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Radiation therapy for subfoveal choroidal neovascular membranes in age-related macular degeneration

A pilot study

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Abstract ● Background: The natural course of the visual acuity of age-related subfoveal choroidal neovascularisation (CNV) membranes is poor. Laser photocoagulation of subfoveal CNV is recommended if the patient is willing to accept a large decrease in visual acuity immediately after treatment. A large proportion of patients with subfoveal CNV do not meet the Macular Photocoagulation Study Group (MPS) guidelines for laser photocoagulation. The fact that so few patients meet these criteria makes further research into new treatment techniques warranted. Ionising radiation may prevent the proliferation of endothelial cells of newly formed subretinal capillaries and may induce obliteration of the aberrant new vessels. ● Methods: In this study, the effect of radiation therapy on subfoveal CNV membranes was evaluated. Four groups of ten patients were treated with external beam radiotherapy (16-MV photons) on an area of 1 cm^2 (macular region) using a lens-sparing technique and total doses of 8–24 Gy. The first group received 8 Gy in one fraction. The second, third and fourth groups received 12 Gy in 2 fractions, 18 Gy in three fractions and 24 Gy in four fractions respectively. The studied parameters included best-corrected visual acuity and membrane size and leakage on the fluorescein angiogram. We included 17 occult and 23 classic CNV membranes as defined by the MPS, with a duration of less than 5 weeks at presentation. Complete ophthalmic examination including fluorescein angiography was performed before and 3, 12 and 18 months after radiation treatment. We analysed the angiogram using a standard overprojection sheet. The results concerning the visual acuity and fluorescein angiography (FA) were compared with the extensively published, natural course data. ● Results: The first group (including three cases of occult CNV) received 8 Gy in a single fraction. In this group only four of ten patients had stable visual acuity and stable FA appearance after 21 months follow-up. The visual acuity and FA remained stable after 13.6 months follow-up in seven of the patients in group 2 (12 Gy in two fractions, four occult CNV). The third group (18 Gy in three fractions, seven occult CNV) contained six patients with stable visual acuity, although two of them had CNV deterioration on the FA (11.1 months follow-up). In the last group (24 Gy in four fractions, three occult CNV), with a short follow-up of 5.6 months, eight patients had stable visual acuity and FA appearance. We did not note any regression of the CNV membrane on the angiogram. The visu-

al acuity in groups 2, 3 and 4 decreased to 0.1 or worse in only three cases, three cases and one case respectively after at least 6 months follow-up. ● Conclusion: 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. To date no negative side effects have been observed.

Introduction

Age-related macular degeneration (AMD) is a leading cause of blindness in people over 50 years of age in Europe and the USA. The prevalence of AMD increases with age, from 11% of persons between 65 and 74 years to 27.9% in those older than 75 years [4].

AMD represents an age-related change within the retinal pigment epithelium, photoreceptors and Bruch's membrane. The decrease in phagocytosis of photoreceptor membranes leads to deposition of lipofuscin material (drusen) within Bruch's membrane [4]. Secondary atrophy of pigment epithelial cells, overlying photoreceptors and choriocapillaris results in the non-exudative stage (dry form) of AMD. The exudative stage (wet form) develops when new choroidal vessels penetrate Bruch's membrane, resulting in choroidal neovascularisation (CNV) and serous pigment epithelial detachment (PED) [4].

