Results after β -irradiation ($^{106}\text{Ru}/^{106}\text{Rh}$) of choroidal melanomas: 20 years' experience

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SUMMARY From 1964 to 1984 309 patients with choroidal melanoma were treated with $^{106}\text{Ru}/^{106}\text{Rh}$ β ray applicators (1000 Gy at the apex of the tumour within 7-14 days). In 216 cases (69.9%) this treatment was successful for a mean follow-up period of 6.7 years after irradiation. In 53 cases (17.2%) the eye had to be enucleated, and 40 patients (12.9%) died from metastases within this period. Of the 216 successfully treated patients 114 (52.8%) developed flat scars and 49 (22.7%) retained a visual acuity of 1.5-0.5. Radiogenic late complications with damage to the retinal capillary system were the main causes of visual deterioration, especially in eyes with tumours close to the posterior pole. The survival rate is substantially higher than that for patients whose eyes were primarily enucleated. β Ray applicators with $^{106}\text{Ru}/^{106}\text{Rh}$ can be recommended as an effective tool and a simple and cheap procedure to cure patients with small and medium sized choroidal melanomas. They save the eye without endangering our patients' lives.

Stallard¹ was the first ophthalmologist who treated patients successfully with ^{60}Co plaques and proved that the earlier assumption of absolute radioresistance of choroidal melanomas could not be maintained. After β irradiation of conjunctival melanomas had yielded satisfactory results,² and to reduce the severe radiogenic side effects using ^{60}Co , we tested other radionuclides, and $^{106}\text{Ru}/^{106}\text{Rh}$ was found to be a suitable energy source for treating intraocular tumours.

Freundlich³ had described in 1949 the radionuclide $^{106}\text{Ru}/^{106}\text{Rh}$ for high-dosage local irradiation. The decay of ^{106}Ru via ^{106}Rh to the stable element ^{106}Pa produces β rays having an energy of 3.54 MeV (79%), 3.0 MeV (8%), 2.4 MeV (11%), and 2.0 MeV (2%), so that the depth of penetration into the tissue is greater than by $^{90}\text{Sr}/^{90}\text{Y}$.

As shown in previous studies, $^{106}\text{Ru}/^{106}\text{Rh}$ applicators make it possible to deliver high doses to the tumour without danger of radiogenic damage to the healthy parts of the eye and with a minimum lens exposure.^{4,5}

Material and methods

We used concave mirror-like applicators consisting of pure sheet silver of 1.0 mm thickness which contain $^{106}\text{Ru}/^{106}\text{Rh}$. The shell-shaped applicators have a spherical radius of 12-14 mm. They contain the radioactive material as a thin film of the insoluble ^{106}Ru ruthenium evenly distributed. The fused front window of the applicator on the concave side is 0.1 mm and the back 0.9 mm thick, and it absorbs nearly 95% of the 3.5 MeV β radiation; this is important in practice. The surface dose rate is about 120 mGy per minute, making it possible to apply a dose of 1000 Gy (100 000 rad) at the base of the tumour and 100 Gy (10 000 rad) at its apex in about six days.

$^{106}\text{Ru}/^{106}\text{Rh}$ ophthalmic applicators have two ears by means of which they can be sutured to the sclera. Five types of ^{106}Ru applicators (CCA, CCB, CCC, COB, and COC) are available. For the treatment of tumours in the vicinity of the optic nerve the types COB and COC have a sector cut out specifically for the nerve*.

The surface dose rate for each applicator is measured with a special scintillation probe, which is calibrated by means of a so-called extrapolation chamber. To check the equal distribution of radioactivity the surface dose rate is measured in 9-17

*Obtainable from Isocommerz GmbH, DDR-1115 Berlin, Lindenberger Weg, German Democratic Republic.

