

Long term results of radiotherapy for subfoveal choroidal neovascularisation in age related macular degeneration

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Abstract

Background/aims—Radiotherapy has been proposed as an alternative treatment for patients with subfoveal choroidal neovascularisation (CNV) that is untreatable according to macular photocoagulation study guidelines. This prospective study was designed to evaluate whether radiotherapy may affect the functional and anatomical outcome in a large cohort of patients affected by subfoveal CNV, with a follow up period up to 24 months.

Methods—212 patients (231 eyes) with newly diagnosed subfoveal CNV not amenable to laser therapy were included in this study. Two radiotherapy methods, the lateral beam technique (6 MV, 20 Gy in five fractions) and lateral arc therapy (25 MV, 16 to 20 Gy, in four or five fractions), were used. Comparisons of best corrected visual acuity (VA), fluorescein (FA) and indocyanine green (ICG) angiography, at inclusion and 6, 12, 18, and 24 months after radiotherapy were performed using univariate analysis.

Results—A VA improvement of two or more lines was observed in 34% at 12 months, 31% at 18 months, and 32% of the eyes at 24 months. Paired comparisons of CNV areas in FA and ICG showed no significant change between baseline and each visit. However, 12 and 18 months after treatment, 47% of the eyes showed a decrease of 10% or more in CNV size both in ICG and FA. Radiation side effects included radiation retinopathy (eight eyes), optic neuropathy (four eyes), choroidal vasculopathy (five eyes), and branch retinal vein occlusion (three eyes). **Conclusion**—Compared with the natural course of subfoveal CNV, the results of this prospective study suggest that radiotherapy could stabilise visual and anatomical outcome in selected cases.

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Age related macular degeneration (AMD) is the leading cause of visual loss in industrialised countries.^{1,2} Legal blindness in AMD is related to choroidal neovascularisation (CNV) in 90% of these patients.³ Laser photocoagulation is the effective treatment for visible CNV located at 200 µm or more from the centre of the foveal avascular zone.⁴⁻⁷ Nevertheless, laser photocoagulation results in destruction of the overlying retina and therefore significant visual loss

immediately following therapy.⁸ Besides, laser therapy of classic neovascularisation associated with occult CNV has been considered not beneficial.⁹ Ionising radiation has been reported as an alternative treatment of subfoveal CNV, either by external beam¹⁰⁻¹⁹ or by plaque radiotherapy.²⁰ Comparisons of results are difficult because radiation dose levels.²¹ The purpose of this study was to investigate whether radiotherapy may affect functional and anatomical outcome in a large cohort of patients affected by subfoveal CNV, with a 12-24 month follow up period.

Patients and methods

Two hundred and twelve patients (231 eyes) with age related subfoveal CNV, not eligible for laser photocoagulation treatment according to macular photocoagulation study guidelines,⁶ were enrolled in this prospective study between September 1995 and October 1997.

ELIGIBILITY CRITERIA

Patients of 55 years of age or older with newly diagnosed active subfoveal CNV not amenable to laser therapy were included in this study. All the patients complained of metamorphopsia or recent progressive decrease of visual acuity (VA), with a delay equal to or less than 6 months. Diagnosis of subfoveal CNV membranes was confirmed using fluorescein (FA) and indocyanine green (ICG) angiographies. Three subgroups of patients were defined: classic CNV without occult, occult CNV without classic, and classic associated with occult CNV. Radiotherapy was delivered after the patient's informed consent.

EXCLUSION CRITERIA

Patients were excluded for any of the following reasons: CNV associated with myopia or other macular disease, CNV previously treated by laser therapy, systemic vasculopathy such as diabetes mellitus or uncontrolled systemic hypertension, or previous radiotherapy for ocular or cerebral malignancies.