Drusen which are hyperfluorescent (hydrophilic) on a fluorescein angiogram (FA) appear to predispose to the development of CNV. The chemical composition of Bruch's membrane, the change in the pigment epithelium and the presence of macrophages which stimulate neovascularisation may all be relevant in the development of CNV [3]. The exudative form of AMD has several clinical and angiographical manifestations. The classic CNV is a choroidal capillary proliferation through a break in Bruch's membrane characterized on the FA by a well-demarcated area of early hyperfluorescence and progressive leakage of fluorescein in the late stages. Occult CNV is a subretinal pigment epithelial lesion that is presumed to be a CNV, yet lacks the typical features of classic CNV because of associated exudative or hemorrhagic manifestations, the effect of the overlying pigment epithelium or the vascular growth pattern [16, 22]. Although fibrovascular pigment epithelium detachments (vascularised PED) and late subretinal fluorescein leakage of undetermined source (vascularised retinal pigment epithelium) are the common types of occult CNV, other signs like a notch on a PED and subretinal exudates are also thought to be indicative for occult CNV according to the Macular Photocoagulation Study Group (MPS) [9, 21].

The natural course of the visual acuity of classic 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 [4]. Laser photocoagulation of subfoveal neovascular lesions is recommended if the patient is willing to accept a large decrease in visual acuity immediately after treatment.

On average, after 24 months, visual acuity of laser-treated eyes had decreased three lines from baseline and visual acuity of untreated eyes had decreased four lines [15].

Although there is some beneficial effect of laser photocoagulation on subfoveal CNV membranes, there is still a considerable decrease in visual acuity. The challenge to reduce visual loss due to CNV has brought us to a concept in which we try to stop the growth of the neovascular membrane by the use of radiation therapy. Ultrastructural examination of CNV has revealed that the cone was composed of a fibrovascular membrane characterised by endothelium-lined vascular channels with retinal pigment epithelium. The rim of CNV was composed of fibrin, photoreceptor outer segments and macrophages [14]. A CNV has been noted to grow at an average of 10 μm per day (range 1–24 μm per day) [13].

The treatment of CNV with ionising radiation is based on two hypotheses: ionising radiation may prevent the proliferation of endothelial cells necessary for neovascularisation and may induce the obliteration of aberrant vessels.

The effect of a single dose of 8.7 Gy on normal capillaries has been described by Reinhold [17]. Within hours there is vasodilation and swelling and vacuolation of the cytoplasm of endothelial cells. A few weeks after irradiation loss of endothelial nuclei occurs with a reduction in the number and length of the capillaries and occlusive changes [7, 17].

The clinical effectiveness of ionising radiation (doses between 12.5 and 20 Gy) on diffuse choroidal hemangiomas associated with serous retinal detachment has been demonstrated by Scott et al. [18]. In our opinion occlusive changes will occur in the newly formed subretinal vessels and the irradiation may prevent proliferation of endothelial cells of the aberrant new vessels.

The idea of using radiation for the treatment of newly formed vessels in the eye is not new. As early as 1948, a report was published of the complete collapse of newly formed retinal vessels in proliferative ocular disease (Eale's disease) after intensive roentgen therapy [12].

The aim of the present study was to find a dose to that would halt the proliferation of the CNV, yet entail little risk of cataract development. The most sensitive structure of the eye is the lens. The chance of cataract development is already 50% after a dose of 5.5 Gy. The

latency period, however, is 6.5 years after doses of 4–10 Gy [6]. We therefore developed a technique to avoid irradiation of the lens.

The oncogenic risk is about 0.25%. It should be kept in mind that most of the patients are 65 years or older, so that many of them will not live long enough to express any radiation-induced malignancy.

Materials and methods

The criteria for inclusion in the study were: (1) clinically and angiographically proven classic or occult subfoveal CNV associated with AMD, according to the MPS criteria [16, 21]; (2) age older than 50 years; (3) informed consent.

Exclusion criteria were: (1) CNV associated with pathological myopia, angioid streaks and histoplasmosis: (2) previous photocoagulation of macular disease; (3) previous radiation therapy of eyes or brain.

The study was performed with the permission of the local ethics committee for clinical experiments.

The study population consisted of 40 patients with angiographically proven classic or occult subfoveal CNV membranes associated with AMD. For a rejection error of 5% and a therapeutic effectiveness of 30%, groups should contain 10 patients [18]. The patients were divided into the following four treatment groups:

Group 1: ten patients received 8 Gy in one fraction.

