

Proton Irradiation of Malignant Uveal Melanoma

A five year follow-up of patients treated in Uppsala, Sweden

Peter Naeser,^{1,2} Erik Blomquist,³ Anders Montelius,⁴ and Karl-Åke Thoumas⁵

¹Department of ophthalmology, Uppsala University, ²Department medical cell biology, Uppsala University, ³Department of Radiophysics, Uppsala University, ⁴Department of Oncology, Uppsala University, and ⁵The MR-Centre of Sabbatsberg Nearhospital, Stockholm, Sweden

ABSTRACT

Twenty patients with malignant uveal melanoma were treated at the The Svedbergh cyclotron in Uppsala from 1989 to 1991. Each tumour received a total dose of 54.6 Gy in four equal fractions on four following days. After treatment the melanoma in all eyes showed decrease in size combined with irradiation retinopathy. In eight patients the treatment was successful after five years. Nine eyes had to be enucleated, two due to recurrence and seven due to neovascular glaucoma. Three patients died, two from metastases and one from heart disease. In all patients the visual acuity was dependent on the distance between the irradiation field and the macula or optic nerve. Each patient suffered from transient post irradiation skin erythema and permanent loss of eyelashes and eyebrows when these were included in the irradiation field. The development of secondary glaucoma was positively correlated with tumour volume, but not to the age or sex of the patients. Histological examination of all the enucleated eyes revealed residual viable tumour without obvious radiation damage: mitotic figures were not identified. MRI examination, performed before and after treatment, demonstrated a marked shift in water binding properties after irradiation. The final visual acuity was dependent on the location of the tumour.

INTRODUCTION

The therapy of the malignant melanoma in the eye has always been a challenge to ophthalmologists and oncologists. In contrast to most other malignancies these tumours are very resistant to irradiation which may be one of the reasons for the poor prognosis [1, 29]. Chemotherapy has mainly been reserved for patients suffering for disseminated disease [36]. From the period when enucleation of the eye was the only therapy which could be offered to the patient, even those with vision restricted to the tumour bearing eye, there have been marked technological and therapeutic advances in the subsequent decades [3].

Treatment of tumours with heavy charged particles was introduced by oncologists more than 30 years ago in order to obtain better local tumour control and to decrease the morbidity related to radiation injury of healthy tissues surrounding the target [7, 23]. As protons have a well defined range and small lateral scattering, they are well suited for radiotherapy where geometric precision is

required and can be used to treat tumours located close to critical structures. In the eye the critical structures neighbouring the tumour are the lens, the optic nerve and the macula. Treatment of uveal melanomas with protons was first published 1977 [18] and since then many centers have used this technique for treatment of ocular melanomas [32].

During the period 1989 to 1991, twenty patients with malignant uveal melanoma were treated with protons from the cyclotron at the The Svedberg Laboratory in Uppsala. The main indication for treatment was the threat of vision loss either by the location or by the dimension of the tumour. The present article describes the results of five year follow up, and also discusses some of the implications of our findings in relation to other published data.

MATERIAL AND METHODS

Patients:

Twenty patients with uveal melanoma, nine men and eleven women, were treated at the proton beam therapy unit of the The Svedberg Laboratory in Uppsala from 1989 to 1991. The mean age was 57 ± 13 years and ranged from 31 to 73. The patients were referred from all over Sweden. Each patient was examined by ophthalmoscopy, ultrasound and fluorescein angiography and the clinical appearances were documented by colour photography. In addition each patient was examined by magnetic resonance imaging (MRI) before and at different times after the treatment and the metabolism of the tumours was registered after peroral carbohydrate intake [30,43]. The volume of each tumour was calculated utilizing the diameter and elevation obtained by MRI and the assumption that each tumour was a hemisphere.

Proton irradiation:

The patients were treated with 72 MeV protons from the synchrocyclotron at the The Svedberg Laboratory in Uppsala [26]. The therapy was given with a single, frontal beam with the patient in a seated position. In order to obtain accurate geometrical precision of the irradiation beam to the tumour, the patient's eye was held in position during the treatment by fixation of a small light source located in a co-ordinate system. The co-ordinates of the light were determined individually by a dose planning system [12]. Two x-ray tubes were placed so that two perpendicularly oriented images of the patient's eye could be obtained. The position of the tumour in the eye was visualised by means of tantalum clips sutured on the surface of the sclera. The radiologically dosage regimen used the co-ordinates of the tantalum clips, measured from the two x-ray images, to create a computerised image of the eye. Thus the direction of the eye was determined so that the proton beam avoided the critical structures in the eye. In addition the beam aperture and the maximum proton range was optimised by the programme. Fig. 1 shows an example of a dose plan in a section through the eye. The isodose curves show that the tumour receives a maximum dose while the lens, the optic nerve and the macula are spared. The irradiation cannot, however, be confined solely to the tumour: the irradiation of the tissues between the tumour and the surface of the eye was unavoidable. Exposure of the margins around the tumour was also unavoidable due to small eye movements and the width of the dose fall-off (penumbra). This means that, in cases where the tumour encroaches on the edge

of the optic disc or the macula, these critical structures will be damaged and the vision will not be preserved.

