Preliminary results of proton beam irradiation of macular and paramacular melanomas*

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SUMMARY Proton beam irradiation has been used for the treatment of 60 eyes with choroidal melanomas located 3 mm or less from the fovea. The average follow-up period was 18 months. 86% of the treated lesions showed regression at the time of this analysis, and the 14% that did not were followed up for less than a year. Visual acuity remained the same in 47% of the treated eyes, improved in 20%, and deteriorated in 33%. 58% of the treated eyes had visual acuity of 20/100 or better at the last follow-up examination. Radiation vasculopathy with macular oedema was the most common complication, and it was observed in 22% of the treated eyes. These preliminary observations suggest that proton beam irradiation may be a reasonable alternative to enucleation even for this group of choroidal melanomas, which is considered unfavourable in respect of the preservation of visual function.

Proton beam irradiation has been used for the treatment of uveal melanomas at the Harvard cyclotron since 1975, and 260 patients have been treated so far. Early results have shown that proton beam therapy has increased the number of tumours that can be treated conservatively and has decreased the incidence of ocular morbidity and treatment failure associated with other conservative methods.¹ These accomplishments of proton radiotherapy are based exclusively on the physical characteristics of protons which make possible highly localised dose distributions.² With protons a uniform dose can be delivered throughout the tumour with minimal irradiation to the surrounding tissues. In particular, the lateral sharpness which can be provided with proton beams allows irradiation of tumours located quite posteriorly and close to the macula or the optic nerve. Our usual treatment technique provides a 1.5 mm margin between the visible tumour and the 90% isodose contour, to allow for microscopic extension of the lesion, positional error, and motion during the

treatment. We have therefore advised our patients that a tumour-free area at least 3 mm (2 disc diameters) from the fovea was required for preservation of central vision, since only with such a margin could the dose to the fovea be kept below 50% of the tumour dose. There was no serious expectation of preservation of central vision when lesions were located closer than 3 mm from the fovea. This has proved not to be uniformly true. We report here on the current status of those patients we have treated whose tumours were closer than 3 mm to or involved the macula.

Subjects and methods

From 1975 to the end of 1982 we examined 60 patients with a choroidal melanoma closer than 3 mm to or involving the fovea, who were then treated with proton beam irradiation at the Harvard cyclotron. We have reported previously on the pretreatment evaluation and the technical aspects of the operative technique for the localisation of the tumour, the treatment planning, and the techniques of proton irradiation.¹⁻³ The 35 men and 25 women treated ranged in age from 14 to 78 years with an average age of 57. Radiation was given in five equal dose fractions over

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a period of 8 to 10 days. Each patient received a total dose of 70 CGE. (CGE represents cobalt Gray equivalent and is obtained by multiplying the physical dose in Gray by 1.1, which is our estimate of the radiobiological effectiveness of the proton beam relative to cobalt-60 irradiation). Two patients treated early in the study received 50 CGE.

The melanomas were divided into three categories according to their proximity to the fovea. (1) part of the tumour involved the fovea; (2) posterior margin of tumour less than 1 disc diameter (DD) from the fovea; (3) posterior margin of tumour 1 to 2 (DD) from the fovea. The distance of the posterior margin of the tumour from the fovea was measured in disc diameters from the fundus photographs.

The statement of the dose delivered to the macula in these categories is complicated by three factors: (1) since the macula is in the penumbral region of the beam the dose is not uniform across the macula; (2) since each category covers a range of separations from the fovea, there is a corresponding range of possible doses; and (3) there is a small uncertainty in the position of the beam relative to the eye, which leads to an uncertainty in the dose delivered. For each category we therefore quote the range of possible doses both to the fovea and throughout the macula (considered to be approximately 1 DD in diameter) assuming the alignment was as intended, and also indicate the range of possible doses if the alignment was off by as much as 1 mm (we think that there is only about a 1 in 10 chance the alignment was off by that amount or more).