RADIOTHERAPY

Two radiotherapy methods were used—the lateral beam and the arc therapy techniques. The lateral beam technique, previously described by Chakravarthy *et al*,¹⁰ used a single 6 MV photon beam with hemicircular collimation. The 95% isodose curve dimensions were 30 and 11 mm, respectively. To avoid lens irradiation, the anterior front of the 50% isodose was

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Table 1 Visual acuity and frequency of distorted vision at baseline, 6, 12, 18, and 24 months

	Initial visit No (%) of eyes	At 6 months No (%) of eyes	At 12 months No (%) of eyes	At 18 months No (%) of eyes	At 24 months No (%) of eyes
Visual acuity:					
< 20/200	50/231 (21.6)	45/231 (19.4)	31/154 (20.1)	21/94 (22.3)	11/55 (20)
20/200–20/50	144/231 (62.4)	137/231 (59.3)	90/154 (58.4)	47/94 (50)	29/55 (52.7)
20/40–20/25	37/231 (16)	49/231 (21.2)	33/154 (21.5)	26/94 (27.6)	15/55 (27.2)
Metamorphopsia:					
A <20/200	187/231 (80.9)	81/231 (35)	33/154 (21.4)	14/94 (14.8)	10/55 (18.1)
A ≥20/200	28/231 (12.1)	15/231 (6.5)	6/154 (3.9)	3/94 (3.2)	1/55 (1.8)
	159/231 (68.8)	66/231 (28.5)	27/154 (17.5)	11/94 (11.7)	9/55 (16.3)

positioned 2 mm behind the posterior capsule. In 72 eyes, 20 Gy were delivered in five fractions, on 5 consecutive days (effective dose of 30 Gy).

The lateral arc therapy used a 25 MV photon minibeam in 159 eyes. This method delivered irradiation with a high energy photon beam superimposed on orbital computed tomography scan images. Beam diameter varied between 14 and 18 mm and was adjusted according to the CNV area measured on FA and ICG images. The total dose of 16–20 Gy (in four or five fractions, respectively)—that is, an effective and equivalent dose of 24 and 30 Gy respectively, was delivered on the pathological macular area. Beam distribution affected less than 5% of the lens and of the contralateral ocular structures.

Laser treatment was performed in the following two cases: when choroidal telangiectasia were diagnosed on ICG angiographies during follow up; and when an increase of over 20% in CNV area was noted on FA and ICG images, with VA less than 20/200.

CLINICAL EVALUATION

Baseline data were age, best corrected VA, Amsler test, biomicroscopic findings, intraocular pressure, fluorescein and ICG angiographies. Best corrected VA measured on the early treatment diabetic retinopathy study chart²² and presence of metamorphopsia were recorded at the initial examination and at visits 6, 12, 18, 24 months after radiotherapy. Visual acuity was considered as improved if there was an increase of two lines or more.^{9 13} Mean VA was calculated using logMAR values. At each visit, contrast sensitivity of the treated eye was measured using the Pelli–Robson letter chart.²³ The test was performed in photopic conditions, with best correction, the chart at a distance of 1 metre. Improvement was defined as progression of contrast sensitivity of at least one log step on the Pelli–Robson chart.

The 46 patients with bilateral subfoveal AMD and who underwent radiotherapy in the second involved eye answered a visual function questionnaire 18 months after treatment.

FLUORESCEIN AND ICG ANGIOGRAPHY

FA and ICG angiographies were performed before radiation therapy, 6, 12, 18, and 24 months after radiotherapy. Digital angiographies were obtained with the Topcon angiograph. CNV areas were measured both in FA and ICG late phase images with the IMAGE-NET software. Macular photocoagulation study criteria⁹ were used to classify the CNV in angiographic images. Presence of pigment epi-