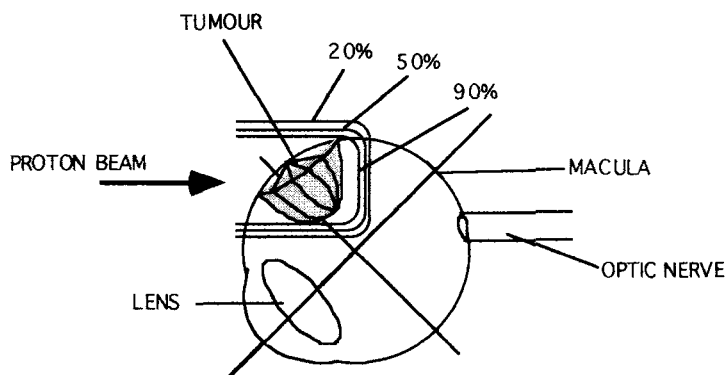


Fig 1. Dose distribution in a section through the eye. The direction of the proton beam is indicated together with the 20, 50 and 90% isodose curves. The tumour is given maximum dose while the lens, macula, optic disc and optic nerve are spared.

The dose planning programme also utilised the x-ray images of the tantalum clips with the patient in the optimal treatment position. These images were used to align the patient in the proton beam.

Between 1989 and 1991, 20 patients with eye melanoma were treated. They were given 54.6 Gy in four equal fractions during four consecutive days.

RESULTS

Clinical features:

Early changes:

The tumours did not display any significant changes immediately post-irradiation.

Retina lying over and at the base of the tumour became oedematous within the first week and later developed the hard exudates characteristic for radiation retinopathy. In addition, there were small haemorrhages in retina over the tumour combined with a shallow exudative retinal detachment. In all cases the retina reattached within a few months.

The vitreous body was undisturbed. Sector opacities appeared in one patient within that part of the lens which was in the irradiation field. The cataract remained stable and did not hinder inspection of the fundus. In all patients the corneal epithelium contained fine punctate defects during the first month and these were treated with artificial tear solutions and ocular lubricants. In one patient the lacrimal gland was irradiated, there was diminished tear production and the patient needed permanent treatment with artificial tears.

The skin which was within the field of irradiation showed redness and dryness which is typical for an acute irradiation reaction. Ulcerations did not occur and the skin was treated with after-sun-creams and fatty creams. Local treatment with corticosteroids had little or no effect. When the acute reaction had settled, there was no significant evidence of irradiation damage. The eyelashes and eyebrows which were irradiated disappeared and did not regrow.

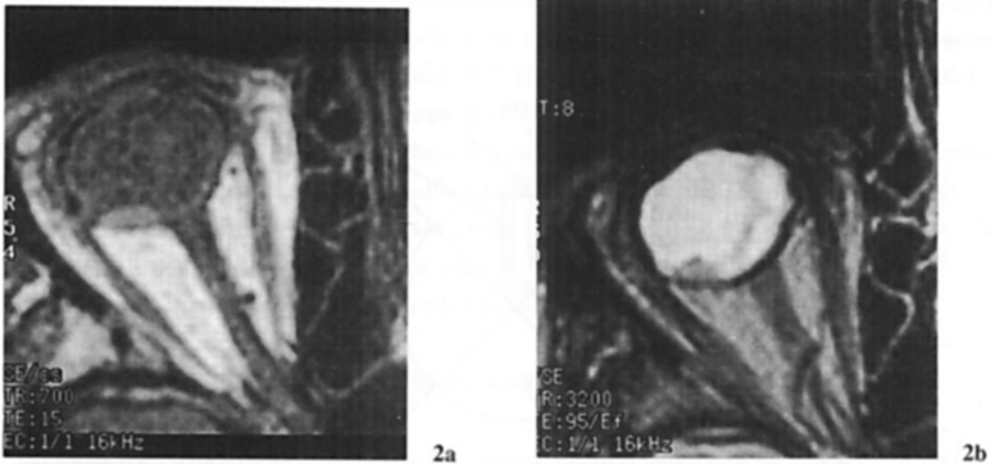


Fig 2. MRI (T1) taken 60 months after proton beam treatment (a). Note the phthisic eye with thickened sclera and the large tumour posterior. Note elongated T2 relaxation time (b) indicating large pool of unbound water in the tumour. Retinal ablation is clearly seen to the right.