Group 2: ten patients received 12 Gy in two fractions of 6 Gy.

Group 3: ten patients received 18 Gy in three fractions of 6 Gy.

Group 4: ten patients received 24 Gy in four fractions of 6 Gy.

The interval between fractions was 1 week.

We used 16-MV photons on an area of 1 cm^2 with a lens-sparing technique. 16-MV photons were chosen because with high-energy photons the dose administered at the surface of the eye is relatively low. To reduce the lens dose the beams were directed 30° from the optical axis in the cranial/caudal direction. With this radiation technique the lens dose is less than 30% of the total dose (Fig. 1). The radiation fields are 1 cm^2 and cross each other in the macular region. Only an area of 1 cm^2 (the macular region) received the total dose. Outside this area the dose decreased to 50% or less of the total dose. Patients were asked to look at a fixed point during irradiation.

All patients had a recent history of acute decrease in visual acuity and were submitted for radiation therapy within 5 weeks after the beginning of the visual acuity drop. After a complete ophthalmic examination, including Goldmann contact-lens biomicroscopy, FA, best corrected visual acuity for distance and Amsler test, the patients were asked to participate in this pilot study. There were no refusals. All patients underwent ophthalmic examination 1 day, 4 weeks, 3 months (and every 3 months thereafter) after radiation therapy.

FA and colour photography were repeated 3 months, 12 months and 18 months after radiation therapy. The initial FA was usually performed within 10 days before the start of the first radiation therapy, although in seven patients there was a longer interval.

The early, mid-venous and late phases 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 post-treatment angiograms was seen, CNV was noted as stable. The interpretation of occult CNV development was more difficult because of the overlying PED and/or the obscuring blood. Some of the occult CNV had a classic component which could be interpreted, others had a leakage from an undetermined source which could be evaluated by comparing the pre- and post-treatment leakage. When the overlying blood disappeared after a few months and the extension of the lesion using an over-projection sheet did not increase, we classified the lesion as stable on FA.

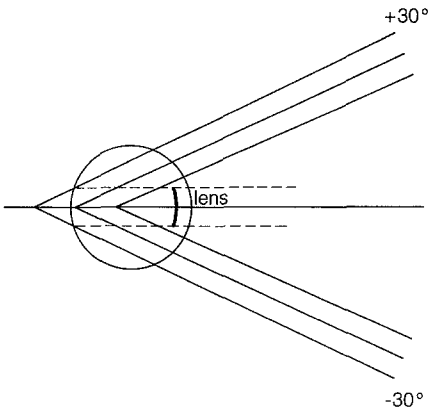

Fig. 1 Lens-sparing technique. The radiation beams are directed 30° from the optical axis

A decrease in visual acuity was defined as a drop of two or more lines on the Snellen test. Stable visual acuity was defined as an increase or decrease within two lines from initial best-corrected visual acuity. A two-line drop of visual acuity in our test is comparable to a three-line drop in the data used in the MPS study on subfoveal CNV [15].

Results

The initial (baseline) FA showed in 23 patients a classic CNV membrane and in 17 patients an occult CNV membrane as defined by the MPS [15]. In a recent article the presenting clinical findings were evaluated concerning the neovascular form of AMD [10]. About 87% of the presenting patients had occult CNV, with ca. 84% having subfoveal disease [10].

It is difficult to include only classic CNV, because of the high number of cases of occult CNV.

Group 1. In the first group (8 Gy in one fraction; Table 1) the mean follow-up time was 21 months (range 17–24 months). The average age was 77.8 years (range 74–87 years). In six patients there was a decrease in visual acuity to 0.1 or worse after radiation treatment. The visual acuity drop occurred in all patients within 3 months after treatment. In the other four patients the visual acuity remained stable with no deterioration of the CNV membrane on the FA. Only one of three occult CNV membranes remained stable.

