RADIOTHERAPY TREATMENT OF AGE-RELATED SUBFOVEAL NEOVASCULAR MEMBRANES IN PATIENTS WITH GOOD VISION

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SUMMARY

This prospective study investigated whether low-dose ionising radiotherapy preserved vision and caused membrane regression in patients with age-related subfoveal neovascular membranes (SFNVMs) or vascularised pigment epithelial detachments (PEDs) and relatively good initial visual acuities. Twenty-five patients with initial Snellen acuities of 6/24 or better were treated with low-dose external beam radiotherapy. Of the patients with SFNVMs, visual acuities were maintained or improved in 58% at 6 months and 53% at 1 year. Neovascular membrane size was assessed by image analysis and showed some regression in 47% and 41% at 6 and 12 months respectively. These results suggest that patients with SFNVMs and good vision may benefit from radiotherapy, faring better than previous reports of the natural history of this condition. Conversely, patients with vascularised PEDs did not appear to benefit from radiotherapy. Only 17% maintained their vision at 1 year and 33% suffered retinal pigment epithelial tears. The results from patients with SFNVMs and good initial vision, excluding those with vascularised PEDs, are encouraging; however, any benefit from this treatment needs to be proven by controlled trials with long follow-up.

The visual prognosis for patients with age-related subfoveal neovascular membranes (SFNVMs) is poor, and as yet there are very limited treatment options. The only treatment which has been shown to give a better prognosis than the natural course of the condition is foveal ablation by laser photocoagulation;[1] however, this has not been widely implemented as there is only marginal long-term benefit at the cost of a significant deterioration in central vision immediately after laser therapy. The results of a previous pilot study on 19 patients suggest that low-dose ionising radiation to the macular region may improve the visual prognosis and cause membrane regression in two-thirds of patients with age-related SFNVMs at 1 year after treatment.[2] This study looked at patients with initial visual acuities of 6/24 or worse. We report a pilot study on a previously unreported group of patients, to investigate whether radiotherapy can preserve vision if used to treat age-related SFNVMs and vascularised pigment epithelial detachments (PEDs) in patients with relatively good initial visual acuities of 6/24 or better.

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PATIENTS AND METHODS

All consecutive patients presenting to the Sussex Eye Hospital between June 1993 and July 1994 with visual deterioration from age-related SFNVMs or vascularised PEDs were considered for the study.

Selection Criteria

The selection criteria for inclusion in the study were:

1. Presence of a well-defined age-related SFNVM or a vascularised PED identified by fluorescein angiography.
2. History of progressive deterioration in vision within the past 3 months.
3. Snellen visual acuity of 6/24 or better.
4. Patient willing and able to have treatment and follow-up fluorescein angiograms at 3, 6 and 12 months.
5. Absence of concomitant macular disease and systemic vascular diseases such as diabetes and uncontrolled hypertension.

Initial Assessment and Treatment

All patients underwent a full ophthalmic examination, including assessment of lens opacities and fundus examination with a 78 dioptre lens after pupil dilatation. Best corrected Snellen visual acuity was measured using an internally illuminated Snellen chart at 6 metres. Fluorescein angiography was performed and the diagnosis of SFNVM or vascularised PED was made by a single observer (A.G.C.). Hertel exophthalmometer and axial length readings were taken for each patient to calculate the distance of both the posterior surface of the lens and the retina from the lateral orbital margin to the nearest millimetre. These measurements were used to enable the radiotherapy to be directed so that the 50% isodose curve lay well behind the lens, and the 90% isodose was situated on the macula. Patients were treated supine in a Perspex immobilisation shell using a single lateral field angled at 7° posteriorly to minimise the dose to the ipsilateral lens and the exit dose to the contralateral eye. Beam position was marked on the immobilisation shell with reference to the lateral orbital margin, and check films were taken on the radiotherapy simulator to record beam position. Field sizes were 4 × 4 cm or 4.5 × 4.5 cm, and an applied dose of 11–12.5 Gy was given in five fractions over 5 days using 6 MV photons.

Follow-up

At each follow-up visit (3, 6 and 12 months) best corrected Snellen visual acuity was measured, a detailed ophthalmic examination was repeated, and fluorescein angiography was performed.

