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Grading choroidal neovascular membrane regression after strontium plaque radiotherapy; masked subjective evaluation vs planimetry

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PURPOSE. *To analyze angiographic changes in choroidal neovascular membranes (CNVM) after strontium-plaque (^{90}Sr) irradiation for exudative age-related macular degeneration (AMD) using masked measurement of the CNVM areas and a masked subjective comparison of CNVM size and leakage.*
METHODS. *We studied the baseline, 3, 6, and 12-month angiograms of 19 eyes treated with ^{90}Sr-plaque irradiation for exudative AMD. The area of CNVM-related hyperfluorescence was measured quantitatively, and the angiograms were subjectively evaluated by a masked grader.*
RESULTS. *In 7 of the 19 eyes the CNVM-related hyperfluorescence was too scattered to be analyzed by planimetry but masked subjective grading correlated with the clinical response to irradiation. In the remaining 12 eyes, the CNVM decreased in size in 67% of the eyes and showed leakage in 67%. Planimetry and subjective assessment of the size and leakage of the CNVMs similarly reflected the regression after irradiation.*
CONCLUSIONS. *CNVM size and leakage frequently diminish after ^{90}Sr-plaque irradiation. Quantitative measurement of the CNVM areas, or a grading system based on masked subjective assessment, give similar results for evaluating these changes. Masked subjective grading can be used even in cases where the CNVM is too scattered to be outlined for planimetry. (Eur J Ophthalmol 2001; 11: 269-76)*

KEY WORDS. *Age-related macular degeneration, Subfoveal choroidal neovascular membrane, Brachytherapy, Planimetry, Radiotherapy*

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INTRODUCTION

For many years the only proven treatment for exudative age-related macular degeneration (AMD) was laser photocoagulation of the subretinal choroidal neovascular membrane (CNVM). Evaluation of the angiographic outcome was bimodal; either the CNVM was destroyed, indicating a favourable response needing no additional treatments, or there was residual or recurrent CNVM, implying additional treatment or an unfavourable outcome (1-3).

With the advent of new therapies, such as photodynamic therapy (4), radiotherapy (5-11) or pharmacotherapies (12), we are faced with a new situation in which a positive effect on exudative AMD may be connected with diminution but not total disappearance of the CNVM. In such a situation, grading the angiographic response to treatment is more difficult.

We recently performed a pilot study on the feasibility of strontium-90 (^{90}Sr) plaque irradiation in the treatment of exudative AMD (13, 14). Here we compare masked subjective evaluation of the angiographic response to a planimetry-based approach for grading regression of the CNVM after irradiation.

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MATERIALS AND METHODS

We studied the baseline, 3, 6, and 12-month fluorescein angiograms (FA) and fundus photographs of 19 consecutive patients treated in the setting of a pilot study of ^{90}Sr plaque irradiation for subfoveal CNVM. Details of the treatment and visual and clinical results have been described elsewhere (13, 14). Thirteen of the CNVMs were of the classic type, 4 were occult and 2 included a subfoveal hemorrhagic component. The lesion had a classic component only in 10 of the 13 eyes classified as classic CNVM. In the other three eyes the classic component formed the subfoveal part of the lesion and covered about 30% of the total lesion area.

In addition, FAs from eight control patients with the same inclusion criteria were analyzed. Five had a classic and three occult CNVM.

The angiograms and color fundus photographs were 30-degree non-stereoscopic images taken with a Canon CF-60Z fundus camera. In FA, Kodak T-Max 400film with Exiter SE 40 and Barrier SB 50 filters were used after an intravenous injection of 12 mg/kg sodium fluorescein (Fluorescite, Alcon, Forth Worth, TX, USA). For the 'early phase' image a frame taken in the early venous phase of the angiogram (typically 30 seconds after injection) was chosen. For the 'late phase' image a follow-up frame (60 to 120 seconds after the injection) was used.

