groups of 10 patients were treated with external beam radiotherapy (16 MV photons) on an area of 1 cm² (macular region) using a lens-sparing technique and total dose of 8 to 24 Gy. The first group received 8 Gy in a single fraction. In this group only 30% had a stable visual acuity and a stable FA after 18 months follow-up. In 50% of patients in group 2 (12 Gy) and 40% of patients in group 3 (18 Gy) the visual acuity and FA appearance remained stable after 18 months of follow-up. In the last group (24 Gy) 80% of patients had a stable visual acuity and FA appearance after 12 months follow-up. Comparison of these findings with the natural history data of subfoveal age-related CNV, suggests a beneficial effect of radiation therapy with a total dose of 12 Gy or more on the progression of CNV membranes.

Abbreviations: AMD—Age-related macular degeneration; CNV—Choroidal neovascularisation; FA—Fluorescein angiogram.

Introduction

AMD is a leading cause of blindness in people over 50 years in Europe and the USA. The prevalence of AMD increases with age to 25% in those older than 65 years [1]. Although only 12% of patients with AMD have the exudative stage with the development of a CNV, they constitute 88% of those who become legally blind [2].

The indications for laser treatment of subfoveal CNV have been well defined by the Macular Photocoagulation Study Group (MPS). But a recent article by Yannuzzi et al. suggests that a large proportion (87%) of patients with neovascular AMD do not meet MPS guidelines for laser treatment.

Because so few patients meet these criteria, further research into new techniques for treatment of this disorder is warranted [3].

The natural course of the visual acuity of subfoveal CNV membranes is poor. When the CNV is initially present within the foveal avascular zone the visual acuity will be 20/200 or worse in approximately 70% of the affected eyes within 18 months [1].

The treatment of CNV with ionising radiation is based on the hypothesis that ionising radiation may prevent the proliferation of endothelial cells necessary for neovascularisation and may induce the obliteration of aberrant vessels [4].

The most sensitive structure of the eye concerning irradiation is the lens. The latency time between the radiation treatment and the development of cataract after a total lens dose of 4 to 10 Gy will be 6.5 years on average [5].

Materials and methods

We included 40 patients with an angiographically proven classic or occult subfoveal CNV associated with AMD and a visual acuity of 0.1 or better at presentation.

This study was performed with permission of the institutional ethical committee for clinical experiments. The first group of 10 patients (mean age 77 years) received 8 Gy in 1 fraction. The second group (mean age 77 years) received 12 Gy in 2 fractions. The third group (mean age 76 years) and the fourth group (mean age 74 years) received 18 Gy in 3 fractions and 24 Gy in 4 fractions respectively. The baseline FA showed in 23 patients a classic CNV membrane and in 17 patients an occult CNV membrane as defined by the Macular Photocoagulation Study Group [6, 7]. Most patients had a recent history of acute decrease in visual acuity based on subfoveal CNV, and were treated within 5 weeks after the beginning of the drop in visual acuity. All patients underwent a complete ophthalmic examination including fluorescein angiography before treatment and 3, 12 and 18 months post-treatment.

The early, mid venous and late phase of the pre- and post-treatment angiograms were analysed using an over-projection sheet for measuring the size of the membrane 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 posttreatment angiograms was seen, the CNV was noted as stable. A decrease in visual acuity was defined as a drop of 2 or more lines at the Snellen test. A stable visual acuity was defined as an increase or decrease within 2 lines from initial best corrected visual

Table 1. Number of patients with a stable visual acuity and a stable fluorescein angiogram after radiation treatment

Group (n=10)	Follow-up (months)		
	6	12	18
8 Gy:7 classic	3	2	2
3 occult	1	1	1
10 total	4	3	3
12 Gy:6 classic	6	6	4
4 occult	1	1	1
10 total	7	7	5
18 Gy:3 classic	3	3	2
7 occult	3	3	2
10 total	6	6	4
24 Gy:7 classic	6	6	?
3 occult	2	2	?
10 total	8	8	?

acuity. We used 16 MV photons on an area of 1 cm² with a lens sparing technique.