Image Analysis

Selected frames from early to mid-venous phase angiograms were subjected to image analysis (Confocal Technologies, Fenestra software) and the area occupied by the SFNVM defined. The area measured was that of the classical component of the SFNVM. We calculated the area of the SFNVM represented as the percentage of that recorded in the pre-treatment angiogram. Regression was defined as a 10% or greater decrease in the SFNVM size. Expansion was a 10% or greater increase in the membrane size. A recurrence was defined as an area of hyperfluorescence within, or at the margins of, an old lesion separate from the original SFNVM. A new lesion was when fluorescence appeared at a previously normal site.

RESULTS

Twenty-five eyes of 25 patients underwent treatment (Table I). Eleven patients (44%) were male and 14 (56%) were female. The age range was from 64 to 94 years, with an average of 76 years. Initial visual

Table I. Details of patients, initial visual acuities and angiographic changes during follow-up

Patient no.	Age (years)	Sex	Visual acuity				SFNVM size (as % of tre-treatment size)		
			Initial	3 months	6 months	12 months	3 months	6 months	12 months
Group A: SFNVM									
1	76	M	6/12	6/18	6/60	6/36	74	91	72
2	76	M	6/9	6/9	6/9	6/9	88	0	0
3	74	M	6/12	6/24	6/18	6/18	102	90	103
4	75	F	6/18	6/60	6/36	6/36	108	293	204
5	78	F	6/12	6/18	6/18	6/12	182	157	179
6	73	M	6/18	6/12	6/60	6/36	83	49	200
7	77	M	6/24	DNA	6/36	6/24	DNA	64	88
8	87	F	6/18	6/36	6/60	6/18	52	27	15
9	69	F	6/24	6/18	6/24	6/60	99	92	NA
10	83	F	6/18	6/9	6/9	6/12	100	89	87
11	74	F	6/18	6/36	6/60	4/60	84	108	138
12	94	M	6/24	6/60	6/36	3/60	99	149	Ref
13	71	F	6/12	6/12	6/9	6/9	34	32	Same
14	74	F	6/24	6/24	6/18	6/36	22	88	Reg
15	73	F	6/18	6/9	6/18	6/6	82	76	Same
16	64	M	6/12	6/12	6/24	6/60	182	256	Exp
17	78	F	6/12	6/12	6/12	6/60	107	127	Reg
18	78	M	6/18	6/18	6/36	6/18	70	81	Same
19	78	F	6/18	6/60	6/36	6/36	79	107	Exp
Group B: Vascularised PED									
20	81	F	6/12	6/24	3/60	3/60	Exp		
21	79	M	6/24	6/24	6/18	1/60	Exp		
22	70	F	6/18	6/12	6/18	6/36	Exp		
23	82	M	6/24	2/60	5/60	6/60	RPE rip		
24	68	F	6/24	DNA	1/60	1/60	RPE rip		
25	73	M	6/24	6/12	6/18	6/12	Same		

DNA, did not attend; Ref, refused fluorescein angiogram; NA, not analysed as angiogram lost; Exp, expanded (no image analysis); Reg, regressed (no image analysis); Same, unchanged (no image analysis).

Table II. Group A: visual acuity after radiotherapy in patients with SFNVM

	Months after treatment		
Visual acuity	3 months (18 eyes)	6 months (19 eyes)	12 months (19 eyes)
Improvement by 2 or more lines	2 (11%)	1 (5%)	1 (5%)
Same (within 1 line of initial visual acuity)	10 (56%)	10 (53%)	9 (47%)
Loss of 2 or more lines	6 (33%)	8 (42%)	9 (47%)

acuities were 6/9 in 1 patient (4%), 6/12 in 7 (28%), 6/18 in 9 (36%) and 6/24 in 8 (32%). Exophthalmometry and axial length readings established that the macula was situated between 2 and 11 mm behind the lateral orbital margin, at an average of 6 mm. Nineteen patients had age-related SFNVMs (group A), and 6 had large PEDs, with evidence of neovascularisation (group B). These groups were analysed separately. All patients had 12 months follow-up.