Table 1 Radiation therapy (8 Gy in one fraction) for subfoveal CNV (group 1)

Case no.	Age (years) gender	Visual acuity		Follow-up (months)	Angiogram results	CNV characteristics
		Initial	Final			
1	74/F	0.25	0.3	22	Stable	Classic
2	76/M	0.3	0.1	17	Deterioration	Classic
3	74/M	0.16	1/60	18	Deterioration	Occult
4	82/F	0.1	0.25	22	Stable	Classic
5	74/M	0.2	2/60	22	Deterioration	Classic
6	87/M	0.3	0.3	24	Stable	Classic
7	74/M	0.3	0.2	22	Stable	Occult
8	77/M	0.4	0.1	19	Deterioration	Occult
9	77/F	0.3	1/60	21	Deterioration	Classic
10	83/M	0.2	0.08	23	Deterioration	Classic

Table 2 Radiation therapy (12 Gy in two fractions) for subfoveal CNV (group 2)

Case no.	Age (years) gender	Visual acuity		Follow-up (months)	Angiogram results	CNV characteristics
		Initial	Final			
1	85/F	0.3	2/60	13	Deterioration	Classic
2	79/M	0.3	0.25	11	Stable	Classic
3	77/M	0.25	0.3	12	Stable	Classic
4	80/M	0.3	0.3	15	Stable	Occult
5	69/F	1/60	1/60	15	Stable	Classic
6	69/F	0.16	0.2	14	Stable	Classic
7	90/F	0.16	0.08	14	Deterioration	Occult
8	58/F	0.5	0.4	14	Deterioration	Occult
9	82/F	0.125	2/60	13	Deterioration	Occult
10	84/F	3/60	1/60	15	Stable	Classic

Table 3 Radiation therapy (18 Gy in three fractions) for subfoveal CNV (group 3)

Case no.	Age (years) gender	Visual acuity		Follow-up (months)	Angiogram results	CNV characteristics
		Initial	Final			
1	72/M	1/60	0.2	10	Stable	Classic
2	82/M	0.3	0.25	12	Stable	Classic
3	80/F	0.25	1/60	8	Deterioration	Occult
4	84/F	0.2	1/60	14	Deterioration	Occult
5	71/F	0.25	0.25	14	Deterioration	Occult
6	79/F	0.3	0.25	14	Stable	Occult
7	75/F	0.25	0.08	10	Deterioration	Occult
8	76/F	0.3	0.3	9	Stable	Occult
9	68/M	0.2	0.25	9	Deterioration	Classic
10	82/F	0.3	0.16	11	Deterioration	Occult

Group 2. The mean follow-up time in the second group (12 Gy in two fractions; Table 2) was 13.6 months (range 11–17 months) and the average age was 77.3 years (range 58–90 years). There was stable visual acuity in seven patients, although one patient (no. 8) had signs of deterioration on the FA. Only one of four (no. 4) occult CNV membranes remained stable concerning the visual acuity and the FA appearance; the other three had a decrease in visual acuity to 0.1 or worse.

Group 3. The third group (18 Gy in three fractions; Table 3) with a mean follow-up of 11.1 months (range 8–14 months) and an average age of 76.9 years (range 68–84 years), contained only three classic CNV membranes. Four patients had a decrease in visual acuity (three with a visual acuity of 0.1 or worse) after radiation treatment and they all had an initial occult CNV. In five patients the visual acuity remained stable, with in three patients no change in FA appearance. In two patients

Table 4 Radiation therapy (24 Gy in four fractions) for subfoveal CNV (group 4)