Late changes:

Seven eyes developed painful haemorrhagic glaucoma combined with total retinal detachment and intraocular haemorrhage during the first 4 to 12 months after treatment. The eyes were enucleated due to pain combined with a subsequent phthisis, the 7th eye after 60 months (Fig. 2a and b). In all these cases histological examination revealed apparently viable spindle cell melanoma (see below). Two eyes were enucleated due to obvious tumour recurrence 18 months after treatment.

Table 1 displays the outcome of the 20 patients at the five-years follow-up. Eight patients still had

| Outcome of treatment | Number | Mean age years \pm sem | Tumour volume $\text{mm}^3 \pm$ sem | Sex |
|----------------------|--------|--------------------------|-------------------------------------|-------------------|
| Remaining eyes | 8 | 59 \pm 4 | 416 \pm 93 | 6 females 2 males |
| Enucleated eyes | 7 | 50 \pm 5 | 1381 \pm 293 ¹⁾ | 4 females 3 males |
| Tumour recurrence | 2 | 57 (46 and 68) | 161 \pm 114 | 1 female 1 male |
| Deceased patients | 3 | 69 \pm 2 | 1142 \pm 389 | 3 males |

Table 1 Result of the treatment listed with respect to number, age, volume and sex. Note that the 7 enucleated eyes had developed painful haemorrhagic glaucoma which was significantly related to the tumour volume. The recurrent tumours were small. ¹⁾ = $p < 0.01$. There is no correlation with sex or age.

their eyes in situ. Nine eyes had been enucleated due to either painful neovascular glaucoma or tumour recurrence. The table furthermore shows that the response to treatment was closely correlated to the volume of the tumours, and that age and sex are not of significance.

The preservation of vision after treatment was dependent on the localisation of the tumour. Six eyes with tumours close to the macula and/or the optic nerve progressed to counting fingers within one to two months. The two eyes with small tumours in the periphery had no change in visual acuity.

Histopathological investigation:

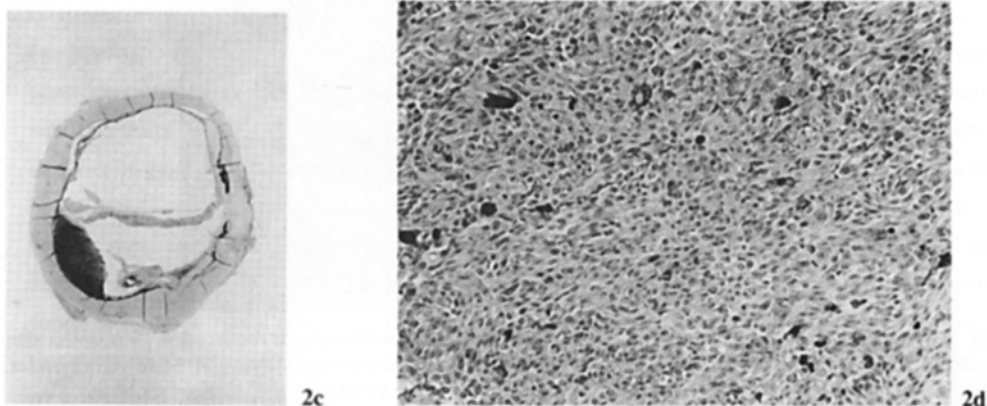


Fig 2 c and d. Horizontal histological section through the phthisic eye which was enucleated 60 months after treatment. Note the thickened sclera and the large tumour mass (elongated dark tumour) in the posterior part of the eye. HE x 3. d) Tumour cells with slight pleomorphism and vacuolated cytoplasm. Note the scattered dark melanomacrophages H&E x 80.

The tumour cells displayed a slight pleomorphism and their cytoplasm was vacuolated. Pigment was seen within some of the cells, but mitotic figures were not identified. The loose stroma contained vessels with hyalinised walls which were surrounded by lymphocytes and heavily pigmented macrophages (Fig 2c and d). In the two cases which were enucleated due to clinically identified recurrence, the main part of the tumour showed similar changes except for the peripheral part where there was the typical appearance of spindle cell melanoma (Fig 3).

Two patients died from metastases and one from heart disease during the first two years after irradiation. The eyes of these patients were not made available for histological investigation.

DISCUSSION

The present report displays the results of proton beam treatment of uveal tumours of different size and localisation performed in Uppsala, Sweden from 1989-1991. Although the series is small, it may add a better perspective to the current trends of melanoma management.

The follow-up in our patients was not difficult. However, the interpretation of the treatment effect and success was difficult due to the very slow regression of the tumour after treatment. This is in conformity with other reports [38, 45]. For this reason we added MRI investigation to the clinical investigation [43]. In this way we were able to observe that the T2-values for melanomas, typical short T2-value, was prolonged after the irradiation, and that recurrence was accompanied by a shift to short T2. The shift in the T2 signal intensity is considered to reflect changes in the metabolic activity of the tumour which may differentiate non-active from active melanomas [43, 44].