Group A (SFNVMs)

Visual Acuity

Visual acuities after radiotherapy are shown in Table II. At 3 months follow-up pre-treatment acuity was maintained or improved (by two or more lines) in 12 patients (67%), and decreased in 6 patients (33%). At 6 months follow-up pre-treatment acuity was maintained or improved in 11 patients (58%), and decreased in 8 patients (42%). At 12 months, 10 patients (53%) had maintained or improved their initial visual acuity, and 9 (45%) had lost two or more lines. Severe visual deterioration to 6/60 or worse occurred in 4 patients (21%) at 6 months and 5 patients (26%) at 12 months. It is of note that 53% of patients had maintained or improved their vision by 12 months.

Fluorescein Angiogram Appearance

The change in SFNVM size on fluorescein angiography is summarised in Table III. At 3 months after treatment the neovascular membrane had regressed in 10 patients (59%), was unchanged in 4 patients (24%), and expanded in 3 (18%). At 6 months follow-up the SFNVM had regressed in 9 patients (47%), was unchanged in 5 (26%), and expanded in 5 (26%). At 12 months the SFNVM had regressed in 7 patients (41%), was unchanged in 4 patients (24%), and expanded in 6 (35%). Fig. 1 illustrates marked regression of a membrane at 12 months, after an initial slight enlargement at 6 months. Fig. 2 demonstrates expansion of a membrane at 6 and 12 months. The average percentage regression was 44% at 6 months, and 48% at 12 months. The average percentage expansion was 96% at 6 months, and 80% at 12 months. Only one membrane regressed completely. A recurrence was seen in 1 patient (6%) at 6 months and 2 (12%) at 12 months after treatment (Fig. 3). A new lesion was seen in 2 patients (12%) at 1 year.

Table III. Fluorescein angiogram appearance after radiotherapy

	Months after treatment		
Progression of SFNVM	3 months (17 eyes)	6 months (19 eyes)	12 months (17 eyes)
Regressed	10 (59%)	9 (47%)	7 (41%)
Same size	4 (24%)	5 (26%)	4 (24%)
Expanded	3 (18%)	5 (26%)	6 (35%)

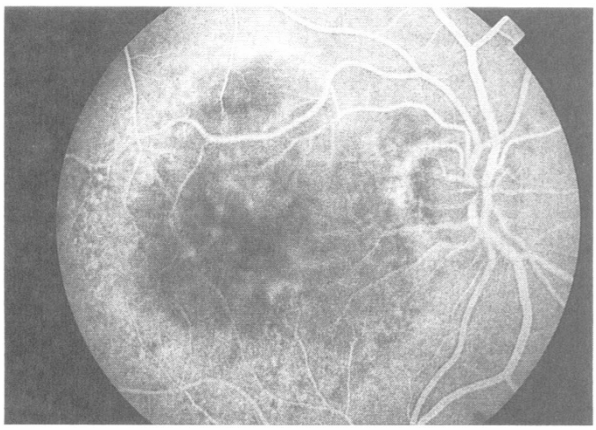
Group B (Vascularised PEDs)

Visual Acuity

The follow-up visual acuities after treatment are presented in Table IV. At 3 months follow-up 3 patients (60%) had maintained their pre-treatment visual acuities, whereas 2 patients (40%) had lost two or more Snellen lines of vision. At 6 months follow-up 3 patients (50%) had maintained their vision, whereas 3 patients (50%) had lost two or more lines. At 12 months only 1 patient (17%) maintained their initial visual acuity, and 5 patients (83%) lost two or more lines. None of the patients with vascularised PEDs showed a visual improvement at 3, 6 or 12 months after treatment. Severe visual deterioration to 6/60 or worse occurred in 3 patients (50%) at 6 months and 4 patients (67%) at 12 months.

Fluorescein Angiogram Appearance

It was not possible accurately to measure the area in vascularisation within the PED in these patients for two reasons: firstly, it was not possible for the image analysis program to distinguish between hyperfluorescence from a neovascular membrane and that from the PED itself. Secondly, there were areas of hypofluorescence within the PED, caused by masking from a combination of luteal pigment and turbid fluid, and this hypofluorescence caused inaccuracies in the measurement of the PED total area. Two patients (33%) suffered retinal pigment epithelial (RPE) tears, so that image analysis of the neovascularisation was not possible (as the window defect obscured the fluorescence from the neovascular membrane). One patient showed a decrease in the area of neovascularisation at 6 months, but this expanded at 12 months. One patient showed no increase in the size of neovascularisation at 6 or 12 months follow-up. The remaining 2 patients with vascularised PEDs exhibited an increase in the area of neovascularisation at 6 and 12 months after treatment (although this was not quantified), with 1 patient demonstrating a recurrent neovascular membrane at 1 year.