For subjective grading of the angiograms, the grader (LL, retinal specialist) arranged the baseline and follow-up angiograms in the order of increasing size or leakage of the CNVM. For each time point of a single patient the grader was given a set of pictures, consisting of one early and one late-phase angiogram image and the corresponding color fundus photograph. Thus, the grader was given the four sets (baseline, 3, 6, and 12-month images) for each patient but did not know the timing of each set of images. After the image sets had been arranged in order of increasing size or leakage, the sets were rated from 1 to 4 so that the set with the smallest/least leaky membrane was given 1 point and the largest/most leaky membrane was given 4 points. Subsequently, the time point of each set of images was identified and the score was allocated to the corresponding time point. The mean score at each time point was then calculated to represent the size or leakage scores of CNVM in a group of patients at a given time point (Fig.1).

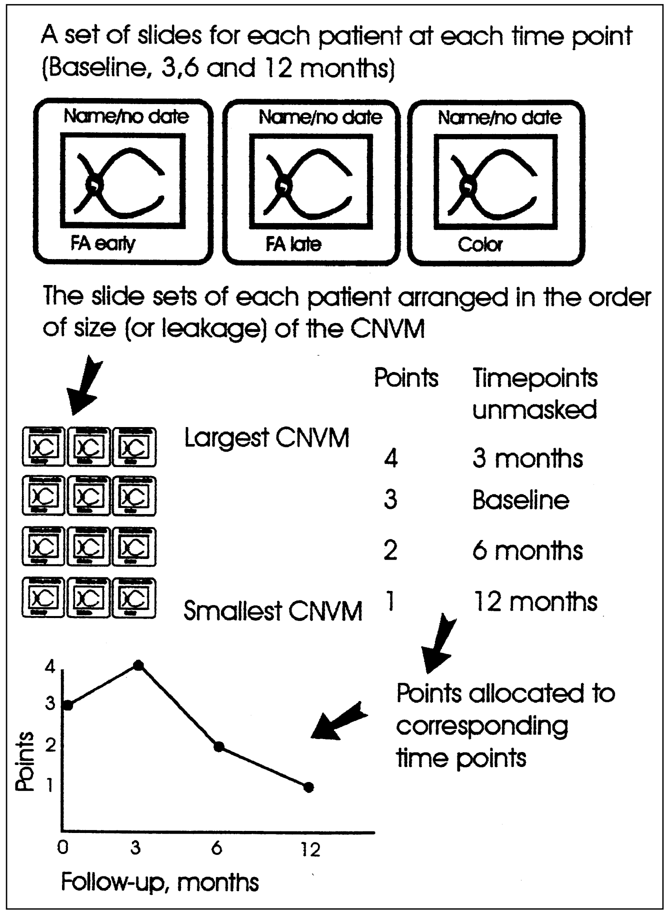

Fig. 1 - *Outline of the masked subjective grading system of the angiograms used to evaluate CNVM size and leakage.*

For planimetry, the image to be analyzed was projected onto a digitizing table. Two anatomical landmarks (usually vascular crossings) were chosen as reference points to be used in all subsequent images of the same fundus. The hyperfluorescent area corresponding to the CNVM was then outlined by a retina specialist using a mouse with a cross-hair ring. In the three lesions containing both classic and occult features, only the area of the classic CNVM was recorded. The size of the delineated area was then calculated with computer software. This calculation used the distance between the reference points as a standard measurement to correct for possible changes in the magnification of the image analyzed. The grader was given early and late-phase angiogram frames and the corresponding color fundus photograph for each session, but was unaware of the timing of the images in relation to follow-up. The image sets for each time point and each patient were analyzed in random order.

To assess leakage, the area of the hyperfluorescence in the early-phase angiogram frame was subtracted from that of the late-phase frame taken at the same time point. The resulting difference, as a percentage of the early-phase angiogram, was considered to represent the leakage of the lesion. The mean of these individual values was used to indicate leakage in a group of patients at each time point.

Statistical analysis of the data was done by the paired t-test or Wilcoxon Signed Rank test, depending on the data analyzed. P less than 0.05 was considered statistically significant.

RESULTS

Planimetric evaluation was not considered possible in seven irradiated eyes for the following reasons: two had an intraretinal hemorrhage in either the baseline or follow-up angiograms obscuring the borders of the lesion, two had a pigment epithelium tear in the follow-up angiograms, one had different-sized angiograms (30° and 60°), and two had a poorly defined lesion at baseline. In all these eyes the subjective evaluation could still be done. The size and leakage scores of these seven eyes are presented separately at the end of the results section.