The impact of the treatment on the visual acuity was dependent on the distance between the

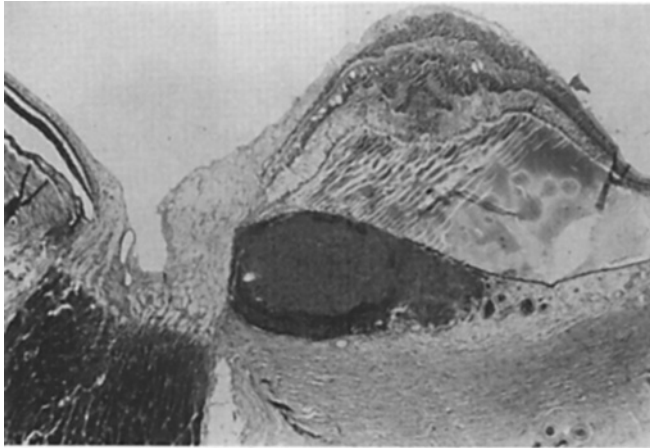


Fig 3. Histological section from the posterior pole of an eye with tumour recurrence 19 months after irradiation. Note the small tumour surrounded by melanomacrophages laying close to sclera under retina. The retina above the tumour recurrence displays irradiation retinitis. Luxol fast blue x 10. In both cases it was clear that the irradiation beam had not encompassed the whole tumour.

irradiated field, and the macula and the optic nerve. In cases where only the optic nerve was implicated, the decrease of vision developed to hand movements or light perception within three to four weeks. This is in agreement with the complications after other types of irradiation [5, 39, 46]. The skin and corneal changes were not serious, and in most cases healed with local therapy within 3-4 weeks. Cataract development was, as anticipated, only an occurrence when the lens was included in the irradiated field. Changes in the vitreous body did not primarily appear, and if they arose they were secondary to changes in the tumour or the retina [11, 13, 15, 22, 37].

The volume of the tumour was decisive for the most severe complication which was the development of secondary, haemorrhagic glaucoma. The reason for this may be that vascular endothelial growth factor is released from the large tumour mass which is not totally destroyed by the protons [16, 17, 28, 31, 37, 42].

Histological investigation of the eyes in the present study and in those of other authors has shown that viable tumour persists for as long as 5 years after treatment [8, 14, 35, 48]. Granulomatous inflammatory reaction which may indicate risk for development of sympathetic ophthalmia has been reported by other authors [25], but this was not the case in our patients.

Due to the continuous development of new methods for treatment, the attitudes to treatment have changed radically. From enucleation as being the only alternative, which of course was intended to maintain the patients life without taking account of loss of vision, it is today possible to preserve vision [41] due to development of varied treatment modalities amongst which irradiation is the most commonly recommended. Various surgical techniques [6, 34] and thermoablation have been applied in a few centers [9, 33]. The results of these which till now have been experimental clinical treatments, have been difficult to assess. Even the results of irradiation may be difficult to evaluate as the biological influence may change not only by the choice of isotopes, gamma or beta emitters, but also the exposure time used in treatment [4].

The mortality from metastatic uveal melanoma has not changed significantly with the various forms of treatment of the primary disease - enucleation, local resection, or irradiation [2, 19, 20, 21, 27, 40, 47]. The problems of prognostic prediction for survival after irradiation are complicated by the fact that with radiotherapy the biological features of the tumour are unknown at the start of the treatment. Even with the histological information provided by the enucleation specimen in the failed cases, prognosis for survival is independent of most of the histological features at present under consideration apart from the presence of epithelioid cells and the size of the tumour. The outcome in small tumours is usually favourable which is a generally accepted conclusion for most tumours. The experience gained from the present study of pathological specimens suggests that enucleation should be favoured for those patients who at the outset are regarded as inappropriate for conservative management and for those patients in whom the response is unfavourable. This would spare such patients from the anxiety resulting from continuous observation and the second, third and sometimes fourth stages of surgical intervention, e.g. cataract surgery and detachment surgery and the surgical treatment of glaucoma for neovascular complications. Furthermore, the high cost of the initial treatment and the subsequent costs incurred in further management should be taken into consideration particularly with reference to the "fate of the melanoma". With a policy based on this philosophy, the quality of life for the patient may be significantly increased [24, 10].

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KEY WORDS

uveal melanoma, radiotherapy, histopathology, proton irradiation, MRI

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Offprint requests to:

Peter Naeser, MD, PhD
 Department of Medical Cell Biology,
 Biomedicum
 Box 571
 S 751 23 Uppsala, Sweden