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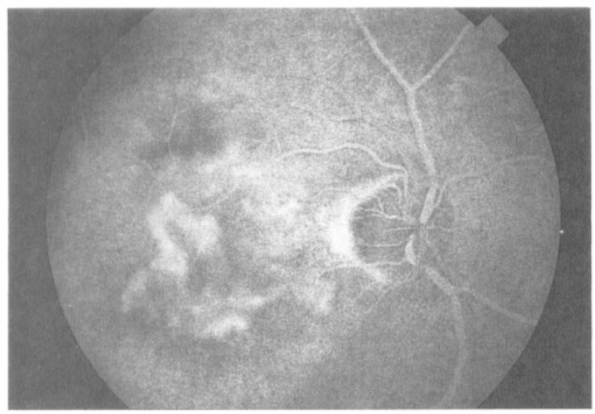

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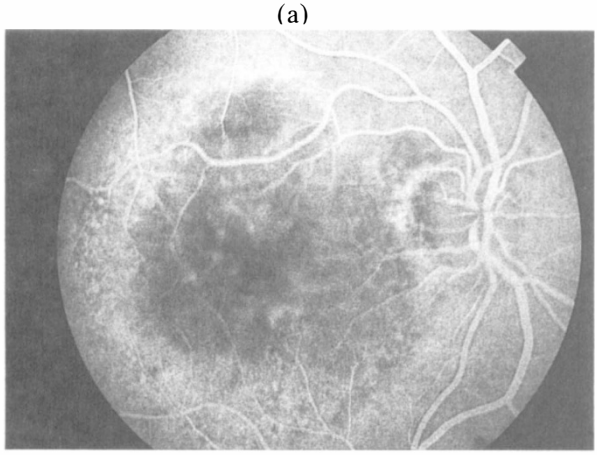

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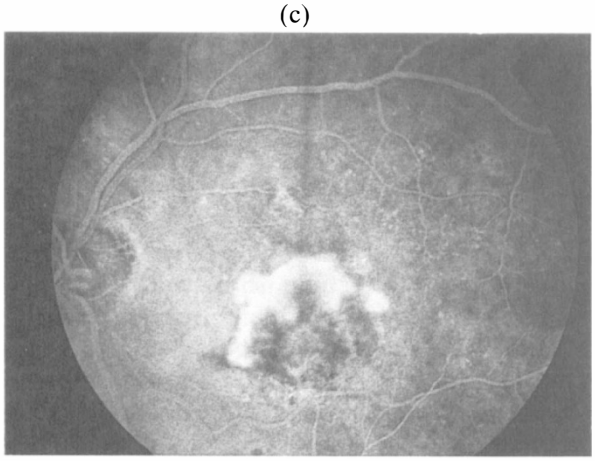
Fig. 1. *(a) Pre-treatment fluorescein angiogram showing a 1.5 disc diameter classical subfoveal neovascular membrane (SFNVM). (b) Angiogram at 6 months post-radiotherapy showing a slight enlargement of the membrane, which is less hyperfluorescent. (c) Angiogram at 12 months after radiotherapy demonstrating marked regression of the SFNVM.*



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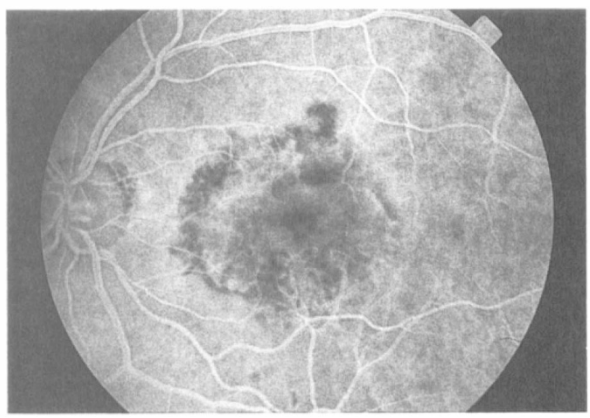

