Age related macular degeneration: A study of patients managed with radiotherapy

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ABSTRACT

Introduction: Age-related macular degeneration (ARMD) is the leading cause of blindness in the west. Radiotherapy affects the evolution of exudative macular degeneration directly by its effect on the endothelium and inflammation modulation. We conducted a retrospective study to evaluate the improvement in visual acuity and healing of sub retinal neovascular membrane (SRNV) following fractionated radiotherapy.

Materials and Methods: 47 patients (58 eyes) of ARMD were retrospectively analyzed. One of the following radiotherapy fractionation schedules was employed in all the patients in this study. a) 15 Gy /5 fractions/1 week (five patients) b) 20 Gy/5 fractions/ 1 week (19 patients) c) 22.5Gy/5 fractions/1 week (21 patients) d) 25 Gy/5 fractions/1 week (two patients). VA and funduscopy was taken at each follow-up for objective improvement and to assess the healing of SRNV.

Results: The median follow-up was 7.23 months. The mean improvement in the VA in the entire group was of 0.44 line. (Median 1, SD 1.04). Overall 75% of the eyes showed either steady vision or an improvement in subjective vision analysis. The deterioration free survival was significantly better in the group that had a relatively short duration of symptoms (P=0.01). Scarring at presentation was a significant adverse factor for improvement in vision after radiotherapy (P= 0.001).

Conclusions: In patients of ARMD treated with radiotherapy, the initial duration of symptoms and scarring of eyes at presentation were significant prognostic variables for improvement in VA after radiotherapy.

KEY WORDS: Age-related macular degeneration, radiotherapy

INTRODUCTION

Treatment of benign disease by ionizing radiations has always aroused keen interest. One such important condition is age-related macular degeneration (ARMD). This disease is the leading cause of blindness in the west and it's prevalence varies from 1% in patients aged 65 to 74 years, to 10% in patients aged 85 onwards.[1,2] It is however a lesser known cause of blindness in the Indian subcontinent, behind commoner conditions such as cataract. There are three major forms of macular degeneration. i) Dry form ii) wet form iii) Pigment epithelial detachment (PED). The dry form, which accounts for 85-90% of patients with ARMD, involves thinning of the macula. Usually no effective treatment is available for this disease. In the wet form (10%) abnormal vessels grow under the retina and lift the retina up.[2] This is known as subretinal neovascularisation (SRNV). ARMD may lead to loss of vision by atrophy of the retinal pigment epithelium or by the development of choroidal neovascular membranes (CNVM) under the macula, which leak serous fluid and blood and ultimately cause a blinding disciform scar. Options currently being investigated fall into two main approaches: elimination or modification of the CNVM (by laser, chemotherapeutic agents, photodynamic therapy, transpupillary thermotherapy, feeder vessel photocoagulation or novel techniques such as submacular surgery and macular translocation) or prevention of the formation of CNVM (by laser prophylaxis, diet or gene targeting.[3] Whilst almost no therapy restores normal visual acuity (VA), any significant visual improvement or even maintenance of the VA over the natural history may be regarded as beneficial. Radiation therapy has been used in treatment of this disorder with varying results ever since the first trial reported by Chakravorty *et al*.[1] Radiotherapy affects the evolution of exudative macular degeneration directly by endothelial toxicity, leading to capillary closure and/or indirectly through its attenuating effects on the inflammatory response, mediated by macrophages and other inflammatory cells.[4,5] We conducted this study to see the response and the toxicity of radiotherapy in the treatment of this disease and to evaluate the role of other factors determining response to radiotherapy. We also intended to see if there was any dose response effect of radiation.