Results

In the first group (10 patients, 8 Gy), only 3 patients had a stable visual acuity and FA after 18 months of follow-up. The drop in visual acuity occurred in 6 patients within 6 months after treatment. The second group (10 patients, 12 Gy) contained 7 patients with a stable visual acuity and FA after 12 months of follow-up, but in 2 patients a deterioration occurred 12 months after treatment. The third group (10 patients, 18 Gy), with 7 occult CNV membranes, showed in 4 patients a stable visual acuity and FA after 18 months of follow-up. After 12 months of follow-up there were 6 stable patients.

Only 2 patients in the fourth group (10 patients, 24 Gy) had a decrease in visual acuity and a FA deterioration after 12 months of follow-up. The other 8 patients were all stable after one year.

The results are summarized in Table 1.

After 12 months of follow-up 60–80% of patients in group 2, 3 and 4 show a stable visual acuity and FA appearance, but after these 12 months 2 eyes in group 2 and 3 deteriorated. None of the patients noticed any side effect of this therapy. Complications such as radiation keratitis were not encountered.

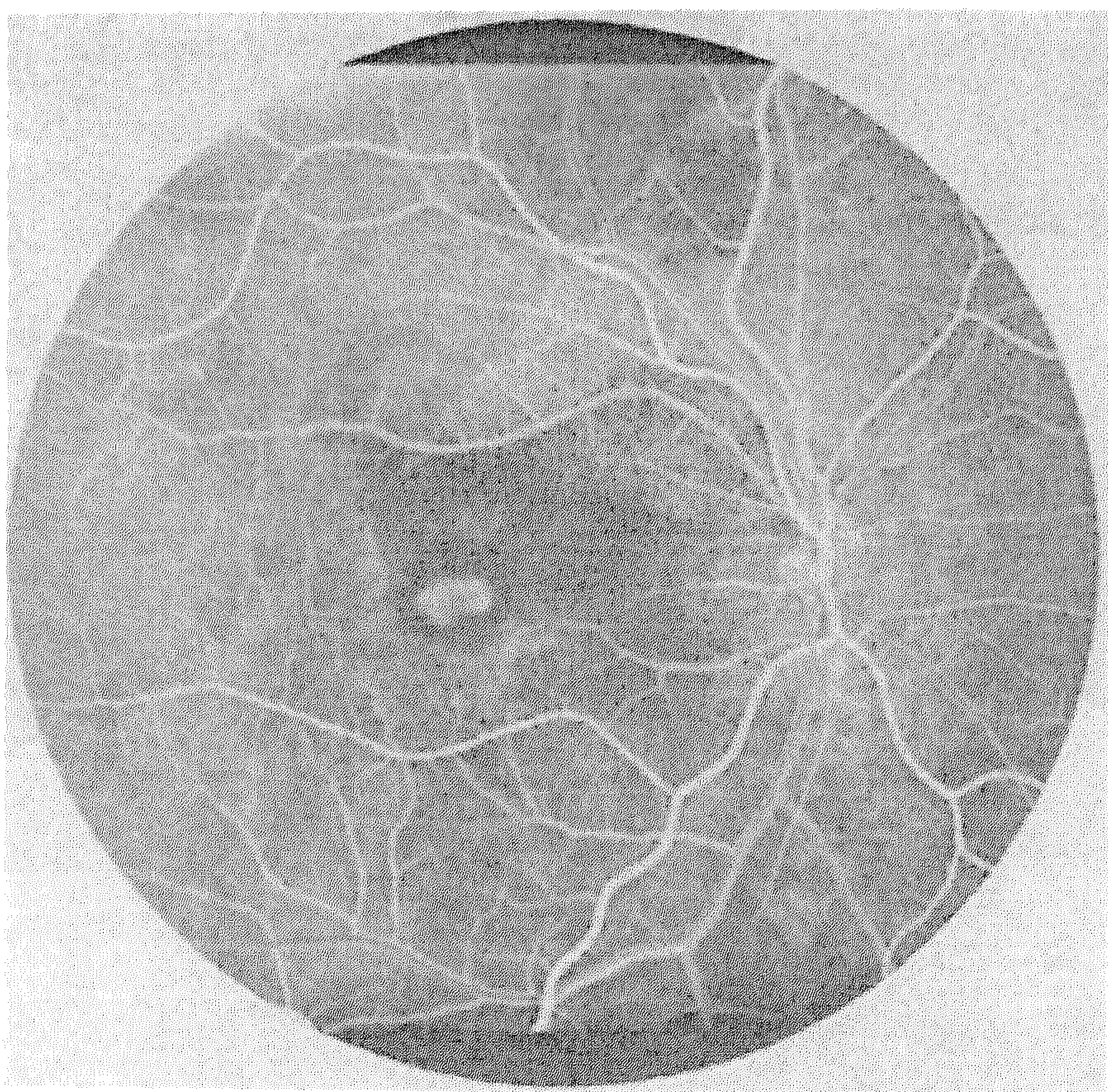


Fig. 1A. Early phase before treatment

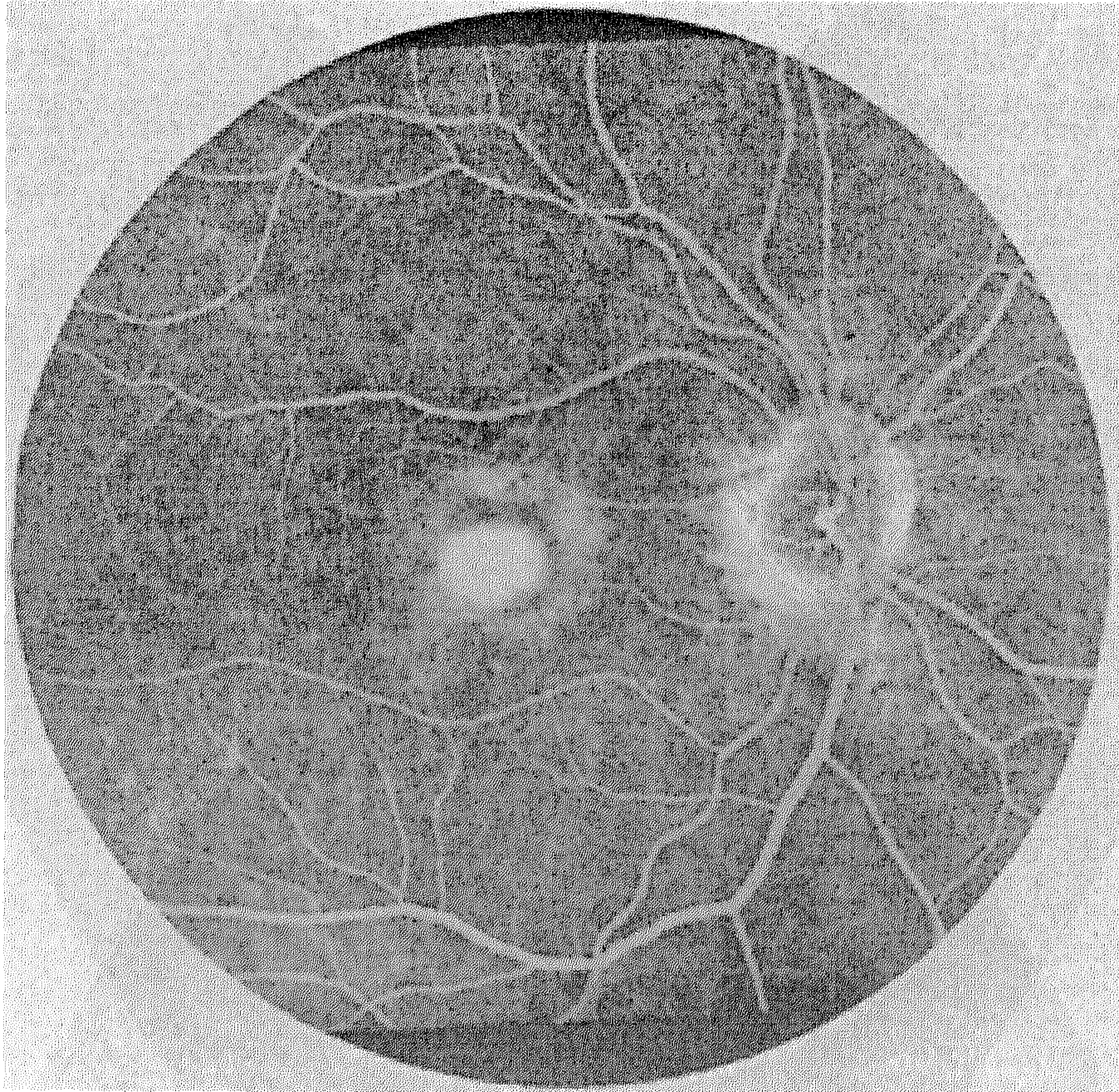


Fig. 1B. Late phase before treatment

Slight changes in lensopacification could not be ruled out, but we did not notice a substantial progression of cataract in our patients.

Case study

Male patient, left eye, visual acuity 0.2, 24 Gy group.
The early phase before and one year after treatment and the late phase before and one year after treatment (Fig. 2, A,B). No progression of the