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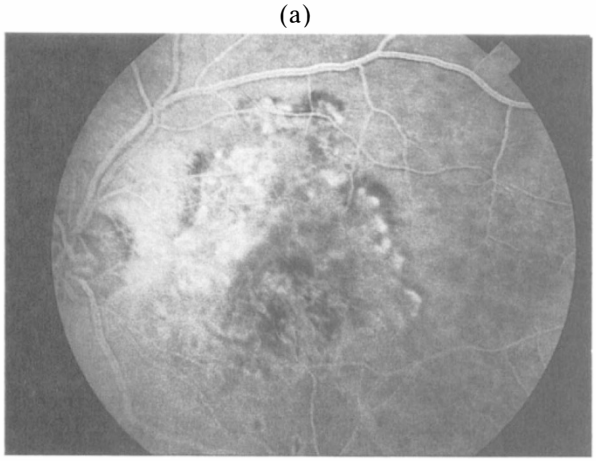
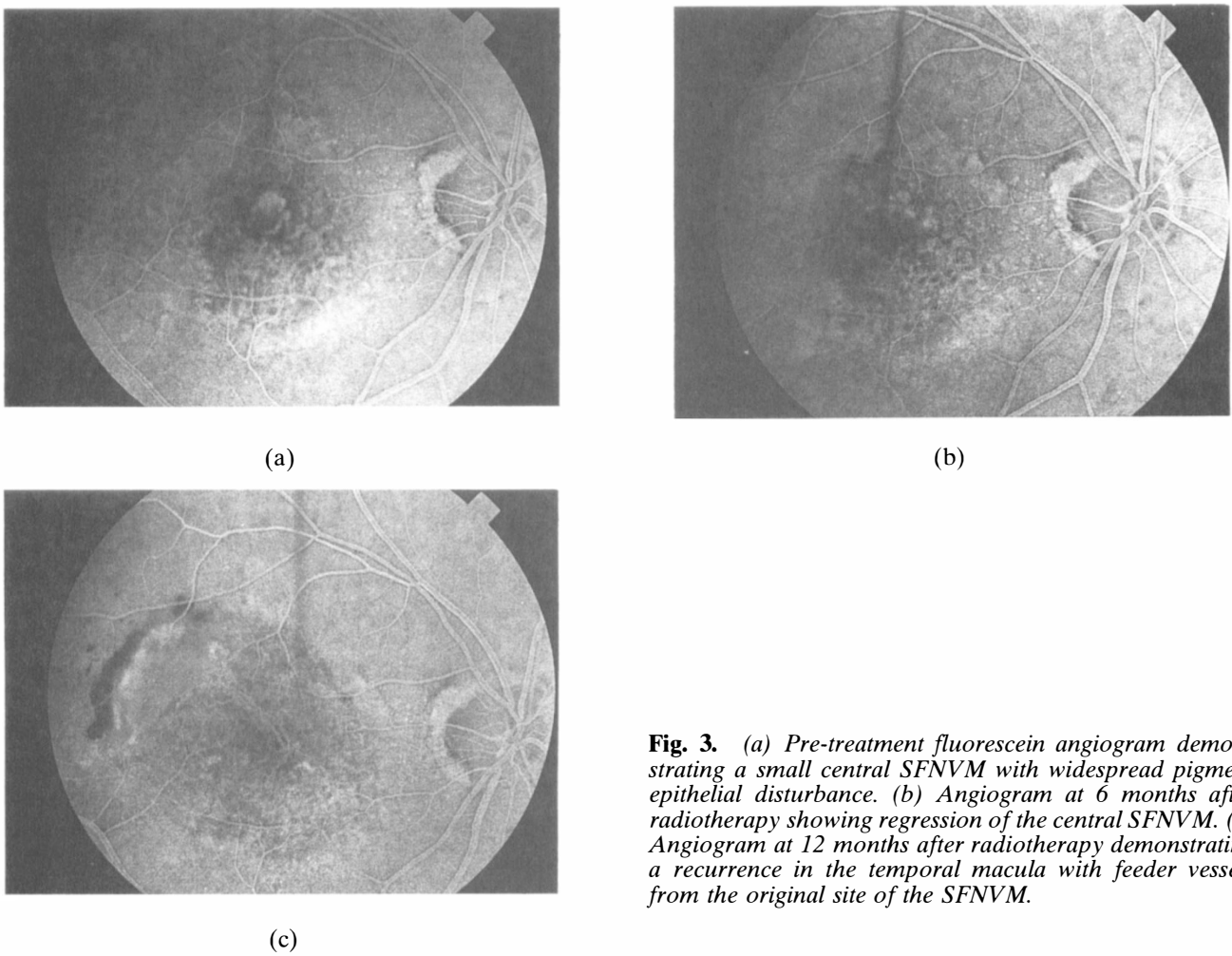