Case no.	Age (years) gender	Visual acuity		Follow-up (months)	Angiogram results results	CNV characteristics
		Initial	final			
1	70/M	0.3	0.25	6	Stable	Classic
2	69/F	0.2	0.2	6	Stable	Occult
3	78/F	0.08	1/60	7	Deterioration	Occult
4	72/F	0.25	0.25	6	Stable	Classic
5	81/F	0.2	0.2	4	Stable	Classic
6	70/M	0.2	0.1	7	Deterioration	Classic
7	83/M	0.16	0.16	4	Stable	Occult
8	74/M	0.5	0.5	6	Stable	Classic
9	75/M	0.16	0.125	5	Stable	Classic
10	71/F	0.4	0.3	5	Stable	Classic

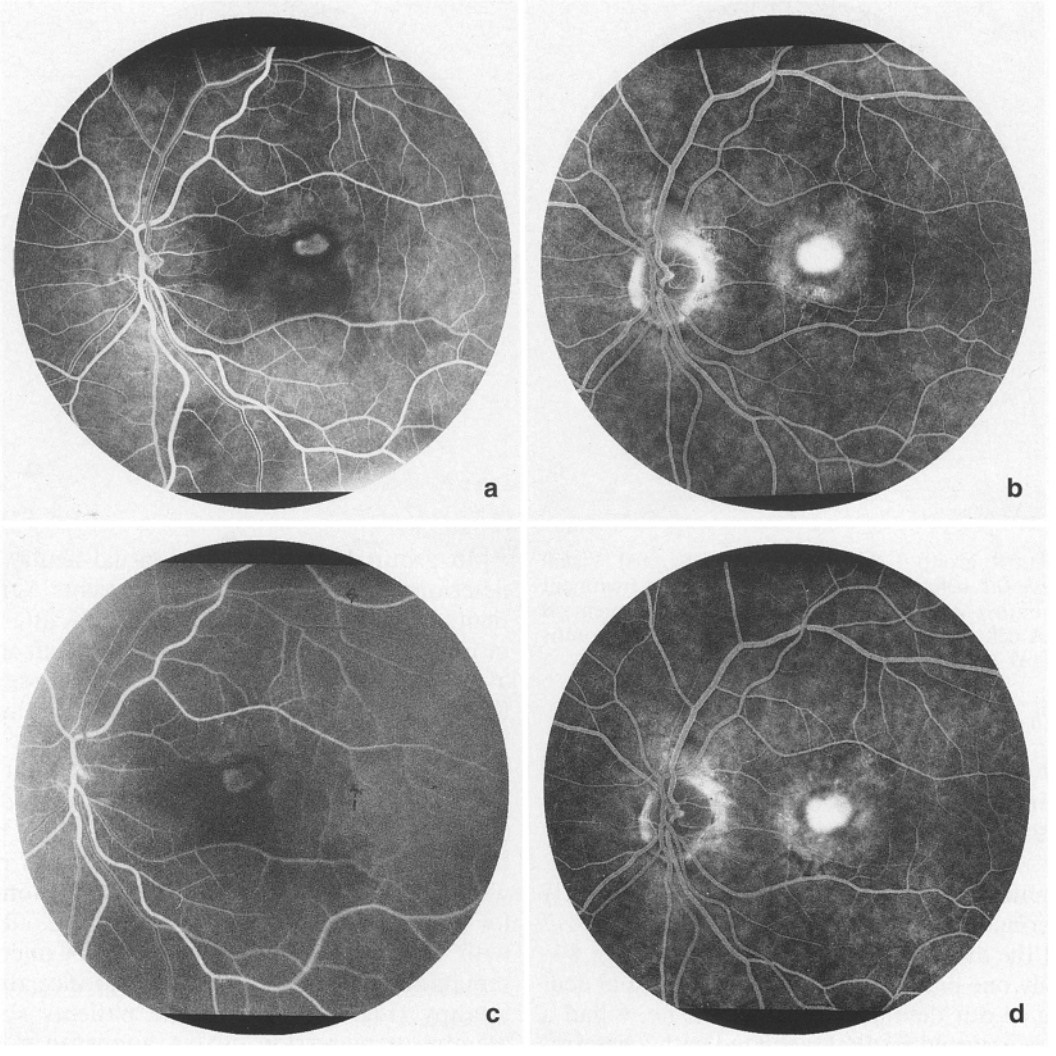

Fig. 2a–d Patient 2, group 2 (12 Gy in two fractions). Visual acuity in left eye 0.3 before treatment and 0.25 after treatment (follow-up 12 months). **a** Early phase of fluorescein angiography (FA) before treatment; **b** late phase of FA before treatment; **c** early phase of FA 12 months after treatment; **d** late phase of FA 12 months after treatment