Fig. 2B. Late phase after treatment

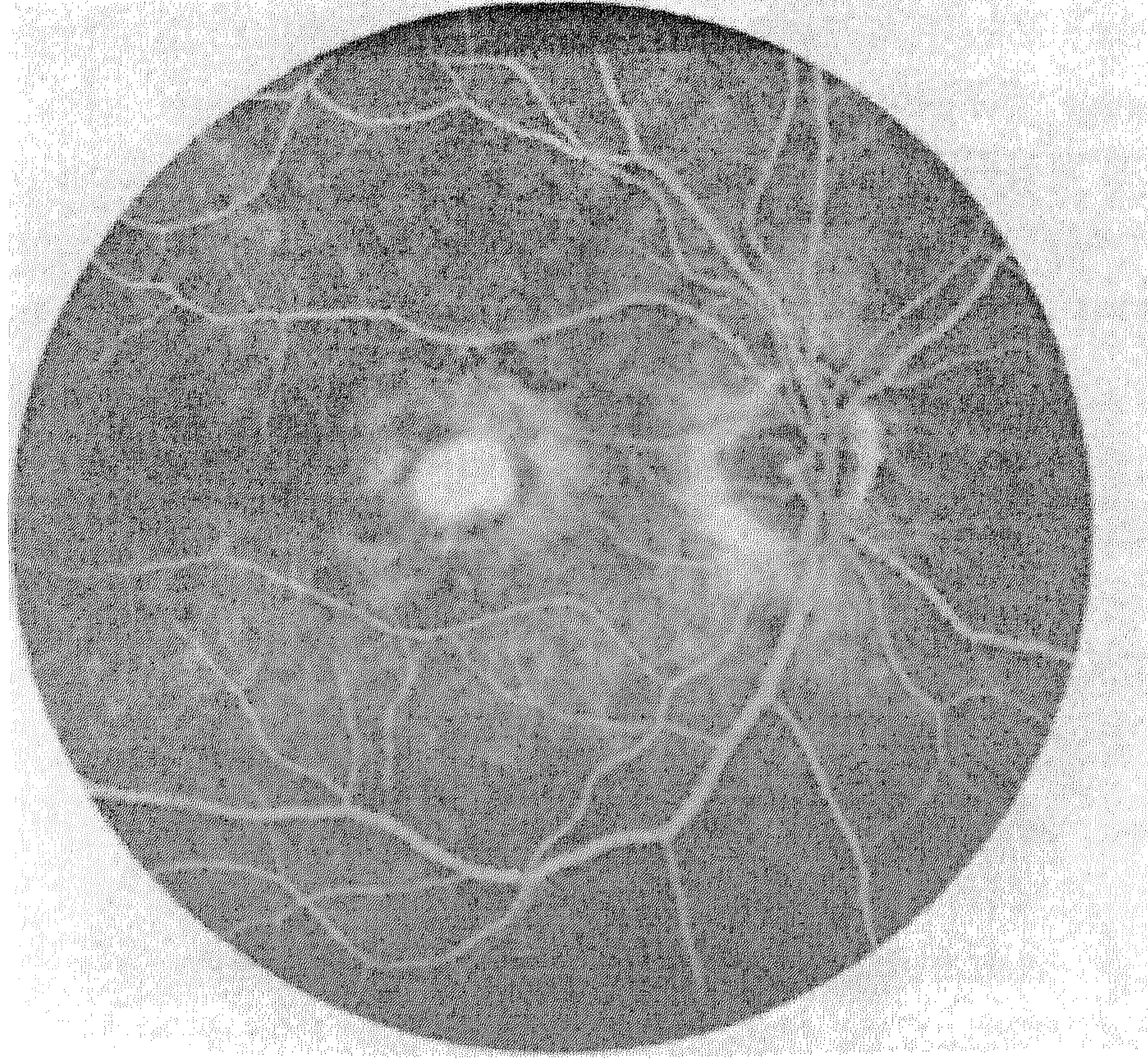