Three months after ^{90}Sr plaque irradiation a decrease in CNVM size of at least 15% was observed in 10/12 (83%) of the eyes. Likewise the three-month follow-up frame was considered to have less severe CNVM than baseline in 6/12 (50%) of the eyes. At six months a decrease in CNVM size of at least 15% was observed in 8/11 (73%) of the eyes. Subjective evaluation indicated that the CNVM was smaller than at baseline in 7/11 (64%). At 12 months a decrease in CNVM size of at least 15% was observed in 8/12 (67%) of the eyes, and subjective evaluation suggested the CNVM was smaller than baseline in 9/12 (75%). The corresponding values obtained using cutpoints other than 15% are shown in Table I.

All the eyes with at least a 15% decrease in CNVM size at 12 months compared to baseline were also considered on subjective evaluation to have a smaller CNVM than at baseline. Likewise, 8/9 of the eyes considered subjectively to have a less severe CNVM

TABLE I - THE EFFECT OF USING DIFFERENT CUTPOINTS AS A CRITERION FOR DIMINUTION OF THE CNVM SIZE OR LEAKAGE. The percentages in the left hand column indicate the decrease in CNVM size required for the eye to be considered to show regression of the CNVM. The other columns indicate the percentages of eyes with regression of CNVMs at the three time points

	Size Proportion of eyes showing CNVM regression		
Cutpoint for CNVM regression	**3 months**	**6 months**	**12 months**
10 %	83 %	73 %	67 %
15 %	83 %	73 %	67 %
20 %	75 %	73 %	58 %
30 %	58 %	64 %	58 %
50 %	42 %	55 %	50 %
	Leakage Proportion of eyes showing CNVM regression		
Cutpoint for CNVM regression	**3 months**	**6 months**	**12 months**
10 %	67 %	64 %	67 %
15 %	67 %	64 %	67 %
20 %	67 %	64 %	58 %
30 %	67 %	55 %	58 %
50 %	42 %	55 %	58 %

at 12 months than at baseline had at least a 15% decrease in CNVM size by planimetry.

The mean size of the CNVM (as a percentage of baseline) of all irradiated eyes was 114.5% (SD= 235.7) at 3 months (p = 0.07, paired comparison with baseline), 88.8% (176.2) at 6 months (p = 0.2) and 313.4% (875.9) at 12 months (p = 0.3). In eyes in which the CNVM was subjectively considered to be less severe at 12 months than at baseline, the mean CNVM area was 32.1% (36.6) of baseline at 3 months (p = 0.2), 16.4% (20.5) at 6 months (p = 0.008) and 21.4% (35.3) at 12 months (p = 0.008). In eyes in which the CNVM was considered to be larger at 12 months than at baseline, the measured mean CNVM area was 258.5% (372.8) of baseline at 3 months (p = 1.0), 282% (277.1) at 6 months (p = 0.2) and 897.5% (1458.6) at 12 months (p = 0.5) (Fig. 2a).

In masked subjective analysis the mean size score of the CNVM for the 12 irradiated eyes was 2.8 at baseline, 2.8 at 3 months (p = 1.0), 2.3 at 6 months (p = 0.4) and 2.0 at 12 months (p = 0.4). The corresponding mean size score for eyes considered to show regression of the CNVM during follow-up was 3.6 at baseline, 3.4 at 3 months (p = 0.5), 2.0 at 6 months (p = 0.008) and 1.0 at 12 months (p = 0.008); for eyes showing growth of the CNVM during follow-up it was 1.3 at baseline, 1.8 at 3 months (p = 0.2), 3.0 at 6 months (p = 0.006) and 4.0 at 12 months (p = 0.002) (Fig. 3a).