thelial detachment (PED), exudates, haemorrhages, and retinal pigment epithelium atrophy was recorded. CNV size evolution was assessed using the following ratio: [(final area – initial area)/initial area] × 100. We used this ratio to analyse paired comparisons of CNV areas between two follow up visits. Results obtained with this analysis method were independent of the patient's refraction, and allowed assessment of CNV course. Changes of CNV area were thus considered significant when growth or reduction of at least 10% of the initial area was observed.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Science program (SPSS). Comparisons on qualitative factors before and after radiotherapy were analysed by χ^2 analysis (incorporating Yates's correction). The Wilcoxon matched pairs signed rank test was used to compare VA and angiographic CNV areas, at different follow up times. The arithmetic difference in VA was computed as: follow up – baseline (initial logMAR – final logMAR). Mean comparisons of VA and CNV areas were tested using the Mann–Whitney–Wilcoxon rank sum W test, considering the two radiotherapy techniques and the two CNV groups (occult *v* mixed). Follow up beyond 12 months was incomplete and tests were performed using case by case exclusion of missing data. *p* Values below 0.05 were regarded as significant using two tailed tests.

Results

Two hundred and twelve patients (231 eyes) were included in the study. There were 144 female (68%) and 68 male (32%) patients. The mean age of patients was 77 years (range 56–95 years). There were 116 right eyes (50.2%). In 145 patients (62.8%), the contralateral eye was already affected by AMD. At the scheduled follow up visits (6, 12, 18, and 24 months), data were available in 231, 154, 94, and 55 eyes, respectively. CNVs were classified as occult in 71.4% (165/231 eyes), mixed in 26% (60 eyes), and classic in 2.6% (six eyes).

VISUAL OUTCOME AT 6, 12, 18 AND 24 MONTH EXAMINATION

The distribution of VA and metamorphopsia at baseline and at the follow up visits are presented in Table 1. A statistical difference was found between initial VA and VA at each follow up visit. VA changes during the study are listed in Table 2. An improvement of two or more lines was observed in 31% at 18 months

Table 2 Visual outcome 6, 12, 18, and 24 months after radiotherapy

	At 6 months No of eyes (%)	At 12 months No of eyes (%)	At 18 months No of eyes (%)	At 24 months No of eyes (%)
Classic CNV group:				
Improved	3/6 (50)	3/5 (60)	1/2 (50)	1/2 (50)
Stable	2/6 (33.3)	0	0	0
Decreased	1/6 (16.7)	2/5 (40)	1/2 (50)	1/2 (50)
Occult CNV group:				
Improved	66/165 (40)	34/106 (32.1)	17/66 (25.7)	11/40 (27.5)
Stable	57/165 (34.5)	49/106 (46.2)	26/66 (39.4)	14/40 (35)
Decreased	42/165 (25.5)	23/106 (21.7)	23/66 (34.9)	15/40 (37.5)
Mixed CNV group:				
Improved	14/60 (23.3)	16/43 (37.2)	10/24 (41.7)	6/13 (46.1)
Stable	30/60 (50)	15/43 (34.9)	5/24 (20.8)	1/13 (7.8)
Decreased	16/60 (26.7)	12/43 (27.9)	9/24 (37.5)	6/13 (46.1)
Global results:				
Improved	83/231 (36)	53/154 (34.4)	29/94 (30.9)	18/55 (32.7)
Stable	89/231 (38.5)	64/154 (41.6)	31/94 (33)	15/55 (27.3)
Decreased	59/231 (25.5)	37/154 (24)	34/94 (36.2)	22/55 (40)

and 32.7% of the eyes at 24 months. At the same time, a significant loss was found in 36% and 40% of the eyes, respectively. The relative frequencies of improved or decreased VA were similar at 6, 12, 18, and 24 month visits. The percentage of patients complaining of metamorphopsia was statistically lower 6 and 12 months after radiotherapy ($p = 0.01$), and similar 18 and 24 months after compared with the baseline values (paired comparisons).

Visual outcome was compared in the classic, occult, and mixed CNV groups (Table 2. The difference of the logMAR between baseline and each visit was not statistically different in the occult CNV group compared with the

mixed CNV group. The number of patients with classic CNV was too small to allow any comparison.