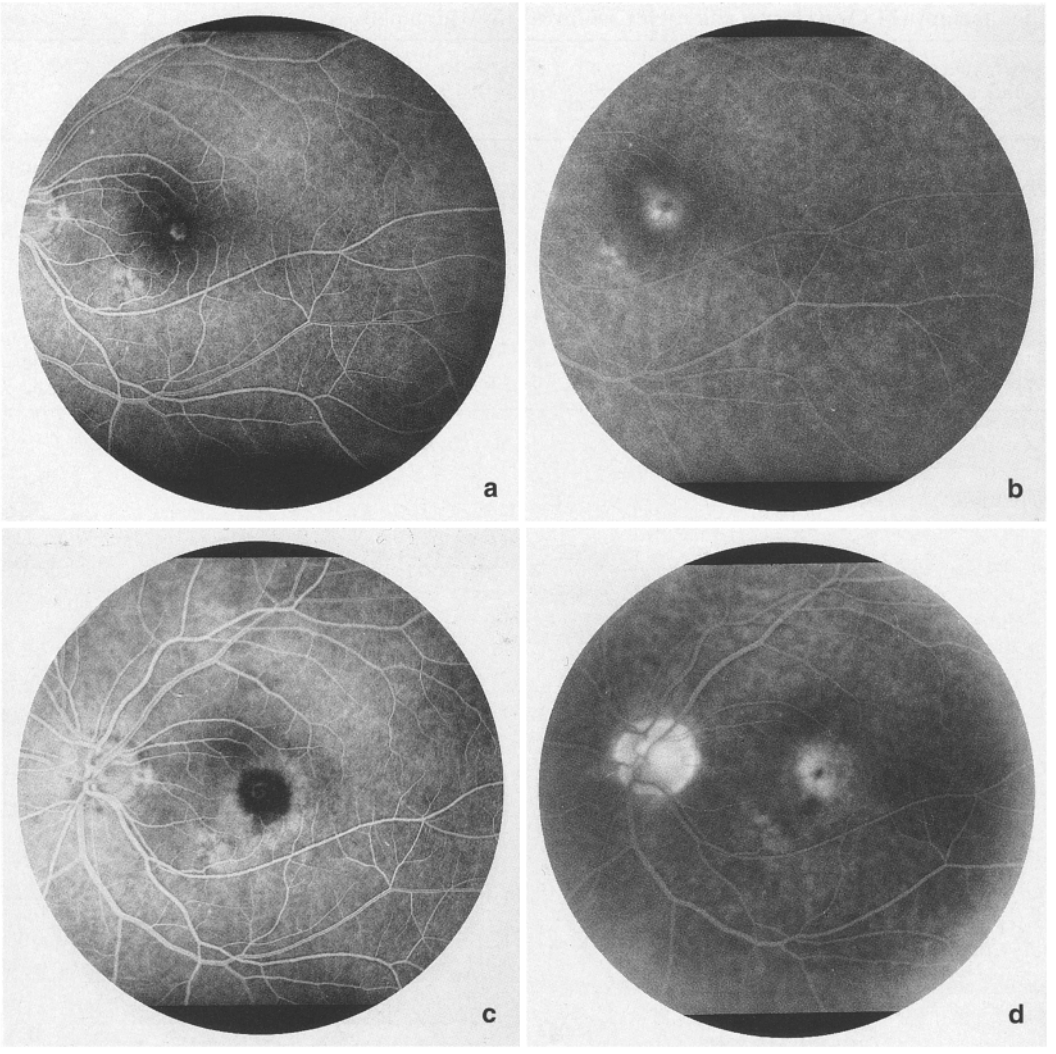

Fig. 3a–d Patient 9, group 3 (18 Gy in three fractions). Visual acuity in left eye 0.2 before treatment and 0.25 after treatment (follow-up 9 months). **A** Early phase of FA before treatment; **B** late phase of FA before treatment; **C** early phase of FA 3 months after treatment; **D** late phase of FA 3 months after treatment

(nos. 5, 9) FA deterioration occurred. Patient no. 1 had an increase in visual acuity because of the disappearance of subretinal fluid associated with the CNV.

Group 4. The mean follow-up in the fourth group (24 Gy in four fractions; Table 4) was 5.6 months (range 4–7 months) and the average age was 74.3 years (range 69–83 years). Only one patient had a decrease in visual acuity according to our definition, but patient no. 6 had a slight decrease in visual acuity associated with a deterioration on the FA. The other eight patients, including two with occult CNV membranes (nos. 2, 7), had stable visual acuity and FA appearance.

In group 1 a decrease in visual acuity and an FA deterioration occurred in six patients. Only four patients had stable visual acuity and FA after therapy (21 months follow-up). In three patients of group 2 the visual acuity and FA deteriorated, and in seven patients there was a stable situation (13.6 months follow-up). The third group, with seven initial occult CNV membranes, had six patients with stable visual acuity after treatment but two of them showed FA deterioration (11.1 months follow-up). In group 4 stable post-irradiation visual acuity and FA occurred in 8 patients, but with a relatively short follow-up (5.6 months). Except for the two patients (nos. 5, 9) in group 3, all the patients with stable visual acuity had a CNV membrane that remained unchanged on FA appearance after radiation therapy (Fig. 2). None of the patients showed CNV membrane regression on FA appearance. If a drop in visual acuity or a deterioration on the angiogram was noticed, it occurred within 3 months after treatment (Fig. 3).

None of the patients noticed any side effect of this therapy.