Subjective assessment considered leakage at three months was less than at baseline in 8/12 (67%) of the eyes. A decrease of at least 15% from baseline value was observed in 8/12 (67%) of the eyes by planimetry. At 6 months the corresponding ratios were 6/11 (55%) for subjective assessment and 7/11 (64%) for planimetry, and at 12 months 8/12 (67%) for both methods. Planimetry gave (as a percentage from baseline values) mean values for leakage in all irradiated eyes of 105% (132.4) at 3 months (p = 0.9), 150.5% (214.7) at 6 months (p = 1.0) and 169.9% (281.4) at 12 months (p = 0.9). The corresponding values in the subjective evaluation were 47.3% (95.6) at 3 months (p = 0.2), 29.6% (57.6) at 6 months (p = 0.02) and 0.05% (63.3) at 12 months (p = 0.008). Subjective assessment gave increases in leakage during follow-up of 220.3% (127.9) at 3 months (p = 0.5), 472.7% (68.2) at 6 months (p = 0.6) and 518.5% (195.1) at 12 months (p = 0.3) (Fig. 2b). The mean leakage score of the CNVM for the 12 eyes was 2.8 at baseline, 2.5 at 3 months (p = 0.3), 2.8 at 6 months (p = 0.9) and 1.9 at 12 months (p = 1.0). The corresponding mean leakage score for eyes considered to show regression of the CNVM during follow-up was 3.6 at baseline, 2.9 at 3 months (p = 0.03), 2.5 at 6 months (p = 0.05) and 1.0 at 12 months (p = 0.008); for eyes considered to show growth of the CNVM during follow-up the means were 1.3 at baseline,1.8 at 3 months (p = 0.2), 3.3 at 6 months (p < 0.0001) and 3.8 at 12 months (p = 0.1) (Fig. 3b).

CNVM size and leakage increased in all control patients. The mean size of the CNVM at 12 months was 839.8% (1177.9) (p = 0.008) and the mean leakage 661.6% (795.6) of the baseline value (p = 0.008) (Figs. 2c and 2d).

As mentioned earlier, planimetric evaluation could not be done on seven irradiated eyes as the borders of the lesions were too poorly defined to be outlined (Figs. 4 and 5). Subjective analysis considered 5/7 of these eyes had a less active CNVM at follow-up than at baseline. This evaluation correlated with the clinical drying of the neurosensory detachment in these eyes. The mean size score of the CNVM for these eyes was 2.4 at baseline, 2.6 at 3 months (p = 0.8), 3.1 at 6 months (p = 0.3) and 1.9 at 12 months (p = 0.5). The mean leakage scores were 2.8 at baseline, 2.3 at 3 months (p = 0.6), 3.0 at 6 months (p = 0.8) and 1.8 at 12 months (p = 0.2).

DISCUSSION

There is wide variation in CNVM responses after radiation therapy for AMD. Chakravarthy et al (5) reported a decrease in size of at least 10% in 83% of treated eyes at 12 months and total disappearance of the CNVMs in 6/19. In the randomized study by Bergink et al (6), the treated eyes showed stabilization, but no regression of the CNVM whereas the lesions increased in size in untreated eyes. Hollick et al (7) had a decrease in CNVM size of at least 10% in of the 41% of their patients at 12 months, only one membrane regressed completely. Martin et al (8) reported a significant (> 10%) decrease of the CNVM in 65% of eyes at 12 months. Sasai et al (9) found that at 12 months the size of the CNVM had decreased or was unchanged in 83-91% of eyes. On the other hand, Stalmans et al (10) found a progressive growth