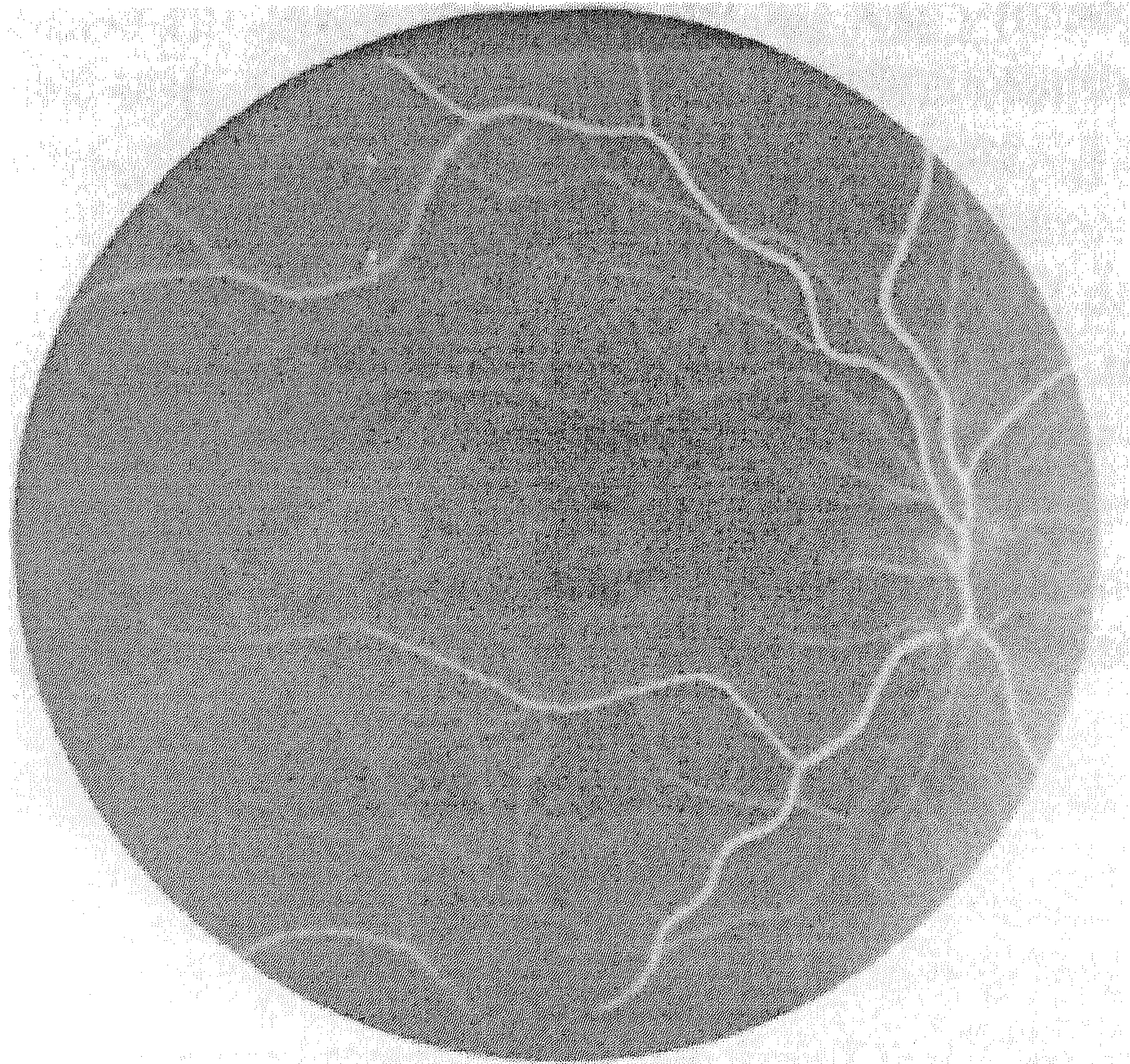