These results are shown in Table 1. For category 2, for example, the fovea most likely received the full tumour dose, although with 1 mm misalignment it could have been as low as 68%. On the other hand a part of the macula would probably have received 75% of the tumour dose and could have received as little as 45% if a 1 mm misalignment was in the correct direction, or as much as 100% if the mis-

Table 1 Radiation dose to macula

	Fovea		Macula	
	Intended alignment %	1 mm mis-alignment %	Intended alignment %	1 mm mis-alignment %
<i>Category 1</i>				
Minimum dose	100	100	100	100
Maximum dose	100	100	100	100
<i>Category 2</i>				
Minimum dose	90	68	75	45
Maximum dose	100	100	100	100
<i>Category 3</i>				
Minimum dose	50	20	28	5
Maximum dose	90	100	75	90

Table 2 Location and size of tumours

Size	Distance from fovea		
	Fovea involved	<1 DD	1-2 DD
Small	0	2	3
Medium	5	10	11
Large	9	13	7
Total	14	25	21

alignment was in the opposite direction. Broadly speaking, category 1 corresponds to the full dose to the entire macula; category 2 corresponds to near full dose probably being delivered to the fovea, but with part of the macula probably receiving only 75% or so of the full dose; and category 3 corresponds to the fovea probably receiving from 50% to 90% of the full dose while part of the macula would probably get from 28% to 75% of the tumour dose.

The melanomas were divided into small, medium, and large lesions according to the largest diameter and height of the tumour. The diameters of the tumour were measured with calipers on the sclera during exposure of the globe for the suturing of the tantalum markers, and the heights were measured ultrasonographically. Tumours with a largest diameter of 10 mm or less and/or a height 2 mm or less were considered small. Tumours with a largest diameter greater than 15 mm and/or a height greater than 5 mm were considered large, and the intermediate lesions were categorised as medium in size. Follow-up examination included a complete routine ocular examination, indirect ophthalmoscopy, slit-lamp biomicroscopy, and fundus drawings. Fundus photography, fluorescein angiography, and ultrasonography were performed at different intervals to record the status of the tumor.

The distribution of the tumours according to their location and size is shown in Table 2. Twenty-nine (48%) of the melanomas were large, 26 (43%) were of medium size, and only 5 eyes had small tumours. In 14 eyes (23%) the fovea was involved, in 25 (42%) the distance of the tumour from the fovea was less than 1 DD and in 21 (35%) 1 to 2 DD. The relationship

Table 3 Length of follow-up

Time, months	Number of eyes	Percentage of eyes
>6	15	25
6-12	17	28
13-24	13	22
25-36	7	11
37-48	4	7
49-82	4	7
Total	60	100

Fig. 1A

Fig. 1 Choroidal melanoma less than one DD from fovea. A, B: Before treatment (A: ordinary fundus picture, B: wide angle of the same tumour). C, D: five months after treatment (C: Ordinary fundus picture, D: wide angle of same tumour).

Fig. 1B

Fig. 1C

Fig. 1D

between size of the tumour and distance from the fovea was not statistically significant.

The length of follow-up in these patients ranged from 2 months to 82 months, with an average of 18 months (Table 3). For purposes of analysis the follow-up period was broken into two intervals: 'short' in 32 patients who were followed up less than a year, and 'long' in 28 patients observed for longer than one year.

Results

We observed disappearance of the lesion or formation of a flat scar in 11 eyes (Fig. 1). Forty-one of the

tumours decreased in size, and the 8 that remained stable were in patients who were followed up for less than a year at the time of this analysis.