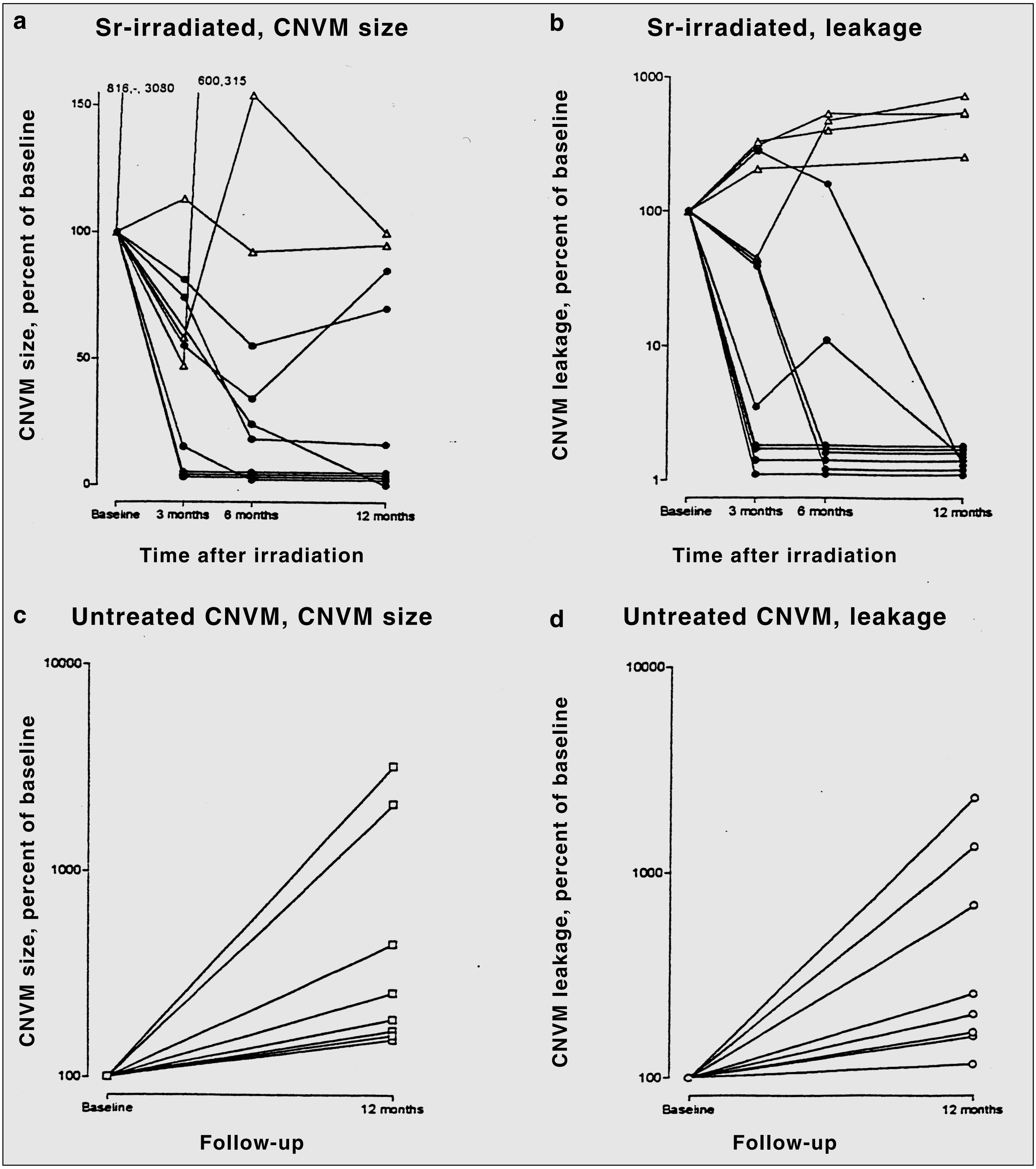

Fig. 2 - ***a)*** *The size and* ***b)*** *leakage of the CNVM given as a percentage of baseline 3, 6, and 12 months after radiotherapy, measured by planimetry. The filled circles represent eyes considered to show regression of the CNVM in subjective analysis; the open triangles represent eyes with further growth of the CNVM during follow-up. In Figure* ***2a*** *the CNVM size scale is linear; in Figure* ***2 b*** *the CNVM leakage scale is logarithmic. The size* ***c)*** *and* ***d)*** *leakage of the CNVM at baseline and at 12 months in untreated patients.*

