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REVIEW

Radiotherapy for age-related macular degeneration: no more pilot studies please

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Age-related macular degeneration (AMD) is a major health problem for the United Kingdom. Currently, AMD accounts for the majority of the 124 000 blind registrations in the over 65 age group.[1,2] This demonstrates that AMD is also an immensely frustrating condition for patients and their doctors as current treatments are extremely limited both for the atrophic form[3] and for choroidal neovascularization (CNV).[4–8] CNV while accounting for 10% of the disease, disproportionately causes up to 88% of the legal blindness associated with AMD.[9] Conventional laser treatments for CNV improve vision in only 5% of cases and are suitable only for a minority of patients.[4,10] Therefore, there is a pressing need for novel and effective therapies. Investment in research makes sense financially as well, as the considerable costs to the NHS in managing visually impaired patients could be significantly reduced with better treatments for CNV.

One possible novel therapy for the treatment of CNV associated with AMD is ionising radiation. Radiotherapy seems rational because of its known ability to inactivate rapidly proliferating cells such as the capillary endothelium of CNV. Such cells typically manifest impaired radiation damage repair relative to adjoining slowly proliferating cells. A differential survival response might therefore be exploited with CNV destroyed through DNA breaks that normal tissues have time to repair before undergoing cell division.[11–15] Although radiation dose fractionation with multiple small treatments over many days is commonly used to reduce normal tissue complications in the treatment of malignancies, since CNV is not a true neoplasm, arguments have been made that there may be no therapeutic advantage to dose fractionation,[16] especially if the volume irradiated can be restricted to the region of macula (it is an axiom of radiotherapy that the probability of complications is proportional to the size of the target volume). In the journal this month, however, a radiotherapy trial is reported which shows no benefit in AMD. Should we therefore abandon this treatment in AMD? The short answer is no, because of the theoretical rationale for why radiotherapy may work and a series of studies which have given enticing hints that it may still be of benefit in AMD.

Research into radiotherapy as a treatment modality for AMD started in earnest 10 years ago after Chakravarthy *et al*[17] demonstrated significant regression in (CNV) following external beam radiotherapy in an animal model and later in a phase I study.[18] Since then a multitude of small pilot studies using standard fractions of 2–3 Gy with a total dose of 10–20 Gy have been published, some showing better maintenance of visual acuity in treated eyes,[11–14,19] while others failed to show any benefit.[15,20–22] Overall, prior to the study by Hoeller *et al* there have been 10 randomised control trials (RCT),[15,23–30,30,31] three nonrandomised trials[15,21,32] and eight case series each with over 100 people in the study[22,33–39] (see Table 1). Among the above RCTs, three studies demonstrated a significant reduction in visual loss when comparing radiotherapy to very low-dose (effectively sham) radiotherapy[25] or observation.[26,29] The National Institute for Clinical Excellence recognises the modest benefits from radiotherapy while justifying its restricted usage within ethically approved quality clinical trials in the UK.[40]

Part of the challenge with radiotherapy is in finding an appropriate radiation regimen. The difficulty lies in the many different ways and dosage schedules by which ionising radiation can be applied to the eye. The biologically

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Table 1 Summarising results from relevant Randomised Control Trials

Authors	*CNV type*	*Pt nos*	*Dose*	*FU (months)*	*Reported visual acuity results*			
						P-values		*P-values*
Bergink *et al*[29]	Classic/occult	32	Observed	12	52.2% ⩾3 lines lost		40.9% ⩾6 lines lost	
		36	4 × 6 Gy		32.0% ⩾3 lines lost	0.03	8.8% ⩾6 lines lost	0.002
Char *et al*[30]	Classic/occult	14	Observed	7–32	5.5 mean lines lost			
		13	1 × 7.5 Gy		1.9 mean lines lost	0.046		
Hart *et al*[24]	Classic/predominantly classic	100	Observed	24	82% ⩾3 line lost		72% ⩾3 line near VA lost	
		99	6 × 2 Gy		70% ⩾3 line lost	0.08	67% ⩾3 line near VA lost	0.47
Holz *et al*[23] (RAD study)	Classic/occult	104	Sham Rx	12	3.7 mean lines lost		53% ⩾3 lines lost	
		101	2 × 8 Gy		3.5 mean lines lost	0.528	51% ⩾3 lines lost	0.88
Kobayashi *et al*[26]	Classic/occult	50	Observed		+0.563 mean logMAR change			
		51	10 × 2 Gy		+0.226 mean logMAR change			<0.0001
Valmaggia *et al*[25]	Classic/occult	52	1 × 1 Gy	18	3.23 mean lines lost			
			4 × 2 Gy		1.73 mean lines lost	0.011		
			8 × 2 Gy		1.93 mean lines lost	0.050		
Marcus *et al*[27]	Classic/predominantly classic	42	Sham Rx	12	3.39 mean lines lost			
		41	7 × 2 Gy		4.14 mean lines lost	0.35		