At inclusion, PED was present in 36% (83/231) of the eyes. There was no statistical difference in mean VA at initial, 6, 12, and 18 month visits in patients with or without initial PED. Twenty four months after treatment the mean VA was lower in the group of patients initially diagnosed with associated PED ($p = 0.03$). The mean VA changes (final logMAR – initial logMAR) in these two groups of patients were similar at each visit.

Contrast sensitivity was measured in 44 consecutive patients included at the end of the study. Fifty per cent (22/44) and 37.5% (9/24) of the patients improved their contrast sensitivity at the 6 and 12 month follow up visits, respectively, compared with the initial data. However, these changes were not statistically significant.

CHANGES OF CNV SIZE AFTER RADIOTHERAPY

Paired comparisons of CNV areas in FA and ICG showed no significant change between baseline and each visit. Distribution of eyes with 10% or more reduction of CNV size compared with baseline values is presented in Figure 1. Both 12 and 18 months after treatment, 47% of the eyes showed 10% or more reduction of CNV size in FA as well as in ICG. When post-treatment measurements of CNV-size were normalised relative to the initial size (100%), the median size of CNV membranes in FA after 6, 12, 18, and 24 months was 93%, 77%, 100%, and 60%, respectively. In ICG, similar results were noted: 100% at 6, 12, and 18 months, and 74% at 24 months. When considering specifically the occult CNV group, the median size at 6, 12, 18, and 24 months was 93%, 80%, 103%, and 65% in FA and 98%, 90%, 85%, and 85% in ICG. In the mixed CNV group, the median size at the same times was 97% 70%, 83%, and 100% in FA, and 107%, 100%, 133%, and 60% in ICG.

RESULTS IN THE TWO RADIOTHERAPY GROUPS

At inclusion, there was no significant difference between the two groups of patients treated (lateral arc therapy and minibeam irradiation) in terms of age, sex, frequency of metamorphopsia, VA, and CNV areas (FA and ICG). During the course of the study, comparison of the two groups revealed no significant difference in VA and CNV area changes.

COMPLICATIONS FOLLOWING RADIOTHERAPY

Ocular complications occurring after radiation therapy are presented in Table 3. Four patients were diagnosed with homolateral optic neuropathy between 6 and 18 months after completion of radiotherapy. Extensive investigation found no detectable cause, and therefore it was considered that this occurrence was probably related to radiation therapy. In these cases, dose levels of 16 Gy in four fractions (one eye) and 20 Gy in five fractions (three eyes) were used. One patient with optic neuropathy recovered without specific treat-