MATERIALS AND METHODS

63 patients were enrolled in this retrospective study. The inclusion criteria for this study were 1) Patients were not considered suitable for LASER photocoagulation by the referring ophthalmologist due to subfoveal location 2) Eyes having sub retinal neovascular membrane 3) Increase in size in neovascular membrane during the past six months or onset of symptoms lesser than six months 4) Age greater than 30 years 5) Patients willing for radiotherapy. In all cases, the initial work up included a detailed history and the total duration of symptoms, history of smoking, diabetes mellitus and hypertension. Pretreatment ophthalmologic evaluation included detailed examination of the fundi, VA and Fundus fluorescein angiography (FFA) in all the cases. All the patients were explained the investigative nature of the study and informed consent was obtained. Of the 63 ARMD patients seen in our hospital, 16 did not receive radiotherapy. Reasons for this were varied and included patients lost after first outpatient visit, patients who were not given radiotherapy because their vision remained stable over past six months or more and patients who were unwilling for radiotherapy and opted for other forms of treatment. One patient was 24 years of age and was not treated in view of the rare occurrence of ARMD in this age group. In the final analysis only 47 remaining patients were considered. Since 11 patients had bilateral involvement so in all 58 eyes were treated.

Radiation treatment

In each patient, immobilization was achieved by use of thermoplastic mask. CT planning was done for all patients in the supine position and fiducial radio-opaque markers placed at the lateral canthi. All the relevant structures such as the lens, posterior retina and the contra lateral eye were outlined. It was ensured that the 90% isodose adequately covered the ipsilateral macula and optic disc, with less that 50% falling on the ipsilateral posterior lens capsule. Patients were treated most commonly with a single lateral portal with 5-15 degree posterior tilt [Figure 1]. Asymmetric fields of 3×3 cm size were used in all the patients to prevent divergence into the opposite eye. The other portals, which were used were true lateral portals (in patients where the opposite eye or lens was not a consideration) or bilateral fields (in patients in which both eyes were simultaneously treated). One of the following radiotherapy fractionation schedules was employed in all the patients in this dose escalation study. a) 15 Gy/5#/1 week (five patients) b) 20 Gy/5#/1 week (19 patients) c) 22.5Gy/5#/1 week (21 patients) d) 25 Gy/5#/1 week (2 patients). The dose was prescribed at Dmax in the patients treated with ipsilateral technique. In patients who were treated with bilateral parallel opposing portals the dose was prescribed at the mid separation. All the patients completed the planned radiotherapy as scheduled.

Patients were seen at follow-up monthly for three months, three monthly for the first year and subsequently every six months. At each follow-up, both the ophthalmologist and the radiation oncologist evaluated the patient. The response was graded subjectively as 1) no change 2) worse 3) better. VA and funduscopy was taken by the qualified ophthalmologist was repeated at each follow-up for objective improvement and to assess the healing of SRNV.

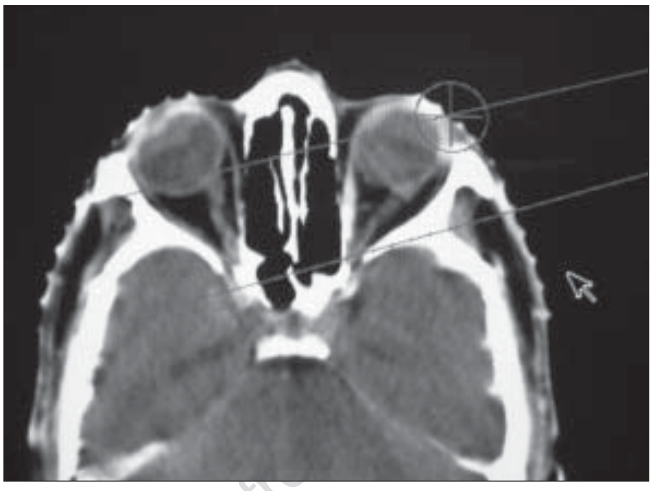

Figure 1: Beam arrangement of the treatment with posterior tilt to spare the opposite eye

Statistical

The analysis was done using SPSS software (version 10). The deterioration free survival was calculated using Kaplan Meyer survival analysis. Long rank test was used to compare the groups in the survival analysis. The Chi square test was used to see the significance of other factors affecting the response to radiation.

RESULTS

Patient characteristics are given in Table 1. The median follow up was 7.23 months (SD 9.67).

