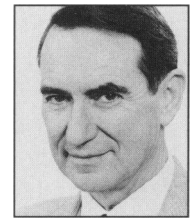
External Beam Radiotherapy in the management of subfoveal choroidal neovascular membranes of the eye:

A new treatment for an old disease



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The exudative form of Age-Related Macular Degeneration (ARMD) is associated with a particularly poor visual prognosis and accounts for 88% of ARMD sufferers who are registered blind.[1] In this disease, characteristic changes occur in the posterior pole of the eye within the confines of the macula which is the region of the retina responsible for central vision. When visual loss results from progressive degeneration of the retinal pigment epithelium and photoreceptors the condition is known as dry macular degeneration. In a significant proportion of eyes there is invasion of the sub-pigment epithelial and sub-retinal spaces by new blood vessels originating from the choroid. The infiltrating vessels are enmeshed in fibrous inflammatory tissue constituting a choroidal neovascular membrane (CNVM).[2] The natural history of a CNVM is one of rapid expansion with increasing leakage of fluid and blood associated with progressive severe visual loss. The neovascular channels within the membrane eventually stop perfusing and involute with the development of a fibrous disciform scar. The morphogenesis of the scarring process destroys the retinal pigment epithelium and the photoreceptors and is incompatible with normal central visual function.

Laser photocoagulation has been used for many years to ablate those choroidal neovascular membranes which are located outside the foveal avascular zone.[3] Laser photocoagulation of the foveal avascular zone will of necessity destroy the foveal photoreceptors resulting in complete loss of the central 5° of visual field and an immediate fall in visual acuity. In 1991 the Macular Photocoagulation Study Group (MPS) showed that well-defined sub-foveal membranes no larger than 3.5 disc areas benefit from laser photocoagulation.[4] In this study, patients treated with laser photocoagulation showed on avèrage a 3.3 line fall in acuity from baseline while controls showed a 3.7 line drop at 12 months; a difference of 0.4 lines. With continuing follow up, at 18 months and at 24 months, treated patients had visual acuities which were one line or two lines of vision better than that which was found in the no treatment group.[4] However as already stated, treatment destroys the fovea and there is an immediate marked fall in visual acuity (on average a fall of 3 lines on the Snellen chart).[5] It is therefore questionable whether a long-term marginal visual benefit at the cost of an immediate significant deterioration in vision is worthwhile. Understandably alternative treatment modalities are being sought.

It has been known for a long time that ionising radiation can limit cell growth and division, with rapidly dividing cells showing a greater degree of susceptibility to the lethal effects of ionising radiation.[6] Ionising radiation has been used to limit contraction and scar formation in surgical wounds for over 40 years and the elegant studies of Grillo and Potsaid were the first to shed light on the primary role of fibroblasts in wound repair and their inhibition by radiation.[7] In our laboratories, studies carried out in the experimental animal have shown that low dose ionising radiation applied focally at the site of an ocular perforation causes a marked reduction in the vascularity of the granulation tissue with an associated decrease in the proliferation of scar tissue and traction retinal detachment. Focal radiotherapy did not adversely affect the adjacent healthy retina and choroid as evidenced by histological examination.[8] We have also determined the radiosensitivity of retinal microvascular endothelial cells in vitro and in vivo and the results indicate that a single dose of radiation in the region of 500 cGy is sufficient to arrest division in 99% of irradiated endothelial cells. [9]

In addition to the high degree of radiosensitivity of vascular endothelial cells, the use of radiation has other theoreticae advantages. Following laser, recurrent neovascularisation has been identified as the principal cause of continuing visual loss. It has been suggested that, the inflammatory element of the CNVM appears to be an important component in the formation of the membranes, release of enzymatic products and its remodelling.[10] Treatment of CNVM by laser photocoagulation results in damage to tissue which can evoke an inflammatory response with

further recruitment of macrophages. These inflammatory cells are potent inducers of neovascularisation through the production of cytokines and angiogenic growth factors.[11] As inflammatory cell recruitment is inhibited by low doses of ionising rays, treatment of the CNVM by this modality is unlikely to provoke recurrent neovascularisation. Thus the studies carried out in our laboratories have provided the theoretical basis for the use of low-dose ionising radiation as a suitable treatment modality in the management of sub-foveal CNVM of ARMD. The next logical step was a phase I/II Clinical trial to determine whether low-dose radiation to the macular region could influence the natural course of age-related sub-foveal neovascularisation. These phase 1/11 trials were commenced in 1990 and the results of these studies have been reported extensively in the scientific literature.[12-14]