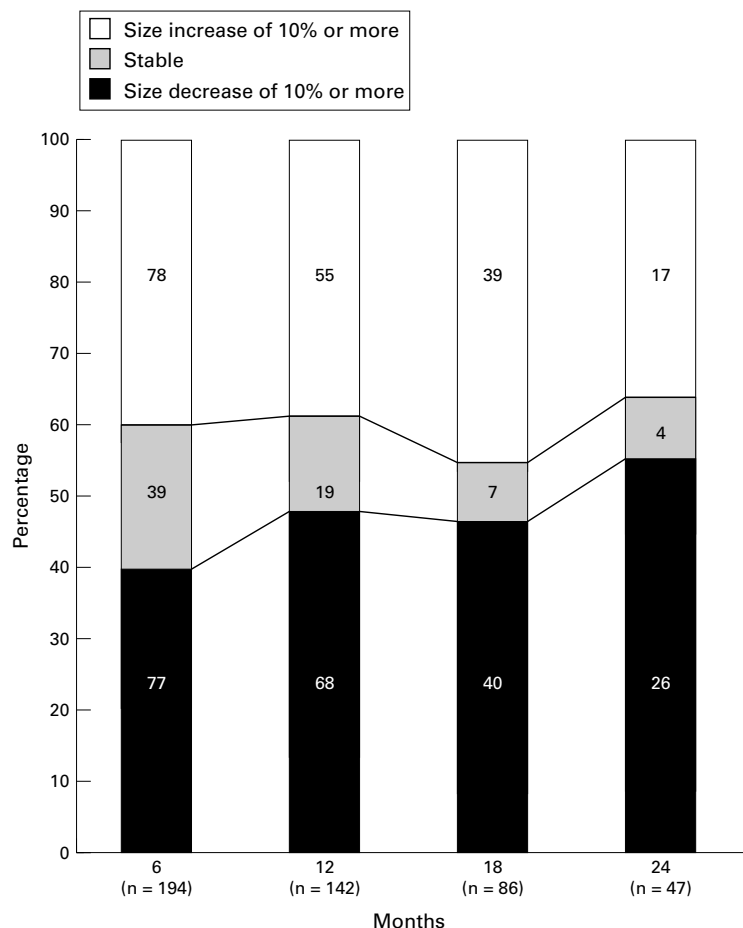


Figure 1 Distribution of eyes with decrease of CNV size in ICG angiography.

Table 3 Ocular complications after radiation therapy

Complications	At 6 months (n=231)	At 12 months (n=154)	At 18 months (n=94)	At 24 months (n=55)
Optic neuropathy	2 (1 LAT, 1 LBT)	1 (LBT)		1 (LAT)
Radiation retinopathy	1 (LAT)	2 (LAT)	3 (2 LAT, 1 LBT)	2 (LAT)
Choroidal telangiectasia	1 (LAT)	1 (LBT)	1 (LAT)	2 (1 LAT, 1 LBT)
Choroidal haematomas	2 (LAT)	2 (LAT)	2 (LBT)	1 (LBT)
Vitreous haemorrhage		1 (LBT)		
Branch retinal vein occlusion	1 (LBT)	2 (LBT)		

LAT=lateral arc therapy (159 eyes); LBT=lateral beam technique (72 eyes).

ment within 9 months and the three others had stable features 8 months after diagnosis.

Radiation retinopathy was diagnosed in eight patients treated with dose levels of 16 Gy in four fractions (four eyes) or 20 Gy in five fractions (four eyes). Choroidal telangiectasia were observed in ICG images in five patients when treatment with dose levels of 20 Gy in five fractions was performed. Branch retinal vein occlusion was diagnosed in three patients (one eye 16 Gy, two eyes 20 Gy) and there was no indication for photocoagulation. However, examination found no detectable cause of venous occlusion. Mild side effects such as ocular irritation, conjunctivitis, and dry eyes were noted with both radiotherapy techniques, and were treated with symptomatic drugs. No evolutive cataract occurrence was noted in this series. No rubeosis iridis, neovascular glaucoma, severe retinal haemorrhages, or subtotal exudative retinal detachment have been diagnosed in our patients during follow up.

Table 4 Visual function questionnaire (46 patients, 18 months after radiotherapy)

Question	Affirmative No of answers (%)
Subjective vision of the affected eye before radiotherapy was:	
Don't know	1 (2.2)
Good	1 (2.2)
Intermediate	12 (26.1)
Poor	12 (26.1)
Very poor	19 (41.3)
Blind	1 (2.2)
At the present time, how would you consider the subjective vision of the treated eye:	
Don't know	1 (2.2)
Good	8 (17.4)
Intermediate	8 (17.4)
Poor	19 (41.3)
Very poor	10 (21.7)
Blind	0
When considering the treated eye, do you experience any difficulties in reading small print in newspapers:	
Don't know	1 (2.2)
No problem	2 (4.3)
Some difficulty	4 (8.7)
Constant difficulty	9 (19.6)
Extreme difficulty	8 (17.4)
Impossible to read	22 (47.8)
When considering the treated eye do you experience any difficulties in usual handwriting:	
Don't know	1 (2.2)
No problem	1 (2.2)
Some difficulty	6 (13)
Constant difficulty	16 (34.8)
Extreme difficulty	7 (15.2)
Impossible to write	15 (32.6)
How would you assess the results in the treated eye:	
Don't know	1 (2.2)
Excellent	3 (6.5)
Satisfactory	17 (37)
Limited	12 (26.1)
Poor	10 (21.7)
Not beneficial	3 (6.5)
Would you advise this treatment to a close friend or relative affected by the same pattern of age related macular degeneration:	
Don't know	2 (4.3)
Definitely	30 (65.2)
Maybe	8 (17.4)
Probably not	4 (8.7)
Definitely not	2 (4.3)