(c)

Fig. 2. *(a) Pre-treatment fluorescein angiogram showing a 2 disc diameter classical SFNVM. (b) Angiogram at 6 months post-radiotherapy demonstrating membrane expansion. (c) Angiogram at 12 months after treatment showing further expansion of the SFNVM.*



(a) (b) (c)

Fig. 3. *(a) Pre-treatment fluorescein angiogram demonstrating a small central SFNVM with widespread pigment epithelial disturbance. (b) Angiogram at 6 months after radiotherapy showing regression of the central SFNVM. (c) Angiogram at 12 months after radiotherapy demonstrating a recurrence in the temporal macula with feeder vessels from the original site of the SFNVM.*

DISCUSSION

The mature retina is relatively radioresistant to low-dose radiation applied in small treatment fractions, whereas vascular endothelial cells are far more sensitive. Low doses of radiation have been shown to cause regression of ocular choroidal haemangiomas,[3] and to decrease the neovascular proliferation that occurs in healing ocular wounds after penetrating injury.[4] The radiosensitivity of retinal vascular endothelial cells is thought to be attributable to higher rates of proliferation, nuclear chromatin conformation, antioxidant status and environment.[5] The effect of radiotherapy on proliferating endothelial cells is thought to be only one of the mechanisms through which radiotherapy has its beneficial effect on the progression of choroidal neovascularisation. Radiotherapy also has an attenuating effect on the inflammatory response, which is thought to play a role in the development of choroidal neovascularisation, so that the stimulus for the formation of a large disciform scar is reduced.[6]

Table IV. Group B: visual acuity after radiotherapy in patients with vascularised PEDs

	Months after treatment		
Visual acuity	3 months (5 eyes)	6 months (6 eyes)	12 months (6 eyes)
Improvement by 2 or more lines	0	0	0
Same (within 1 line of initial visual acuity)	3 (60%)	3 (50%)	1 (17%)
Loss of 2 or more lines	2 (40%)	3 (50%)	5 (83%)

Table V. Comparison of visual acuities in treated eyes and natural course of SFNVMs, in patients with initially good acuities of 20/100 or better

Visual acuity	Untreated	Treated
	(Guyer *et al.*)[7]	
Loss of 4 MPS lines at 6 months[a]	42%	21%
Loss of 6 MPS lines at 6 months[b]	28%	5%
Loss of 4 MPS lines at 12 months[a]	49%	21%
Loss of 6 MPS lines at 12 months[b]	33%	21%
	(MPS Group)[1]	
Remained at 20/100 or better at 12 months	21%	47%
Deteriorated to 20/200 or worse by 12 months	66%	26%

[a]Loss of 4 MPS lines is equivalent to a 2.5-fold increase in the visual angle.
[b]Loss of 6 MPS lines is equivalent to a 4-fold increase in the visual angle.

The first publication on the use of low-dose radiation to treat subfoveal choroidal neovascular membranes appeared in 1992; however, no beneficial effect was demonstrated at the very low doses used (8 Gy).[7] Chakravarthy *et al.*[2] used a slightly higher dose of ionising radiation (10 or 15 Gy) to treat patients with age-related SFNVMs and poor initial visual acuities of 6/24 or worse. Vision was maintained or improved by at least one Snellen acuity in 78% and 63% of patients at 6 and 12 months, respectively (and by at least two lines in 84% and 68% of patients at 6 and 12 months, respectively). In our study we treated a different group of patients, those with age-related SFNVM and relatively good initial visual acuities of 6/24 or better, to investigate whether radiotherapy can preserve vision. In addition we included vascularised PEDs. We showed that in patients with SFNVMs, excluding vascularised PEDs, vision was maintained or improved by at least two Snellen lines in 58% of patients at 6 months and 53% at 12 months. Significant neovascular membrane regression occurred in 68% of Chakravarthy's patients at 6 months compared with 47% of our patients with SFNVMs. At 1 year 77% of Chakravarthy's treated patients showed membrane regression, compared with 41% of our patients. Membrane size was stabilised in a further 24% of our patients.