The mean improvement in the VA in the entire group was of 0.44 line. (Median 1, SD 1.04). Overall 75% of the eyes showed either steady vision or an improvement in subjective vision. Improved or steady VA was recorded in 77% of the eyes [Table 2]. In the present study, there was no gain in line once the symptom duration had crossed 10 months. Figure 2 presents the relation between initial duration of symptoms and gain/loss of lines in VA.

The deterioration free survival was significantly different in the group that had a relatively short duration of symptoms (<4 months) compared to the group having longer duration of symptoms (>4 months). (Log rank $P=0.01$) [Figure 3]. Figure 4 presents the graphical comparison of patients who received a higher dose of RT (group a and b) compared to those who received lower dose (group a and b).

The univariate analysis for various factors did not show any significance for variables such as initial VA and dose of

Table 1: Patient characteristics

Age (Years)	N	Percent
<50	13	20.6
50-70	31	49.2
>70	19	30.2
Sex		
Male	42	66.7
Female	21	33.3
Treated		
Yes	47	74.6
No	16	25.4
Smoking		
Yes	4	6.3
No	59	93.7
Diabetes		
Yes	6	9.5
No	57	90.5
Hypertension		
Yes	7	11.1
No	56	88.9
Cataract		
Yes	25	39.7
No	38	60.3
Side		
Left	24	38.1
Right	28	44.4
Both	11	17.5
Portals		
True single lateral	8	12.7
Post oblique	28	44.4
Bilateral	11	17.5
Duration of symptoms (Months)		
<4 months	27	46.6
>4 months	31	53.4
Dose and fractionation		
15 Gy/5#	7	12.1
20 Gy/5#	24	41.4
22.5 Gy/5#	24	41.4
25 Gy/5#	3	5.2

Table 2: Patient impression and change in visual acuty for all analysable patients

	N	Percent
Patient impression		
Worse	15	25.9
Unchanged	12	20.7
Better	31	53.4
Change in visual acuity		
Loss of line	13	22.4
No change	10	17.2
Gain of line	35	60.3

radiotherapy delivered. However the duration of initial symptoms and the presence or absence of initial scarring was highly significant. (P=0.003) [Table 3].

Table 3: Univariate analysis for various factors as determinants for improvement in visual acuity

Factor	*P* value
Age	0.912
Sex	0.401
Smoking	0.241
Diabetes	0.166
Hypertension	0.594
Duration of symptoms	0.003
Cataract	0.07
Dose and fractionation	0.161
Initial visual acuity	0.682
Scarring at presentation	0.001

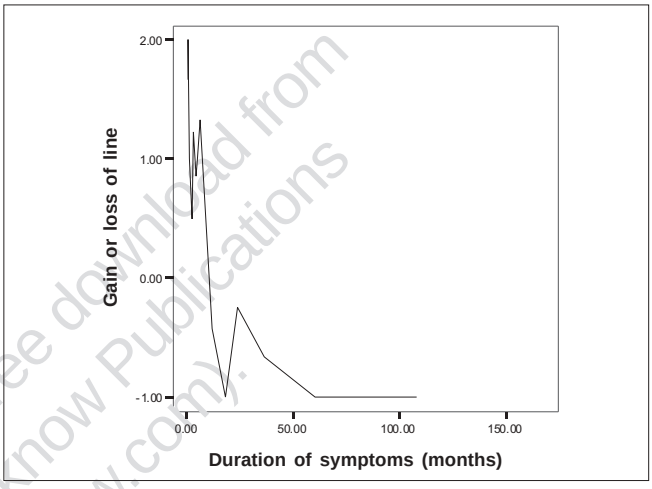

Figure 2: Change in visual acuity after radiotherapy with respect to initial duration of symptoms