VISUAL FUNCTION QUESTIONNAIRE AFTER RADIOTHERAPY

Of the 46 respondents (Table 4), 16 patients (34.8%) considered their vision after radiotherapy as "good" or "satisfactory". Furthermore, 22 patients (47.8%) found their vision significantly or moderately improved after treatment. However, as many as 22 patients (47.8%) experienced major difficulties in writing. At the inclusion, the VA of the fellow eyes not treated by radiotherapy was as follows: less than 20/200 in 34 eyes (74%) and between 20/200 and 20/50 in 12 eyes (26%). In these eyes, the mean CNV area (ICG images) was 11.1 disc area (SD = 7.1, range 0.4–29.7).

Discussion

The natural history of eyes with AMD has shown a poor visual prognosis, especially when CNV is associated.²⁴ The visual prognosis of eyes with AMD depends on the type of CNV both under observation and after laser treatment.⁹ Laser photocoagulation may be effective, but the functional and anatomical outcome depends on the CNV type as well as on its location. Therefore, it is considered that laser treatment of occult CNV should not be recommended.^{4 25} In a recent study, even treatment of classic CNV in eyes with classic and occult CNV was considered not to be beneficial.⁹

Radiotherapy has been used as an alternative treatment in selected cases of eyes with subfoveal CNV. However, the reported results are controversial.^{10–19 21} Comparisons between different studies are difficult, because size of CNV was measured most often on FA, and ICG was infrequently used. ICG analysis allows better assessment of CNV²⁶ and therefore was systematically performed in our series. Many authors—for example, Hart *et al*¹⁴ and Finger *et al*¹³ emphasised the need for a long follow up in a larger series in order to better assess radiotherapy. This study was therefore conducted with a minimum follow up period of 6 months and a large population has been evaluated at 12, 18, and 24 months.

The results reported in this study are slightly different from those of the first clinical trials. In our series of mainly occult and mixed CNVs, improvement of VA was noted in 34% and 32% of eyes at 12 and 24 months after treatment. However, statistical analysis showed no significant difference compared with baseline VA. In a previous study,¹⁰ 52% of 19 patients had improved vision (two or more lines) 12 months after treatment. In 81 eyes treated with palladium-103 ophthalmic plaque brachytherapy or external beam irradiation,¹³ VA of 79% of the eyes had one or more lines

improvement 3–18 months after treatment. Bergink *et al*¹¹ and Churchill *et al*¹⁸ reported stable VA in 60–70% of the patients at 12 month follow up. Nevertheless, these encouraging findings were not confirmed in other series. More recently, in a randomised controlled study in 75 patients, Bergink *et al*¹⁹ showed that 30% of treated patients (*v* 52% of control patients) had lost three or more lines of VA at 12 month follow up. In one study, VA improvement of one line or more at 12 months was reported in only 13.2% of patients.¹⁷ Even worse results were reported in another recent study¹⁶ in which only 7.2% of 111 eyes improved by two or more lines with follow up ranging between 1 and 3 years. When compared with historical control groups from the interferon study,²⁷ in which 16.2% of eyes had one or more lines VA improvement, our results suggest that 16–20 Gy radiotherapy (effective dose 24–30 Gy) could stabilise visual acuity at least up to 18 months after treatment.