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Table 1 Types of applicator

Source type	External diameter (mm)	Inactive edge (mm)	Spherical radius (mm)	Nominal activity	
				(MBq)	(mCi)
CCA	15	0.5	12	15	0.4
CCB	20	0.5	12	18.5	0.5
CCC	25	0.5	14 (on request: 13)	26	0.7
COB	20	0.7	12	18.5	0.5
COC	25	0.7	14 (on request: 13)	22	0.6

For all types the approximate surface dose rate is 120 MgY/min (12 rad/min) $\pm$ 30%.

different positions of the surface in water. The results refer to the activity at the centre of the applicator.

Between January 1964 and December 1984 309 patients (168 male, 141 female) suffering from choroidal melanoma were treated with $^{106}\text{Ru}/^{106}\text{Rh}$ β -applicators. The average age was 52.25 years. The tumour destructive dose—following Stallard's recommendation—was at least 100 Gy at the apex of the tumour. Thus values above 1000 Gy may be reached at the tumour base. An irradiation period of 8 to 14 days seemed to be the optimum exposure time.

The conjunctiva, Tenon's capsule, and, if necessary, muscles were incised under local or, better, general anaesthesia so that the applicator could be placed on the sclera as closely as possible to the tumour base, which had to be carefully localised by transillumination or diathermy. Details of the surgical procedure have been published.^{4,5}

Tumour regression was recorded on follow-up examinations by fundus photography, ultrasonography, and fluorescein angiography. The average follow-up period was 6.7 years. One hundred and eighty-eight patients were followed-up for more than five years (average 9.4 years) and 87 were observed for more than 10 years after irradiation.

To describe the extent of the primary tumour the pretreatment clinical classification, designated TNM, was used as recommended by the International Union against Cancer (UICC).⁷

Results

Out of 309 treated patients 190 (61.5%) are alive and have both eyes intact, in 44 (14.2%) the eye had to be enucleated, and 75 patients (24.3%) died—40 from metastases and 35 from other or unknown causes (Fig. 1).

In this study those patients whose tumours had either changed to a flat scar or had shrunk to a still appreciable greyish or black mass with scarring of the tissue around the tumour, which had remained unchanged for more than one year, were considered

Fig. 1 Results after β irradiation with $^{106}\text{Ru}/^{106}\text{Rh}$ plaques of 309 patients.

Fig. 2 Results after β irradiation with $^{106}\text{Ru}/^{106}\text{Rh}$ plaques of 309 patients.

to have been treated successfully. Moreover those patients who died later from other causes than metastases and whose choroidal melanoma had shrunk or cicatrised were also included as successfully treated cases. Only those patients who died from metastases or whose eyes had to be enucleated were counted as failures.

Thus 216 patients (69.9%) out of 309 were treated successfully and have been under observation for a mean period of 6.7 years after irradiation (shortest period one year, longest 21 years). Fifty-three (17.2%) patients' eyes had to be enucleated because of tumour new growth but they have not died from metastases. Forty patients (12.9%) died from proved metastases in this period of 20 years (Fig. 2).

One hundred and eighty-eight patients could be followed up for more than five years (101 patients for 5–9 years, 63 patients for 10–14 years, and 24 patients for 15–21 years). Out of the group with long-term follow-up for a mean period of 9.4 years 110 (58.5%) could be regarded as successfully irradiated, 36 (19.2%) had to have the eye enucleated and are still alive, and 42 (22.3%) died—18 (9.6%) of the latter from metastases and 24 (12.7%) from other causes (Fig. 3).

Out of the 24 patients who died from other causes four had to have the eye enucleated. Therefore, as

Fig. 3 Long-term results after β irradiation with $^{106}\text{Ru}/^{106}\text{Rh}$ plaques of 188 patients.

Fig. 4 Long-term results after β irradiation with $^{106}\text{Ru}/^{106}\text{Rh}$ plaques of 188 patients.

shown in Fig. 4, 130 (69.1%) patients could be regarded as successfully treated cases, 40 (21.3%) had to have the eye enucleated and are either alive or died from other causes than metastases, and 18 patients died from proved metastases.