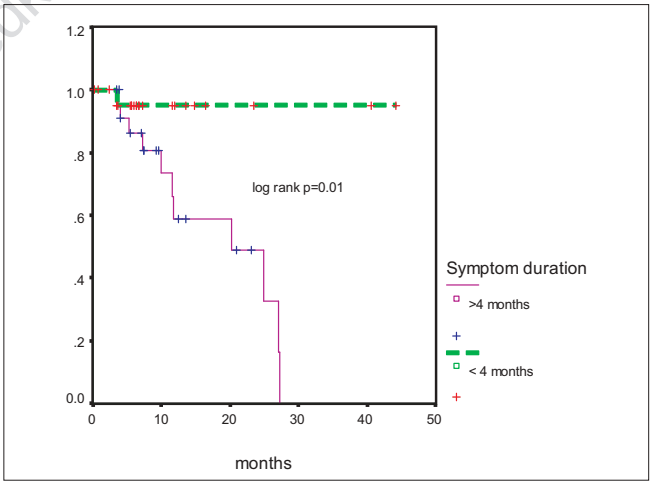

Figure 3: Deterioration free survival versus symptom duration

DISCUSSION

We found that duration of initial symptoms had a profound effect on shown to be important and significant as a prognostic variable for visual stability of improvement. This is explained by the fact that the neovasculature structure will be more susceptible to radiotherapy in early stages rather that when the active proliferation has settled and had been replaced by fibrosis or scarring. This finding strengthens the belief that radiotherapy in ARMD should be started as soon as possible. On the same lines, even initial scarring which is an indicator of the duration of the ARMD onset is a significant variable. Fibrotic and scarred retinas have much less proloferative tissues and hence poor response to radiotherapy.

Although there is a definite dose response curve with increasing dose of radiotherapy, the difference between response to low

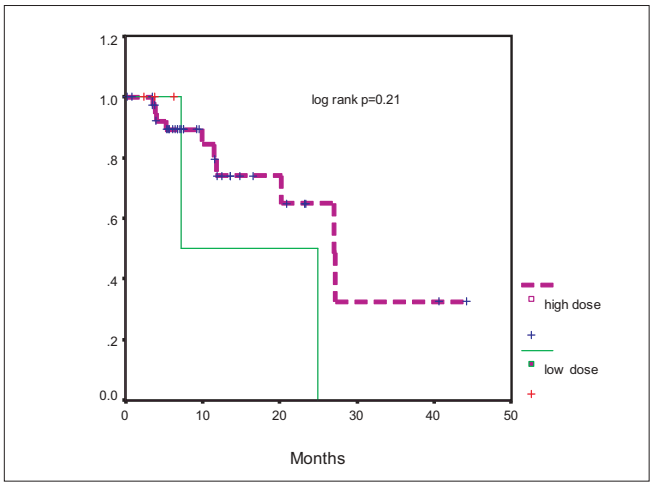

Figure 4: Deterioration free survival versus radiotherapy dose

or high dose does not attain significance. However factors such as age and sex were not found to have any bearing on radiotherapy response. Smoking, diabetes and hypertension too were not observed as risk factors, though the absolute numbers are small. Initial visual acuty has also been suggested to be an important prognostic determinant of the benefit from radiotherapy. Our study has not demonstrated this to be a significant independent variable.

In our study, as many as 74% of the analysed subjects had either stable or improved vision at last follow up and this compares very favorably with historical controls.[1,6,7] Similarly 77% patients have shown objective response to radiotherapy (in visual acuity).

Some authors have found a discrepancy between improvement in CRNV and improvement in visual acuity. One study concluded that although radiation inhibits CRNV, its effectiveness in improving VA might not be evident.[6]

Various groups have reported their results on the course and response of ARMD patients to radiotherapy. The results have been variable and in most of the series the numbers are small and the follow up short. Also different doses and fractionation schedules have been employed and therefore it is hardly surprising that the results have been varied. Subjective means, VA and FFA have usually assessed response. Table 4 presents important studies in ARMD using radiotherapy as the treatment modality. Most of the nonrandomized and randomized studies have shown a dose response effect in ARMD with a demonstrable benefit with using radiotherapy. The only randomized controlled trial that did not show a clear benefit was by Marcus.[9] However, they used low BED (14Gy/7#). We have used a dose higher that this in nearly half of our patients. Although this group has shown higher VA improvement in our study, this difference is not significant in our analysis. It may be important to stratify the cases before for initial duration of symptoms and perhaps even initial VA before they are randomized for different radiotherapy dose regimes.