Complication such as radiation keratitis or radiation retinopathy were not encountered. Slight changes in lens opacification could not be ruled out, but we did not notice a substantial progression of cataract in our patients. We are aware of the fact that the follow-up is still short and that some side effects become apparent only after several months or years.

Discussion

The prevalence of AMD in a general population over the age of 65 years is about 25%. Although only 12% of patients with AMD have the exudative stage, they constitute 88% of those who become legally blind [8]. No control group was included in this study because the natural course of subfoveal CNV membranes is well documented [3, 5, 11, 19]. The natural course of classic CNV membranes in AMD has been described by Bressler et al. [3]. A subfoveal CNV, with an initial visual acuity of 0.1 or better, shows in at least 70% of the eyes a visual acuity of 0.1 or worse after 21 months follow-up. Guyer et al. found that 77% of eyes with a subfoveal CNV had lost at least four lines of visual acuity after 24 months follow-up [10]. The natural course of occult CNV membranes with initial visual acuity of 0.25 shows a decline of at least three lines in 63% of patients after 28 months follow-up [5]. The natural course of a PED with a CNV is even worse. Some 86% of patients with initial visual acuity better than 0.2 and a subfoveal CNV associated with a PED had final visual acuity of 0.1 or worse after 48 months follow-up [20].

The MPS recommends laser photocoagulation for classic subfoveal CNV membranes if the patient is willing to accept a large decrease in visual acuity immediately after treatment. In the long term, treated patients had less decrease in visual acuity from baseline. Persistent or recurrent CNV was observed in 51% of the laser-treated eyes by 24 months after initial treatment without influence on the visual acuity [14]. Perifoveal laser photocoagulation has also been proven effective in the short-term preservation of visual acuity, but this treatment led to a six-line visual acuity loss after 42 months in 76% of the patients [8]. Compared with eyes in natural history studies, eyes treated with unconventional scatter macula photocoagulation had less visual loss from baseline but did not recover visual acuity of 0.2 or better more frequently [21].