Overview of results

Fifty three patients with sub-foveal neovascularisation on fluorescein angiography were identified for inclusion into the study. The angiograms of all these patients showed early leakage of dye seen as hyperfluorescence which increased in intensity and area and which involved the foveal avascular zone. The patients were fully counselled on the nature of their condition and treatment options available. From January 1992 those patients who fitted the MPS criteria for foveal ablation[4] were offered this treatment but all declined. Any patient with pre-existing ocular disease (eg. glaucoma, high myopia, chronic inflammatory or neoplastic disorders) was excluded as were those with systemic disorders (diabetes, uncontrolled hypertension) or a known life-threatening disease at enrolment into the study. Informed consent to participate in the radiotherapy study was obtained in all treated cases. Those patients who declined radiotherapy were followed up as a non-randomised comparison group (A total of 41 eyes received radiotherapy and 13 eyes of 12 patients were followed up as controls).

In the initial stages of the study (first 19 patients) two treatment regimes were used with patients receiving either lOGy (2Gyx5 fractions) or l5Gy (3Gyx5 fractions).[12] The analysis of the initial results showed stabilisation of central visual function in treated patients which was accompanied by regression of the neovascular membrane which was documented angiographically. By contrast central vision in the comparison group deteriorated significantly and the neovascular membrane was seen to expand. The long-term follow up data on 41 treated and 13 controls for periods up to 60 months confirmed that radiotherapy appeared to induce regression of CNVM which was associated with maintained visual acuity (Table 1). In those patients who received IOGy, the rate of regression of the neovascular membrane was slower than that observed in those who received 15Gy although final visual acuity was similar between groups. The lack of statistical significance in visual outcome between these two groups may have been due to the small size of the pilot study or the absence of any real difference between the two doses of radiotherapy.

3Gy fractions are known to be associated with a higher risk of optic neuropathy hence a new treatment regime was instituted consisting of 12Gy delivered as 2Gy fractions x 6. In order to allow for the radiobiological effectiveness of these fractionation schedules the nominal standard dose (NSD) which is expressed in rets was calculated for each treatment regime. In a seminal piece of work Harris and Levene[15] have shown that there was a significant increase in the risk of visual loss not only with fraction sizes exceeding 2 Gy but also when the NSD exceeded 1500rets. In practice the majority of radiotherapists do not prescribe in fraction sizes in excess of 2Gy particularly when the field of radiotherapy includes the brain and the eye. These are important considerations as ARMD is a non-life-threatening condition and since central vision is already poor in ARMD sufferers, it would be questionable clinical practice to compromise optic nerve function by any therapeutic intervention. In this context it should be noted that at least one investigator has reported sight-threatening retinopathy in a patient with dysthyroid ophthalmopathy treated with external beam radiation at a total dose of 20Gy given in 10 fractions over periods of 10 to 14 days.[16] Our calculations based on the information provided in this paper show that the NSD in these patients was in the region of 1120 to 1160 rets and thus we feel it prudent to restrict the dose and fraction size to ensure a ret value below 1000. In our study the NSD which is expressed in rets did not exceed 1000 rets in the 10 or 12Gy group and 1200 rets in the 15Gy group. On the basis of our clinical impression we are now electing to treat all subsequent patients with 12Gy each as the NSD is kept to below 1000 rets, giving us a wider margin of safety than a dose of 15Gy.

Throughout the duration of the study, our patients were monitored for any possible adverse side effects which could be attributed to radiotherapy. Transient conjunctival irritation was reported by one patient with resolution within three weeks from radiotherapy

TABLE 1

Summary of Published Phase I/II studies

Group	Radiation	Dose	Fraction	NSD	No. Treated	Cont	Reference	Results
Chakravarthy et al	6 MV P	10 15	5 x 2 5 x 3	571 857	19	7	BJO 1993;77:265-273	Stabilisation of VA in 63% at 12 months
Bergink et al	16MVP	8 12 18 24	Ix8 2x 6 3 x 6 4 x 6	900 952 1224 1417	17	none	Graefes. Arch 1994; 232: 591-598	Stabilisation of VA with doses in excess of 12Gy in 48% at 12 months
Bergink et al	16 MV P	8 12 18 24	1x 8 2x 6 3 x 6 4 x 6	900 952 1224 1417	40	none	Doc Ophthal 1995;90: 67-74	Stabilisation of VA with doses in excess 12Gy in 57% at 18 months
Finger et al	6 MV	14.4	8 x 1.2 10x 1.44	695 642	75	none	Ophthalmol 1996; 103: 878-889	Stabilisation of VA in 48% at 9 months
Berson et al	6 MVP	14 15	8 x 1 75 1 x 1.88	G86 735	52	none	Int. J Radiat Oncol. Biol, 1996;36:861-865	Stabilisation of VA in 79% at 7 months
Freire et al	Not stated	14.4	8 x 1.8	685	39	none	Int. J. Radiat Oncol. Biol, 1996;36:857	Stabilisation of VA in 92% at 3 months
Valmaggia et al	6 MeV E	5 8	4 x 1.25 4 x 2	409 493	46	none	Klin. Monats 1996; 208:315-317	Stabilisation of VA with doses in excess of 8Gy in 72% at 6 months
Hart et al	6 MV P	10 15	5 x2 5 x 3	571 857	41	13	BJO 1996; 80:1046-1050	Stabilisation of VA in 65% at 48 months