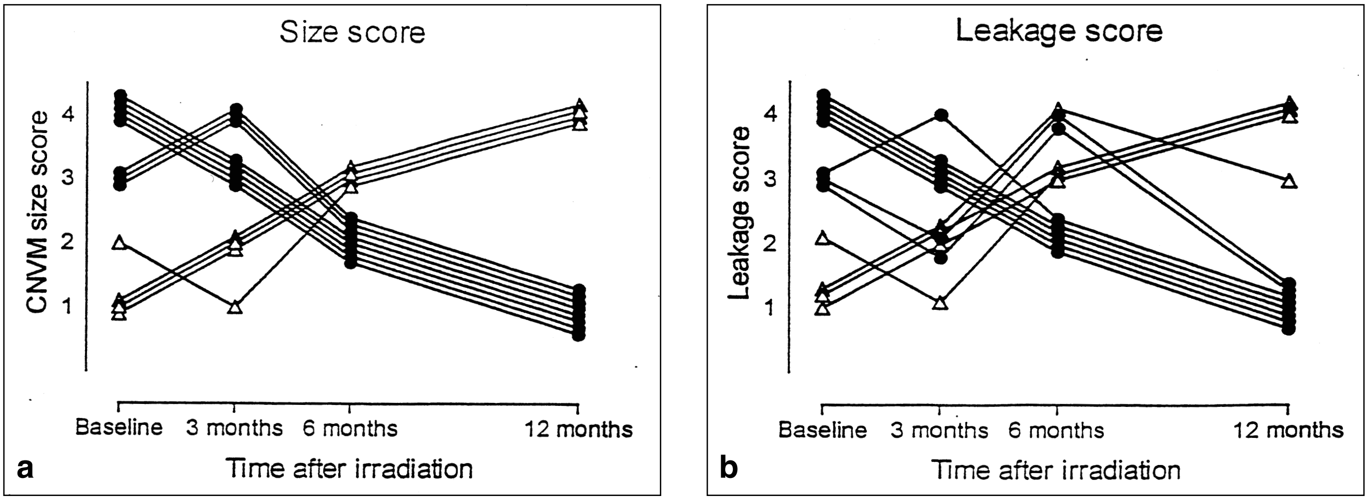

Fig. 3 - ***a)*** *The mean size score and* ***b)*** *the mean leakage score at given time points calculated from masked subjective assessment of the CNVMs. The filled circles represent eyes considered to show regression of the CNVM in subjective analysis; the open triangles represent eyes with further growth of the CNVM during follow-up.*