Except for the limited benefit of laser photocoagulation there is no therapeutic modality for patients with CNV membranes. In 1992 we reported the preliminary results of this study [2]. Chakravarthy et al. recently reported a beneficial effect of teletherapy with 6-MV photons (doses of 10 Gy or 15 Gy in five fractions) on subfoveal CNV [7]. Visual acuity was maintained or improved in 78% and 63% of the patients at their 6- and 12-month follow-up examination, respectively. Significant CNV regression was recorded in 68% and 77% of treated patients at 6 and 12 months after irradiation. No differences were seen between patients who received 10 Gy and those who received 15 Gy. The vaso-occlusive response became obvious at 6 months after irradiation [7]. The present work showed that a single fraction of 8 Gy had no beneficial effect. Only four of the ten patients had stable visual acuity and FA appearance after 21 months, which is comparable with the natural history of subfoveal CNV membranes. In the second group (12 Gy in two fractions) and the third group (18 Gy in three fractions), visual acuity remained stable for at least 12 months in seven and six cases, respectively. These results are comparable with the outcome of the study by Chakravarthy et al. [7]. In contrast with their angiographically proven CNV regression we could note only inhibition of the expansion of the CNV membranes in the majority of our patients with stable visual acuity. Two patients (nos. 5, 9) of the third group had FA deterioration but stable visual acuity. These patients had a period of 4 weeks between the baseline FA and the first radiation treatment. Compared with the other groups, the fourth group (24 Gy in four fractions) had only a short follow-up (5.6 months), but it is promising that eight of the ten patients of this group had stable visual acuity and FA appearance. The differences in angiographic outcome between the two studies may be due to differences in treatment volume. In the present study only 1 cm^2 of the choroid was irradiated, while Chakravarthy et al. treated more than 50% of the choroid. Other reasons for differences in post-treatment changes in FA appearance are a delay of more than 10 days between the initial angiogram and initiation of treatment (group 2, nos. 7, 8, 9; group 3, nos. 3, 5, 9; group 4, no. 6) and a larger percentage of occult CNV membranes in the present study. The presence of an occult CNV membrane (17/40 patients) sometimes made it difficult to compare the initial and final FA. It should be noted that in contrast to the study by Chakravarthy et al., in which only four of the 19 patients had an initial visual acuity of 6/24 or more, in our study 22 of the 40 patients presented with initial visual acuity of 25/100 or more. We also excluded patients with previous laser treatment, whereas the other study contained five patients with previous laser treatment in the macular region.

To date we have seen no side effects of the radiation therapy. According to the literature the lens is the most sensitive part of the eye for radiation damage [1, 6, 17]. With the lens-sparing technique, the expected lens dose is less than 30% of the total dose. In group 3 (18 Gy) and group 4 (24 Gy), with lens doses of 6 Gy and 8 Gy,

respectively, there remains a possibility of cataract development.

In conclusion, stable visual acuity was observed in six to eight of the ten patients in each of the groups 2, 3 and 4 (12 Gy, 18 Gy and 24 Gy), associated with a stable CNV membrane on FA in all except two cases. The MPS data show that 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 within 3 months of follow-up [15]. The visual acuity in our groups 2, 3 and 4 decreased to 0.1 or worse in three, three and one patient, respectively, after at least 6 months follow-up.

Although the follow-up period is still short (especially in group 4), patients treated with total doses of 12 Gy or more seem to do better than one might expect from the natural history of this disease. To date no negative side effects have been observed. Longer observation will show whether the proposed treatment is indeed safe. The positive results of the present study, however, warrant further investigation to determine the role of radiation therapy in the treatment of CNV membranes.

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