and thereafter this patient has remained asymptomatic. Another patient suffered transient alopecia areata involving an area 2cm diameter at the beam exit point. Both these patients received 15Gy. Significant progression of cortical and posterior subcapsular lens opacities with accompanying loss of acuity was observed in the treated eyes of two patients (both had received 15Gy) after 36 months post-treatment. Cataract extraction and intraocular lens insertion has been carried out in both these patients. Post-surgery, vision returned to the level measured prior to the onset of lens opacities. Radiation induced retinal

vasculopathy (microvascular abnormalities, leakage and cotton wool spots) or optic neuropathy (disc pallor) were not observed clinically. Angiograms were scrutinised for evidence of retinal microvascular abnormalities and none was found.

Discussion and Summary

Various novel treatments have been proposed in recent years for the management of CNVM untreatable by laser. Interferon α 2a which is a potent inhibitor of vascular endothelial cell proliferation and migration in culture has been used systemically in the treatment of sub-foveal CNVM.[17] To date this treatment option has not proved significantly effective and it is also associated with severe secondary effects which may be local or systemic. Other experimental therapies involve the use of thalidomide, retinoids, and amiloride[19] all of which are known to possess antiangiogenic properties. The results of such treatments are as yet unavailable. Surgical excision of CNVM has been attempted[20] but the outcome is significantly better in younger patients with presumed ocular histoplasmosis rather than ARMD.[21] Transposition of the retina has also been considered, however these are all highly invasive procedures and it is doubtful whether central visual function can be preserved or improved by such drastic surgery.

Radiotherapy is attractive as it can be delivered to a precise location, it is non-invasive and has no systemic side effects at low doses. Since the publication of our original studies on radiotherapy in ARMD there has been increasing interest in this treatment modality .External beam radiation as employed by other centres in the management of CNVM has included dose regimes ranging from 8Gy to 24Gy (Table 2). The fractionation schedules varied considerably and fraction sizes as large as 8Gy have been used.[22-23] Where cyclotron facilities were available proton beam irradiation has been used which with its highly collimated beam and sharply defined Bragg Peak effect has theoretical advantages in the treatment of CNVM.[24] Alternatively brachytherapy rather than teletherapy has also been tried with some investigators using Pd 103 or Sr 90 plaques (beta emitters) designed to deliver doses between 12.5 and 15Gy to the region of the CNVM.[25-26] Most of these recent reports suggest a positive treatment effect in the short term. Although no adverse effects have been reported in any of these studies it should be noted that the follow-up times have in general been less than one year.

In summary the basis for the use of ionising radiation to inhibit growth of CNVM of ARMD has been underpinned by many years of information gleaned from basic laboratory studies. These studies are now quoted extensively in the literature by researchers worldwide as the rationale for commencing clinical trials of this treatment modality in ARMD. Our preliminary phase I/II trials are also enshrined in

TABLE 2

Distribution of Visual Acuity in Treated Eyes Between O and 48 months post Radiotherapy

	O	3	6	12	18	24	36	48
LogMar (Snellen)	n=41	n=41	n=41	n=41	n=30	n=29	n=25	n=9
O.O 0.6 (6/6 - 6/24)	27%	29%	39%	26%	23%	21%	20%	45%
0.78 - 1.1 (6136 -5/60)	49%	46%	46%	42%	47%	38%	56%	33%
1.2-1.78 (4/60 -1/60)	24%	25%	15%	32%	36%	41%	24%	22%

Distribution of Visual Acuity in Control Eyes Between 0 and 48 months post Radiotherapy

	O	3	6	12	18	24	36	48
LogMar (Snellen)	n=13	n=13	n=13	n=13	n=12	n=l0	n=8	n=4
0.0- 0.6 (6/6 6/24)	47%	31%	31%	8%	0%	0%	0%	0%
0.78 - 1.1 (6/36 -5/60)	38%	54%	31%	46%	58%	40%	38%	50%
1 3 -1.78 (4/60 -1/60)	15%	15%	38%	46%	42%	60%	62%	50%

the literature as they were the first to explore the potential of radiotherapy in the management of subfoveal CNVM. A number of multicentre randomised controlled studies are now progressing and a more definitive answer should be available very soon.

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