VISUAL ACUITY

The pretreatment and most recent postirradiation visual acuities of the treated eyes in relation to the location of the tumour are shown in Fig. 3. The level of visual acuity remained the same in 28 (47%) eyes, improved in 12 (20%), and deteriorated in 20 (33%). In eyes with tumours involving the fovea the visual

Fig. 2A

Fig. 2B

Fig. 2C

Fig. 2D

Fig. 2 Fluorescein angiography pictures of Fig. 1. A, early and B, late before treatment. C, early and D, late 5 months after treatment. Visual acuity is 20/30 (20/40 before treatment).

acuity remained unchanged in four, improved in three, and deteriorated in seven. In category 2 the visual acuity remained the same in 14 eyes, improved in five, and deteriorated in six. In category 3 the visual acuity remained the same in 10 eyes, improved in four, and deteriorated in seven. The changes in visual acuity in relation to the size and the location of the tumours are shown in Fig. 4. Of the 29 eyes with large tumours the visual acuity remained unchanged in 12 (41%), improved in four (14%), and deteriorated in 13 (45%) ($p < 0.05$). In the 26 eyes with medium size tumours visual acuity remained unchanged in 11 (42%), improved in eight (31%), and deteriorated in seven (27%). The relationship between visual acuity status and the duration of follow-up is shown in Table 4. Patients with worse

visual acuity have been followed up for a longer period of time ($p < 0.05$). The improvement in visual acuity noted in some of the treated eyes after proton beam irradiation resulted from resolution of serous detachment which involved the fovea. There were several reasons for the decrease in visual acuity seen in 20 patients, and these are given in Table 5.

RADIATION VASCULOPATHY-MACULAR OEDEMA

The most common cause for decrease of visual acuity was the development of radiation vasculopathy and macular oedema secondary to damage of the macular and paramacular vessels (Fig. 5). Macular oedema developed in 13 eyes (22%) and resulted in deterioration of visual acuity in eight. In the remaining five eyes the visual acuity improved in two and remained unchanged in three. The distance of the tumour from the fovea did not influence the development of macular oedema ($p < 0.8$); in five instances it was observed in cases in which the tumour was at a distance

Fig. 3 Visual acuities before and after proton beam irradiation in 60 eyes with macular and paramacular melanomas.

of 1-2 DD from the fovea (five eyes). No difference was observed in the average age of patients with macular oedema (58 years) compared with those who did not have it (55 years). Markedly decreased visual acuity was observed in all four diabetic patients with paramacular choroidal melanomas. In these eyes the most recent visual acuity was counting fingers in two (initial 20/40) and hand movements in the other two (initial 20/70 and 20/100). The most recent visual acuities in all eyes with macular oedema are shown in Table 6.

Fig. 4 Results of visual acuity before and after treatment in relation to size and location of tumours.

Table 4 Visual acuity and follow-up

Visual acuity	Length of follow-up		
	Short	Long	Total
Better	8	4	12
Same	18	10	28
Worse	6	14	20
Total	32	28	60

Table 5 Causes of decreased visual acuity

Cause	No.
Increase of retinal detachment	5
Radiation retinopathy—macular oedema	8
Vitreous haemorrhage	3
? Radiation damage to photoreceptors	3
Cataract	1

Fig. 5A

Fig. 5B

Fig. 5 Fluorescein angiography pictures of choroidal melanoma. A: Before treatment. B: Eight months after proton beam irradiation. Tumour regressed but macular oedema is present (visual acuity 20/70).

Table 6 Macular oedema

Last visual acuity	Eyes
20/20-20/40	3
20/50-20/100	5
20/200-CF*	3
*HM	2

*Two eyes with CF vision and the 2 with HM in diabetic patients (CF=counting fingers, HM=hand movements).