Fig. 2A. Early phase after treatment



membrane size in the early phase and no progressive leakage in the late phase after treatment.

Discussion

In this study a control group was not included because there is well documented information about the natural course of subfoveal CNV membranes [1, 8, 9, 10]. The natural course of classic CNV membranes has been described by Bressler *et al.* A subfoveal CNV, with an initial visual acuity of 1/10 or better, shows in at least 70% of the eyes a visual acuity of 1/10 or worse after 18 months follow-up [1, 9].

The natural course of occult CNV is even worse [11].

The Macular Photocoagulation Study Group (MPS) compared the visual acuity after laserphotocoagulation of subfoveal CNV with the natural course findings of subfoveal CNV [6, 7]. The visual acuity of eyes with untreated subfoveal CNV with an initial visual acuity of 0.1 or better, will decrease to 0.1 or worse in 44% of eyes after 3 months follow-up and in 80.5% of eyes after 24 months of follow-up [6].

Laserphotocoagulation of subfoveal CNV has some beneficial effect, but the patient must be prepared for a large decrease in visual acuity immediately after treatment [6]. After 18 months follow-up 7 patients in the 8 Gy group had a visual acuity of 0.1 or worse, which is comparable to the natural course data. In the 12 Gy and 18 Gy group, 3 and 4 patients respectively had a visual acuity of 0.1 or worse after 12 months, but in both groups 2 other patients had a drop in visual acuity after 18 months of follow-up. Although the follow-up in the 24 Gy group is not exceeding 12 months, 8 out of 10 patients remained stable, and only 2 patients had a decrease in visual acuity to 0.1 or worse.

When compared to the natural course data (44% of eyes a visual acuity of 0.1 or worse within 3 months), the patients treated with 12, 18 and 24 Gy show less loss of visual acuity (20%–40% a visual acuity of 0.1 or worse within 12 months). There is a possibility that the radiation treatment has decreased or stopped the growth speed of the neovascular membrane.

A Belfast study group reported a beneficial effect of teletherapy, with 6 MV photons and total doses of 10–15 Gy in 5 fractions on subfoveal CNV. After 12 months follow-up the visual acuity was maintained or improved in 63% of patients and they noticed a CNV regression in 77% of patients and the angiogram [12].

Their results concerning the visual acuity are comparable with the results of the 12, 18 and 24 Gy group after 12 months follow-up. In contrast to their angiographically proven CNV regression we could only note an inhibition of the expansion of the CNV membrane after irradiation. The differences in

angiographical outcome may be due to differences in treatment volume. In the present study only 1 cm² of the choroid received the total dose, while the whole choroid of the eye in the Belfast study was treated with the total dose. The presence of occult CNV (43% of the eyes) made it sometimes difficult to compare the initial and final FA appearance in our pilot study.

In conclusion, after 12 months of follow-up patients treated with 12 and 18 Gy total dose, show more patients with a visual acuity of 0.1 or better than you might have expected from the natural course.

The 24 Gy group, with 8 stable patients after 12 months, shows promising results. Although the follow-up is still short, the patients treated with low doses of irradiation seem to do better than one might expect from the natural history data. Until now there are no negative side effects, but longer observation is needed for a definite answer. The results of the Belfast study and this pilot study warrant further investigation to determine the role of radiation treatment of CNV membranes, knowing that cumulative doses of radiation up to 25 Gy causes no observable damage to the neuroretina and optic nerve [4].

The final answer has to come from a randomized study including a control group of untreated patients.

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