Tumour regression. As shown in Fig. 5, 114 (52.8%) of the successfully treated patients had a flat scar after therapy. The other eyes showed more or less evident remnants of the former tumour. The fact that tumour regression after this kind of therapy may take many months is important for avoiding a hasty decision to carry out enucleation. The regression to a

flat, pigment stippled scar depends primarily on tumour size. However, all tumours larger than T1 NO MO (NO=no evidence of regional lymph node involvement; MO=no evidence of distant metastases) left behind an elevated mass, which should be observed carefully during the follow-up period because of some possible reactivation process (Figs. 6, 7).

Visual acuity. Preservation of useful visual acuity is a principal aim of β -ray treatment. As shown in Fig. 8, only 49 (22.7%) out of all successfully treated patients retained a good visual acuity of between 1.5–0.5. About half of the patients (54.2%) had only a poor central visual acuity of less than 0.2 because the macula had been involved in the cicatricial formation after treatment (Fig. 8). Visual field deficiencies corresponding to the retinochoroidal scar were recorded in all our patients.

Enucleation after β irradiation. Enucleation was necessary in 64 cases, mostly within the first year of treatment. The reason for removing the eye was new tumour growth in 54 and loss of visual acuity due to radiogenic side effects in 10 cases. Histological examination of the enucleated eyes showed active new-grown melanoma tissue without damage of the tumour cells in 52, scar tissue containing some tumour cells in four, scar tissue without tumour cells in four, and no reports of a histological examination were available in two cases. Out of all 64 the enucleated patients 11 (17.2%) died from metastases within one to seven years after enucleation; nine patients died from other causes.

Deaths after β irradiation. Seventy five patients of this series died during the follow-up period—40 of metastases, 27 of other diseases than melanoma (cardiac infarction or apoplectic stroke 19, other malignant tumours 6, cirrhosis of liver 1, suicide 1) and eight of unknown causes. Death from metastases was verified by necropsy in 19, laparoscopy in four,

Fig. 5 Tumour regression after β irradiation.

Fig. 6A

Fig. 6 A: Choroidal melanoma of right eye before treatment. B: Same eye two years after β irradiation with $^{106}\text{Ru}/^{106}\text{Rh}$ 1084 Gy within 14 days at scleral surface. C: Same eye eight years after irradiation. Visual acuity 0.5.

Fig. 6C

and by clinical examination in 17 cases. Metastases occurred mainly in the liver, where in some cases an extreme hepatomegaly was produced. 65% died within five years of irradiation.

Enucleation and metastases. Out of 64 patients enucleated because of tumour new growth after irradiation 11 (17.2%) died from metastases,

whereas 29 (11.8%) patients out of the 245 cases without enucleation died from metastases.

Tumour size. As shown in Fig. 9, most of the choroidal melanomas were class T1a or T1b (70.9%). The prevalence of smaller tumours is even clearer in the group of the 216 patients treated successfully (Fig. 10). In the group of 40 patients who later died from metastases or had to have the eye enucleated there was a prevalence of tumours of class T3 (17 cases, 42.5%). Only 10.5% of our patients who could be treated successfully with a follow-up period of more than five years had a melanoma classified as T3. This underlines the well-known correlation between tumour size and therapeutic outcome: the smaller the tumour the better the chance of treating choroidal melanomas successfully with β -rays.

Repeated radiotherapy. Repeated therapy with radioactive applicators was necessary in 16 cases because the tumour continued growing after the first irradiation. The second treatment was successful in seven patients. Nevertheless, four had to have the eye enucleated and five died from metastases.

β Irradiation and xenon coagulation. Light coagulation was additionally performed after β irradiation in 34 cases to occlude the choroidal vessels round the tumour. First, the central rim of the tumour was surrounded by coagulations. Later, if the tumour was not completely destroyed, the surface of the tumour proper was also coagulated. Especially in eyes with the melanoma close to the optic disc and where the applicator could not be placed completely round the tumour, we succeeded in a partially surrounding the central tumour rim with the effects of coagulation.