Discussion

The superior dose distributions provided by protons or helium ions⁴ offer two major clinical advantages in the field of ocular radiotherapy. First they can treat larger tumours than the radiotherapeutic plaques, because the irradiated volume is reduced, and therefore the tolerance of the eye is substantially increased. The second important clinical advantage is the ability to treat lesions close to critical structures like the macula and the optic nerve. In these locations the sharp reduction of dose outside the target volume with the use of protons permits the delivery of potentially tumoricidal doses to the lesion with sparing of the vital and radiosensitive nearby normal structures. In addition the Bragg peak, which is characteristic of heavy charged particles such as protons, allows a very uniform dose distribution throughout the tumour and the margin of normal tissue around the lesion which is included for adequate coverage of the melanoma borders. This cannot be achieved with radioactive plaques, which deliver extraordinarily high doses (up to 45 000 rads) to the base of the tumour and quite substantial doses to the surrounding tissues.⁵

In this study we have attempted to assess the effect of proton irradiation on visual acuity in eyes with tumours closer than 3 mm to, or involving, the fovea. Although there was no serious expectation of preservation of central vision in these eyes in the initial stages of our studies, our preliminary results are rather optimistic. Twenty-four (40%) of the treated eyes had a last visual acuity of 20/40 or better and 35 (58%) of 20/100 or better. Apart from the four eyes in diabetic patients, in which diabetes probably compounded the radiation injury, direct radiation injury to the macula was not the cause of markedly decreased vision (worse than 20/200).

Complications like vitreous haemorrhage, cataract, and retinal detachment or destruction of the photoreceptors by the tumour before irradiation, in cases where the fovea was involved, were responsible for the visual deficit. It is difficult to tell with certainty whether the visual loss is secondary to vascular changes or to the direct effect of radiation on retinal cells, but the data from this study favour the former.

In almost all cases the decreased vision could be explained by the observed retinal vascular complications.

It is possible that some maculae can tolerate our present radiation dose schedule without direct retinal cellular damage from irradiation. There were four patients in the second location category and three in the third who were followed up for more than two years after irradiation and whose most recent visual acuity was 20/40 or better. One patient with a melanoma less than 1 DD from the fovea who has been followed up for seven years after irradiation of the macula to 50 CGY still maintains 20/40 visual acuity. Recent observations of eyes treated with the cobalt plaques suggest that the lowest dose for inducing foveal damage is 10 000 rads.⁶ Although the nature or quality of the radiation, the volume irradiated, and the fractionation scheme used are quite different in the two forms of treatment, making direct comparison difficult, it is worth noting that the ability to deliver a homogeneous dose with protons makes it possible to achieve a very high probability of sterilisation of the tumour with less than 10 000 rads.

The size of the tumour is an important determinant of post-treatment visual acuity. Macular oedema was observed twice as often in eyes with large melanomas as in eyes having medium size tumours. Visual acuity improved in 14% and deteriorated in 45% of eyes with large tumours compared with 31% improvement and 27% deterioration in eyes with medium size tumours.

Diabetes mellitus seems to have a sensitizing effect on the radiation damage of retinal vessels. All four patients with diabetes developed marked vascular changes from radiation even in eyes without diabetic retinopathy. Postirradiation retinopathy is a form of retinal vascular occlusive disorder⁷ very similar to diabetic retinopathy, and the retinal vessels in these patients are more prone to occlusion and leakage. Neovascularisation of the retina developed in one of these eyes and was treated successfully with laser photocoagulation.

Radiation vasculopathy and macular oedema have been observed as early as four months and as late as four years after irradiation (average 10 months) in this study. However, in other studies postirradiation retinopathy has been observed as late as 15 years afterwards,¹⁰ and we could observe more vascular complications in the future. A multivariate analysis is needed to determine the independent effect of multiple variables on visual acuity outcome. These include tumour size, distance from the fovea, radiation dose to the macula, presence of retinal detachment involving the fovea, and follow-up time. Such an analysis will be done when the sample is larger. Nevertheless, our preliminary observations which we

report here make us believe that proton beam irradiation is a reasonable alternative to enucleation for paramacular or macular melanomas. 67% of the eyes treated retained the same vision or improved, and 58% had visual acuity of 20/100 or better at the time of this analysis. Central vision of the treated eyes is not lost, at least for the follow-up period of this study in the majority of the cases, and some can retain very good vision years after irradiation.

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