Evaluation of visual performance may include not only morphoscopic VA but also other tests, such as contrast sensitivity. This test is more appropriate in assessment of visual function related to daily activities.²⁸ We used the Pelli–Robson test, which was previously demonstrated as effective in measuring contrast sensitivity²³ and already used in AMD patients.²⁹ In the sample of patients with contrast sensitivity measurement, no significant change after radiotherapy was noted. These are preliminary results concerning only a small series, and should be further analysed.

AMD creates considerable handicap in daily life^{30 31} because of decreased visual performance. We inquired about the influence of radiotherapy in our patients' daily behaviour, using a simple six item questionnaire. Patients' subjective answers suggested that even 18 months after radiotherapy they were heavily restricted in key daily activities. For instance, 65% and 50% of patients were unable to read or write, respectively. Forty three per cent of the patients were satisfied after radiotherapy, but these results should be qualified by the fact that untreated eyes experienced a poor functional and anatomical outcome. Furthermore, the follow up of the treated eye is not long enough to permit comparisons with the untreated eye.

In this study, analysis of radiotherapy effects covered evolution of the anatomical features besides functional status. Assessment of CNV areas in FA and ICG indicated the possibly beneficial effect of radiation treatment on CNV growth. Nevertheless, our results were less encouraging than those of previous published series. For instance, Chakravarthy *et al*¹⁰ reported 83% regression of CNV at 12 months and 91% at 18 months, on FA. In another study,¹⁶ progression of the median size of CNV membranes was noted after radiotherapy, both in classic (264% growth of the original size after 1 year) and occult (134%) groups. In other respects, like Bergink *et al*,^{11 19 32} our findings suggested stabilisation of CNV expansion after radiotherapy.

At the present time, the exact dose of radiation required to treat CNV in humans is not

yet defined. With the lateral beam technique, a dose level of 5 Gy has been reported to be associated with increase of CNV measured in FA after 6 months, even though the VA remained unchanged.¹² In this study, 8 Gy radiotherapy resulted in no change of VA and CNV sizes. Similarly, no efficacy was noted with a single fraction of 8 Gy.¹¹ Doses of 10 Gy in five fractions were not found effective in a recent study.¹⁷ Higher dose levels of radiotherapy (10–15 Gy in five fractions, 24 Gy in six fractions) were reported to have a therapeutic effect.^{10 14 19} Our results after 20 Gy radiotherapy (4 Gy fractions, equivalent dose of 30 Gy) are not consistent with previously reported dose levels,¹⁶ but the dose fractions were different (2 Gy fractions—that is, an equivalent dose of 20 Gy). A significant difference of effective dose in these studies could explain the conflicting results.

Tolerance of radiotherapy was also investigated in the present study. Optic neuropathies and retinal vasculopathies probably related to radiation were diagnosed in four and eight patients, respectively. The doses ranged between 16 and 20 Gy in five fractions. Radiation optic neuropathy has been described within a total dose of 45–50 Gy but a single dose of 7 Gy or more can lead to nerve demyelination, resulting in blindness.³³ As fraction size appears to be correlated with the risk of occurrence of optic neuropathy,³⁴ the fractions used in this study could explain the higher frequency of this complication. The risk of retinal vasculopathy increases with fraction size,¹⁷ especially for doses higher than 40 Gy.^{33 35}

Pathogenesis of CNV growth remains unclear. Radiotherapy could minimise size and intensity of CNV proliferation. Focal radiotherapy has been reported to limit the proliferation of granulation tissue and markedly reduce inflammatory cell recruitment in an animal model of perforating ocular injuries.³⁶ Chronic lesions due to radiotherapy include obliteration of capillary bed and thickening of vascular walls.³³ As a result, normal tissue is replaced by fibrosis. These cellular effects could explain the inhibitory effect on angiogenesis.

In conclusion, compared with the natural evolution of subfoveal CNV, our prospective study suggests that radiation therapy could stabilise both the anatomical and visual outcome until 24 months after radiation. Further randomised clinical trials are needed to conclude to a beneficial influence of radiotherapy on visual and anatomical outcome and to identify visual predictive factors after radiotherapy.

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