Fig. 6B

Fig. 7A

Fig. 7 A: Choroidal melanoma of right eye before treatment, fluorescein angiography. B: Same eye six months after β irradiation with $^{106}\text{Ru}/^{106}\text{Rh}$ 1048 Gy within four days at scleral surface. C: Same eye five years after irradiation. Visual acuity 0.3.

The results obtained in our 34 cases with light coagulation were as follows: patients successfully treated, 21; patients living but with eye enucleated, 4; patients dying, 9 (from metastases 4).

Fig. 7B

Fig. 7C

Fig. 8 Visual acuity after β irradiation.

Fig. 9 Tumour sizes before treatment (TNM classification).

Fig. 10 Tumour sizes before treatment of 216 successfully treated patients.

Fig. 11 Survival rate of patients ($n=309$) with choroidal melanoma treated with $^{106}\text{Ru}/^{106}\text{Rh}$ β ray applicator. Broken line indicates deaths from metastases, solid line deaths from any causes.

Radiogenic side effects. Radiogenic tissue damage must be expected after each kind of radiotherapy, particularly the serious late effects which may occasionally occur after β irradiation. Exudative reactions occurring a few days after irradiation, such as chemosis, choroidal detachment, and even transient retinal detachment, should not be regarded as serious complications, because of their good prognosis. Against earlier expectations the primary concern is now the postradiation retinopathy that has frequently followed β irradiation, sometimes even years after initially successful treatment.

Radiogenic complications which led to deterioration of visual acuity were as follows: macular destruction because of scarring around the tumour, 83; atrophy of the optic nerve, 23; macular degeneration, 16; postradiation retinopathy with oedema of the optic disc, 17; partial cuneiform cataract without loss of vision, 5; total cataract, 7; vitreous haemorrhage, 10; secondary glaucoma, 3; thrombosis of the central retinal vein, 2; scleral necrosis, 1; exudative reactions

such as choroidal and retinal detachment with spontaneous improvement, 21.

Most of the patients (83) with a tumour 1 to 2 disc diameter away from the posterior pole showed a destruction of the macula, because the scarring round the tumour necessarily involved this retinal area.

Survival rate after $^{106}\text{Ru}/^{106}\text{Rh}$ therapy. The survival rate was calculated by the life table method. As shown in Fig. 11, survival rates of 84.3% (deaths from any causes) or 88.7% (deaths only from metastases) after five years and 65.8% (deaths from any causes) or 79.5% (deaths only from metastases) after ten years could be achieved. In this diagram the survival rates of patients who died from metastases and those who died from other causes were plotted separately. A comparison with results published in previous studies⁶⁻⁸ shows that survival after local β irradiation is better than after enucleation.

Discussion

The traditional treatment of patients suffering from choroidal melanoma was enucleation of the involved eye as soon as diagnosis was made. More recently the value of enucleation has been questioned, and some authorities have even speculated that this procedure may impair prognosis.^{9,10} This hypothesis has provoked objections,¹¹⁻¹³ so that additional studies will be needed to determine whether our ideas on the management of choroidal melanomas are correct.

Although in the past believed to be ineffective in the treatment of intraocular melanomas, radiotherapy has recently become more generally accepted, especially the use of radioactive plaques and charged particle irradiation.¹⁴⁻¹⁶ Some investigators, including ourselves have shown that patients treated by conservative methods such as photocoagulation or irradiation as alternatives to enucleation have a relatively low incidence of metastases, but convincing randomised prospective studies are still lacking.⁸

The choice of therapy depends on certain conditions, and each case should be considered individually. In selecting the most effective therapeutic approach the following factors must be carefully weighed: size of the melanoma, its extent and location, its activity, the condition of the other eye, and the age, general health, and last but not least the psychological status of the patient.¹⁷

The results presented in this study lead us to the conclusion that β irradiation is an effective procedure especially for the treatment of small and medium sized choroidal melanomas (T1 and T2). Additional light coagulation or a second β irradiation make it possible to treat even larger tumours in two steps.