Our results are not as good as those presented by Chakravarthy *et al.*, and there are a number of explanations for this difference. Firstly, there was an average delay of 6 weeks between the diagnostic fluorescein angiogram and the commencement of radiotherapy, whereas angiography was performed within 96 hours of commencing treatment in Chakravarthy's study. This time interval was due to delays caused by the development and assessment of the angiograms, referral to the radiotherapy department and time for the shells to be made. It is well recognised that neovascular membranes can grow rapidly, with accompanying visual deterioration, and so the baseline acuity and angiographic measurements are not truly representative of visual acuity and angiographic status at treatment. This would mean that the follow-up measurements underestimate the actual effect of the treatment. Secondly, we treated a different group of patients with relatively good initial visual acuities, and so the number of Snellen lines lost appears to be greater, as these patients have more lines to lose. The membranes were probably at an earlier, more active stage in the disease process, before they had reached a stable late phase (with corresponding poor acuities), and so their response to radiotherapy may appear less dramatic.

A final possible source of error was that we did not plan the radiotherapy with the aid of CT scanning, which was used in Chakravarthy's study. The decision not to perform CT scans was taken to avoid the inevitable delay in treatment this would have caused. To assess the accuracy of our method we initially performed CT scans on selected patients in their immobilisation shells, and these were used to check the dose distribution produced by our technique. Fig. 4 shows an example of the resultant dose distribution through the central axis of the beam, produced with the aid of CT scanning and computer-assisted calculations of the predicted absorbed dose levels (isodoses). The dose at the macula is seen to be well within the 90% isodose, confirming that the technique was satisfactory.

Natural history studies have shown that the visual prognosis for patients with age-related SFNVM and relatively good initial visual acuities is particularly poor.[1,8] Guyer *et al.*[8] showed that of 36 patients with initial acuities of 20/100 or better (between 6/24 and 6/36), 49% had lost four or more lines of vision and 33% had lost six lines, after 1 year (compared with 21% and 21%, respectively, of our patients). The Macular Photocoagulation Study (MPS) Group[1] showed that of 47 untreated patients with small or medium SFNVMs (up to 2 disc diameters) and initial good acuities of 20/100 or better, only 21% maintained good visual acuities at 1 year, compared with 47% of our patients. This improvement in visual prognosis after radiotherapy is statistically significant (chi-squared $p = 0.034$). Of the untreated MPS Group patients 66% suffered a deterioration in vision to 6/60 or worse at 1 year,[1] compared with only 26% of our patients. Again the difference is statistically significant (chi-squared $p = 0.003$). The MPS Group also showed that over 90% of untreated small or medium lesions expand by 12 months, whereas only 35% of our patients had an increase in membrane size. Table V compares the visual out-

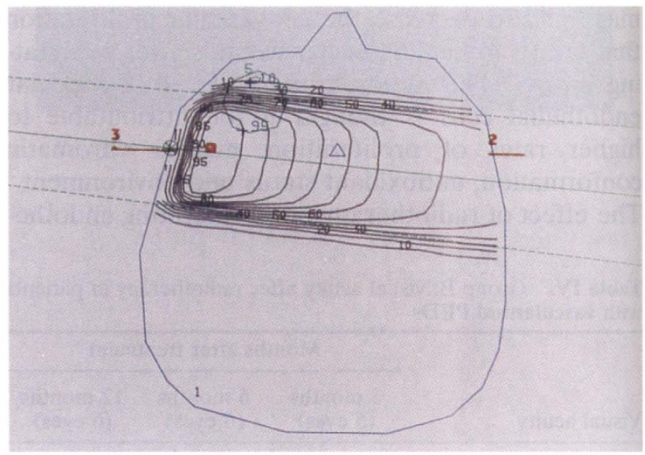


Fig. 4. *Dose distribution through the central axis of the radiotherapy beam, showing that the macula is well within the 90% isodose curve. The lens received less than 20% of the maximum absorbed dose. The number 3 marks the beam centre at the surface.*