effective dose to the macula is a function of the dose per fraction and the number and fractions, not merely the total applied dose. The commonest method employed is external beam radiotherapy, where the amount of dose delivery is often curtailed by the need to avoid collateral tissue damage.[41,42] Newer techniques are being reported which deliver higher biological doses of radiation with a conventional linear accelerator with minimal toxicity[43] and even greater doses have been applied as single fractions using a proton beam that substantially restricts the region of highest dose to the macula. Although proton beams are a costly and scarce resource, methods exist whereby the dose can be equally restricted using highly collimated multiple beams from a conventional medical linear accelerator that are conically convergent on the macula.[44] Brachytherapy, where sealed radioactive plaques are sutured temporarily to the posterior pole and later explanted, even though capable of higher doses and extramacular sparing has been limited by the need for surgery.[45] A greater understanding of radiation biology is needed to refine our clinical studies. Such understanding is now starting to emerge. There is evidence to suggest that higher nonstandard fractions may be beneficial[29,46] in producing CNV regression. Owing to this dose–response effect, better methods of delivering optimum radiation doses to the macula need to be developed in earnest. Presently, the stereotactic irradiation technique utilising a three-dimensional stereotactic system seems most promising in achieving a more precise delivery of higher radiation doses to the macula. Also, recent studies using larger fraction sizes of 3 Gy for recurrent CNV[47] have had promising short-term results and support further investigations using 4 Gy or higher fractions. Some of the most tantalizing results have been achieved with single doses of 14 Gy delivered with a proton beam[48] and suggest stability of visual acuity in some patients over a period of years as compared with only 8 Gy. The toxicity appears to have been acceptable, especially if very large lesions and accordingly larger beam sizes are excluded.[49] Unfortunately, this experience has not been replicated with an adequately controlled study. A proton beam trial intended to see if there is a dose–response between 10, 12 and 14 Gy (no untreated option) is currently in the follow-up phase and preliminary 1-year results were recently reported.[50,51] There was no significant difference between the groups at 1 year but further follow-up is needed. Without a placebo control, the study was not designed to assess the absolute value of the treatments.

Retinal tissue is relatively resistant to radiation retinopathy but significant visual loss is seen at doses greater than 45 Gy.[52–54] Milder side effects of dry eyes and cataract occur when doses exceed 30 Gy.[12,14,42,52,53,55] Fractionation of irradiation helps reduce the toxicity

without reducing the DNA-damaging effect in rapidly dividing cells. This has been used effectively in AMD with total dosage schedules ranging from 10 to 16 Gy, and lately have exceeded 20 Gy or more. Complications have been reduced even at these higher doses. The highest complication rate of 7.5% was reported where 20 Gy (approx. equivalent biological dose of 30 Gy) had been delivered by a conventional lateral beam method.[36] These complications included optic neuropathy, retinopathy, choroidopathy (choroidal telangiectasia), and branch retinal vein occlusion. However, all of these considerations largely ignore the likely additional value of restricting the treatment volume.

Hence in summary, previous research while not being conclusive suggests that there is a therapeutic window at an early stage of neovascularization when an adequate dose of radiation would be sufficient to induce regression of CNV with limited side effects. Previous pilot studies have been helpful in gathering this data, but now no more pilot studies are needed. Rather, these studies have justified evaluating radiotherapy in properly funded RCTs using innovative treatment schedules and modalities. Possible ways to achieve this would be by using multiple dose fractionations with higher doses, the use of precise methods to limit the dose to the uninvolved retina thereby permitting larger even single doses to the macula and perhaps utilising radiotherapy as an adjuvant to steroids, antiangiogenic drugs or photodynamic therapy. A synthesis of the existing data is needed to guide the design of further RCTs to conclusively determine the role of ionising radiation in treating AMD. This may require international collaboration but the prize of improving our treatment of AMD makes it a very worthwhile goal.

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