In previous studies⁴⁻⁶ a 74% (1974), 61.6% (1979),

and 64.4% (1983) cure rates were found. These results are in accordance with the therapeutic results after a long-term follow-up presented in this paper with a healing rate of 69.9%.

The apparent increase in the percentage of successfully treated patients from 64.4% (1964–80) to 69.9% in this paper may be related to the shorter follow-up of the most recent 104 patients, though the average follow-up of 6.7 years was longer in comparison with 5.4 years in the previous series. The slight differences between the percentages of the successfully treated cases in which the tumour regressed to a flat scar—45.5% (1980), 60.5% (1980) of patients observed for more than five years and 52.8% in this paper—are probably caused at random.

These figures suggest that β irradiation with $^{106}\text{Ru}/^{106}\text{Rh}$ plaques will produce a successful therapeutic outcome in about two-thirds of the cases, provided the following recommendations are observed. First, because of the physical properties of $^{106}\text{Ru}/^{106}\text{Rh}$ (at a distance of 6 mm, the dose received is less than 10% of the surface dose) the choroidal melanoma should not exceed 6 mm in height above the scleral surface. Tumour cells at a distance of more than 6 mm from the applicator will not receive the damaging dose of at least 1000 Gy (10 000 rad). Secondly, the distance of the posterior margin should be at least 1 to 2 disc diameters from the nerve head, otherwise radiogenic papillitis with atrophy of the optic disc will prevent useful visual acuity. Thirdly, if the tumour has involved the ciliary body (contrary to former opinion) a special shape of $^{106}\text{Ru}/^{106}\text{Rh}$ plaque can be used with some success. Fourthly, there should be no extension of tumour outside the eye.

Radiogenic side effects and the incidence of complications depend on the dose distribution within the eye. In the case of β irradiation the severity and extension of postradiation retinopathy is less than after ^{60}Co irradiation, with its higher volume dose.¹⁸ The high incidence of visually destructive radiation effects after β irradiation was caused by macular destruction in those cases where the tumour grew close to the macular region. If the tumour comes closer than 2 disc diameters to the optic disc, the dose delivered to the nerve head will result in an increasing incidence of optic atrophy even after $^{106}\text{Ru}/^{106}\text{Rh}$ plaque therapy.

Although it is evident from these and other statistical data that survival rate and local therapeutic results are mainly dependent on the number of tumour cells within the eye, it may sometimes be necessary to irradiate larger tumours because the patient refused enucleation or the tumour occurred in the only eye able to see. In some of these cases I have observed against expectation a surprising shrinkage of the tumours. In questionable situations,

therefore, it seems to be justified to try β irradiation first and to hope for regression before performing enucleation.

My experience suggests that local irradiation is not likely to result in a higher incidence of metastases than enucleation, though the only scientific way to answer this question would be a randomised prospective study. Rotman *et al.*¹⁹ pointed out that those methods of treatment which left the eye in situ (local excision, light coagulation, radioactive applicators) had a greater overall survival rate than enucleation of the eye. A further suggestion is that sterilisation of the tumour by irradiation, in contrast to enucleation, promotes an immune response that may indeed control distal metastasis.²⁰

New radiotherapeutic procedures have been published recently that improve the possibilities of local radiotherapy by ^{125}I seeds¹⁴ and proton beam irradiation¹⁴ or heavy helium ions.¹⁵ Although long-term follow-up examinations are still lacking, the preliminary experience with these new methods is encouraging. The management of choroidal melanomas will probably remain controversial in the near future. In any case β irradiation with $^{106}\text{Ru}/^{106}\text{Rh}$ plaques adds to the possibilities of treating choroidal melanoma.

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Accepted for publication 20 February 1986.