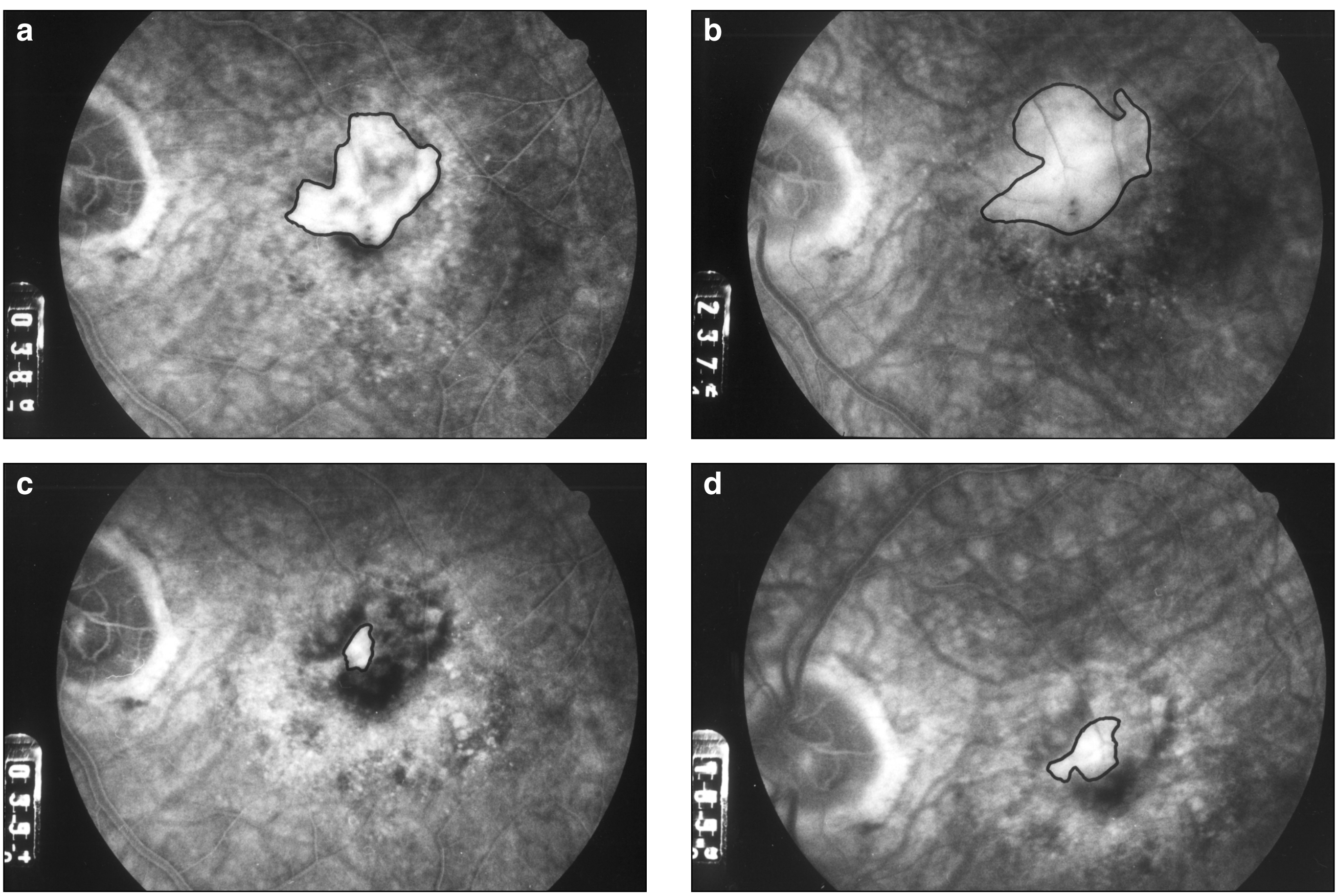

Fig. 4 - *Fluorescein angiograms of an irradiated eye considered amenable for both the masked subjective evaluation and planimetry. The black line outlines the areas used for planimetric evaluation.* ***a)*** *The baseline early-phase angiogram;* ***b)*** *the baseline late-phase angiogram;* ***c)*** *the 12-month early-phase and* ***d)*** *late-phase angiograms. The hyperfluorescence surrounding the CNVM is considered to be due to granular atrophy of the RPE.*

of CNVMs after external beam radiation therapy, with no regression in any of their 111 patients. In other studies with radiotherapy the membrane size was not defined separately (11). In our material a decrease in CNVM size of at least 15% was found in 8/12 of the eyes, and at least 50% in 6/12 of eyes amenable to planimetry of the CNVM. These results resemble those of the original article by Chakravarthy et al (5).

Our data also indicated that the treated eyes could be divided into two groups, responders showing a clear decrease or disappearance of the CNVM, and non-responders with continuing growth, resembling the non-treated control eyes.

Leakage is typical of neovascular tissues in the eye. This may be due to the sparse supporting structures around the the neovascular capillaries, but it may also be caused by a continuing stimulation of the neovascular frond by vascular endothelial growth factor (15), a potent permeability-enhancing substance with a vital role in angiogenesis. Thus a decrease in leakage may be indicative of diminished angiogenetic stimulus after treatment, and evaluation of this leakage would be useful for checking the CNVM response to treatment. To our knowledge, no previous studies have quantitatively evaluated leakage after treatment for exudative AMD.

By defining leakage as the difference in the area of hyperfluorescence between early and late frames of the angiogram, meaningful quantification of the angiogram can be obtained. Shrinkage of the CNVM seemed to coincide with decreased leakage, suggesting that the putative endothelial cell damage caused by irradiation did not increase the loss of CNVM capillary wall integrity.