Studies analyzing the effect of giving a higher dose of radiotherapy as compared to a lower dose too have demonstrated benefit with the former.[10,14] In one study comparing two groups of patients who were treated with a high or a low dose of radiotherapy (10 and 20 gray), there was no difference in the response rates, However, the number of subjects was quite small.[15] Other groups such as Gelisken *et al* have indicated that radiotherapy can be effective in regressing the leakage of the CNV in ARMD. However, despite treatment visual deterioration could continue and new CNV lesions still

Table 4: Trials using radiotherapy in age-related macular degeneration

Study	N (eyes)	Groups	RT dose	Follow- up	Line change/ visual acuity change	*P* value	Comments
Char[7] (R)	27	RT	7.5Gy X1	17 months	1.9 mean lines lost	0.046	
		Observation	-		5.5 mean lines lost		
Kobayashi[8] (R)	101	RT	2.4Gy X 10	2 yr	+ 0.226 mean log MAR change	0.0001	
		Observation	-		0.562 mean logMAR change		
Marcus[9] (R)	41	RT	2GyX7	1 yr	4.14 mean lines lost	Non significant	
	41	Sham	-		3.9 mean lines lost		
Valmaggia[10] (R)	161	RT	1Gy X1	18 months	3.23 mean lines lost	Significant	Less lines lost in 8Gy and 16 Gy arms
		RT	2GyX4		1.73 mean lines lost		
		RT	2GyX8		1.93 mean lines lost		
Ciulla *et al.*[11] (R)	37	RT	8GyX2	12 months	0.61 log MAR	Non significant	Used protons in their study
		Sham	-		0.61 log MAR		
Barak *et al.*[12] (R)	94	St- EBR	20-40Gy	12 months	VA pretreatment (0.82±0.33) Post treatment (0.89±0.33)	-	No significant acute side effects
Churei *et al.*[13] (R)	21	RT	2GyX10	24 months	VA improvement (81%)		
	15	No RT			VA improvement (40%)	0.034	
Marcus[14]	18	RT	2GyX7		Loss 3 or more lines (58%)	-	Benefit for higher dose per fraction
	16	RT	3GyX5		Loss loss 3 or more lines (42%)		

St - EBR = Stereotactic fractionated external beam radiotherapy, R= Randomized, MAR= Minimal angle of resolution, VA= Visual acuity

develop.[16] Altered fractionation too needs to be explored to finally arrive at the final optimal fractionation in treating ARMD. While hypo fractionation may be beneficial since the targeted tissues (arterioles) are essentially radioresistant and by providing a short treatment time, hyperfractionation may benefit by sparing late effects especially retinal sequelae besides being beneficial for the acutely proliferating neovasculature. In a solitary study of its kind, Marcus found a benefit of using (3GyX 5 fractions) compared to (2GyX 7 fractions).[14]

Possible toxic effects on critical structures such as lens and retina are always of concern while irradiating the eye. Cataract as a complication of radiotherapy to the eye is known to occur six months to several years after treatment. It usually occurs in eyes that receive doses of 400cGy of more though it has been reported to occur with a dose of 200cGy or lower.[17] There is evidence to believe that radiation in a dose of less that 25 gray does not affect the normal retina.[18] Radiation induced cataractogenesis however, is a well known in eyes irradiated to this dose range.[19,20] Our precision technique allows the contralateral eye and the ipsilateral anterior chamber to be spared while adequately covering the area of interest. In our study however, in spite of giving a higher dose in some subjects, there has been no increase in early or late toxicity in any patient. No fresh cataractous changes were discovered in any of the patient who did not have such manifestation at presentation, even in the patients in whom higher doses of radiation were used.

Many questions remain to be answered. What is the optimal dose and fractionation schedule for ARMD? When should radiotherapy be initiated in patients? Is reirradiation possible? Can photocoagulation or other treatment modality be combined with radiotherapy for better results? The need of the hour is to conduct prospective trials in this regard so that optimal benefit with radiotherapy can be achieved while keeping the toxic effects to the bare minimum.

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