come of our treated eyes with those of the natural course of SFNVMs as reported by Guyer *et al.* and the MPS Group. The comparison of patients from different centres is problematic; however, the untreated patients from these studies were very similar to our patients (with respect to age, sex, initial visual acuities and SFNVM size). The larger proportion of treated eyes that maintained acuities after radiotherapy and the substantially lower percentage that lost four or more lines or deteriorated to 6/60 or worse, strongly suggests that radiotherapy treatment is more favourable than the natural course of SFNVMs.

There are a number of problems with using image analysis to measure the membrane size. The difficulties with the measurement of neovascularisation associated with PEDs have already been discussed. The measurements depend on a personal assessment of what and where the membrane is, and this is obviously open to observer error. The presence of haemorrhage leads to an underestimation of membrane size. Subsequent measurements do not take account of decreases in fluorescence, which is suggestive of a less active membrane, but merely measure membrane area. We compared our image analysis results with a clinical masked assessment of angiographic membrane progression by three clinicians, and found that they largely agreed. The number of membranes considered to be expanding was the same at 12 months. However, the clinicians assessed the majority of membranes as being unchanged in size rather than regressing, and indeed on image analysis the amount of regression is often small.

The Belfast pilot study[2] included patients with SFNVMs and small areas of associated PED, with no reports of adverse outcome. In this study we included patients with vascularised PEDs. The outcome after radiotherapy in this group of patients was worse than for those with SFNVM. Two patients (33%) had large RPE tears, and deterioration in vision from 6/24 to 6/60 and 1/60. Three patients with vascularised PEDs showed a deterioration in vision (by more than two lines in 2 patients and four lines in the other) and an increase in membrane size. Only 1 patient maintained vision and showed no increase in membrane size.

Several studies have shown that development of choroidal neovascularisation in patients with age-related PEDs is associated with a poor visual outcome. Poliner *et al.*[9] showed that 89% of patients with PEDs and associated choroidal neovascularisation progressed to vision of 6/60 or worse after 1 year, and 76% lost two or more Snellen lines. Singerman *et al.*[10] looked at 27 patients with vascularised PEDs and initial visual acuities of 6/24 or better. After an average of 2.2 years 22% of patients maintained their initial acuities, compared with 17% of our treated patients after 1 year. Seventy-eight per cent lost two or more lines of Snellen acuity, compared with 83% of our patients. The comparison of different patient groups from different treatment centres is problematic, especially when the groups are small and the length of follow-up different, but it appears that treated patients do just as badly as the natural course of the condition. Radiotherapy does not appear to have the same beneficial effect on vascularised PEDs as on SFNVM without significant detachment. This may be because radiotherapy has no effect on the abnormal hydrophobicity of Bruch's membrane (thought to be due to the deposition of neutral lipids) that causes the pigment epithelium to detach as sub-RPE fluid accumulates.[11]

Tearing of the RPE is a relatively common complication of PEDs, occurring in at least 10% of PEDs.[12,13] Not surprisingly an RPE rip is associated with severe visual loss, as was seen with the 2 patients who developed RPE tears during follow-up. It is possible that radiotherapy increases the incidence of RPE tears by causing contraction as the membrane regresses, putting tension on the junction between detached and flat retina.

None of the treated patients showed any complications of radiotherapy; however, the follow-up period was short. Their most recent fluorescein angiograms had no signs of microvascular disease, and they had no increase in lens opacification. The doses used are considered to be well within the 'safe dose' at which the chance of causing radiation retinopathy is very unlikely.[5]

This pilot study suggests that patients with age-related subfoveal neovascular membranes and good vision may benefit from radiotherapy, with an improvement in visual prognosis compared with the natural course of the condition. However, the results do not demonstrate a dramatic regression of the membranes or preservation of vision, and any benefit from this treatment needs to be proven by controlled trials with long follow-up. There appears to be no benefit in treating vascularised PEDs.

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Key words: Radiotherapy, Age-related macular degeneration, Subfoveal, Fluorescein angiography, Pigment epithelial detachment.

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