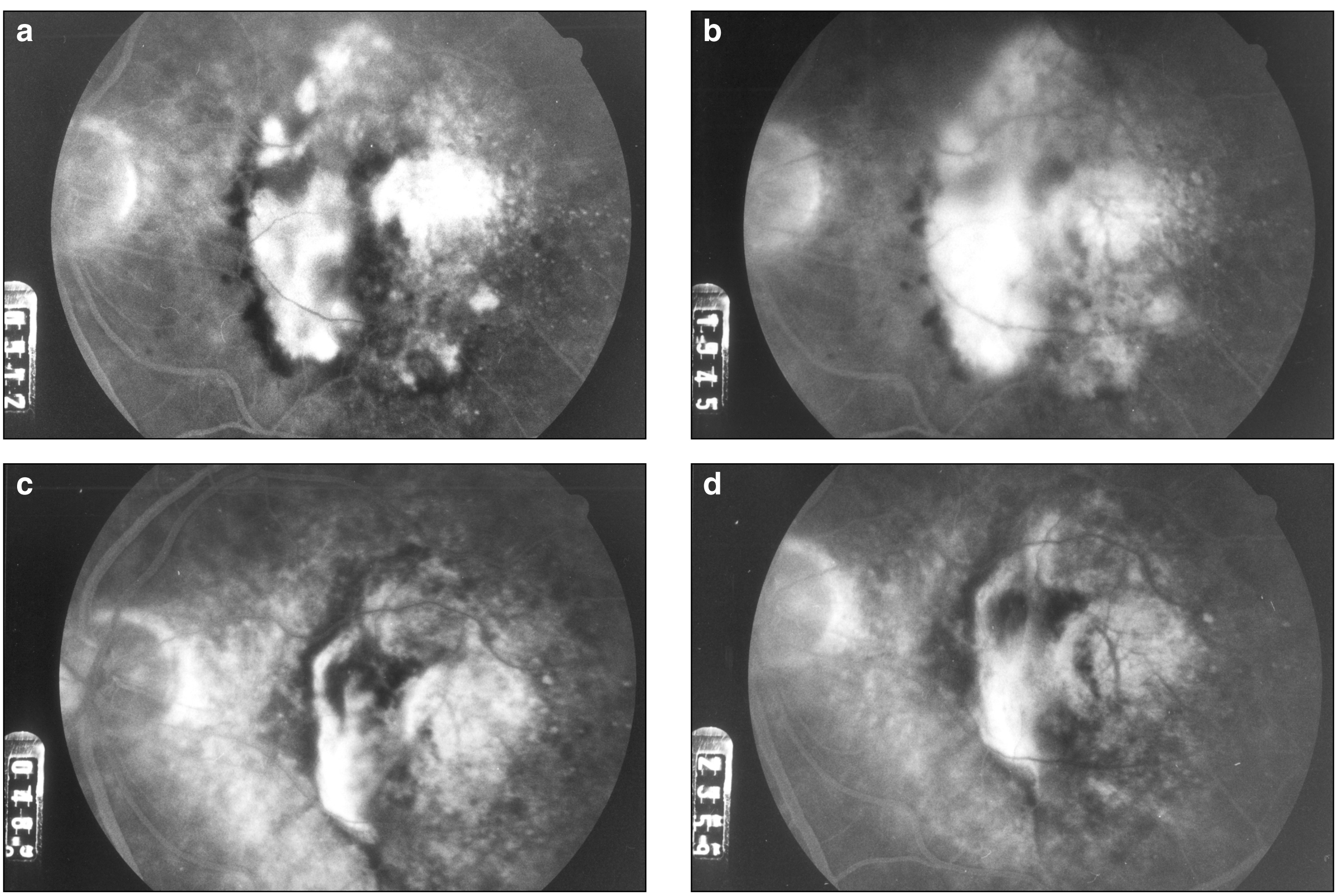

Fig. 5 - *Fluorescein angiograms of an irradiated eye in which the CNVM was too poorly defined to be evaluated by planimetry. Subjective evaluation, however, considered both the size and the leakage of the membrane had diminished at 12-month follow-up.* ***a)*** *The baseline early-phase angiogram;* ***b)*** *the corresponding late-phase angiogram;* ***c)*** *the 12-month early-phase angiogram;* ***d)*** *late-phase angiogram.*

Delineation of the hyperfluorescent CNVM areas in angiograms from eyes with exudative AMD is not easy, especially in eyes with occult CNVM. Prior reference to standard frames and masked evaluation is vital for a reliable result. In this study we compared planimetry with masked subjective grading of the angiograms. The two methods gave similar results. The subjective grading method could also reflect the delayed regression of CNVM in some patients. In seven eyes the area of hyperfluorescence was too scattered for planimetry to be done, but the graders were still able to classify the angiograms in a way that correlated with clinical drying of the maculae.

Difficulties in evaluating the CNVM response to radiation therapy in some previous studies may be connected with the fact that there really was no significant change. After ^{90}Sr irradiation the CNVM either continued to grow, clearly decreased in size or totally disappeared. The differences were probably sufficiently clear to allow them to be documented equally with masked planimetry and subjective grading.

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