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CLINICAL INVESTIGATION

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Results of treatment of choroidal malignant melanoma with high-dose-rate strontium-90 brachytherapy

A retrospective study of 46 patients treated between 1983 and 1995

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Abstract ● Purpose: We review the results of treatment of small to medium-sized choroidal malignant melanomas after high-dose-rate brachytherapy with a strontium-90 applicator. ● Methods: The applicator is positioned against the sclera using an afterloading technique. Brachytherapy is completed in a single session lasting 2–4 h with the patient under local anaesthesia. From September 1983 until March 1995, 46 eyes were treated in this way. Most tumours were 7–11 mm in diameter (range from 4.5–15 mm) with a mean height of approximately 3 mm (range from 1.5–7 mm). Follow-up ranged from 6 months to 12 years (mean 49 months). ● Results: Thirty of the 46 eyes had at the final evaluation a non-evolutive scar (20 of these after a single application, the others with some additional treatment). In 13 eyes the tumours were in involution but their complete destruction was not yet certain, and 3 eyes were enucleated for local recurrence. Three patients developed systemic metastases. No radiogenic complications were noticed. ● Conclusion: Strontium-90 brachytherapy is a valuable and safe treatment technique for small to medium-sized choroidal malignant melanomas. In addition the use of a strontium-90 applicator is inexpensive thanks to this element's long half-life and the short application time.

Introduction

In the 1960s Stallard showed that treatment of choroidal malignant melanoma by means of a radioactive plaque gave survival rates similar to those following enucleation [21, 22]. Stallard used the high-energy gamma emitter cobalt-60. This deeply penetrating irradiation caused major side effects (e.g. radiation retinopathy) [3, 22]. Lommatzsch used the beta emitter ruthenium-106, with fewer side effects [17, 18]. Encouraging results have been published for the gamma emitter iodine-125, which has good penetration and flexible handling [7, 11, 20]. More recently, studies have been published using the low-energy gamma emitter palladium-103, which transmits less radiation to normal ocular structures [4–6]. However, iodine-125 and palladium-103 have short half-lives of, respectively, 60 and 17 days; therefore the applicators must be frequently renewed and recalibrated. Strontium-90, in contrast, has a half-life of 28.5 years.

The use of strontium-90 beta-ray applicators has been described for the treatment of epibulbar melanomas [15, 16], corneal vascularization [1] and pterygium [24, 25], but strontium-90 has not been favoured for the treatment of posterior uveal malignant melanoma.

In the early 1980s, ruthenium-106 applicators were not easy to come by in Western Europe. As an alternative, an epibulbar surface strontium-90 applicator was modified and used in our department for the treatment of an urgent case, with a good result. The very same applicator is still in use today for the treatment of small and medium-sized choroidal malignant melanomas.

Materials and methods

The modified Amersham SIAQ 7321 applicator

An epibulbar SIA surface applicator produced by the Amersham company [28] was modified for use as an applicator for treatment of choroidal malignant melanoma. This epibulbar applicator has a diameter of 16 mm and a radius of curvature of 15 mm. It was loaded with 370 MBq (10 mCi) strontium-90 at the concave side, shielded with 0.1 mm platinum. The radioactive zone coated with strontium-90 has a diameter of 12 mm. The modification of the original epibulbar applicator consisted of removing the shaft. In this process the actual radius of curvature of the applicator has slightly increased to 15.5 mm (Fig. 1). Since no depth-dose curves were available for this modified applicator, dosimetric control and the construction of a depth-dose curve has been established by the Department of Physics (Prof. A. Dutreix) of the Institut Gustave Roussy, Villejuif, France. The dose rate and depth dose have been measured by lithium borate transluminescent dosimetry (TLD) and by densitometric measurement. In 1983 the dose rate at the applicator's surface was measured at 7.2 cGy/s, thus delivering a surface dose of 600 Gy in 139 min. Strontium-90 has a half-life of 28.5 years.

A perforated stainless steel ring with an inner diameter of 16.5 mm and an outer diameter of 18.5 mm was constructed to fix the strontium plaque to the sclera (Fig. 1).

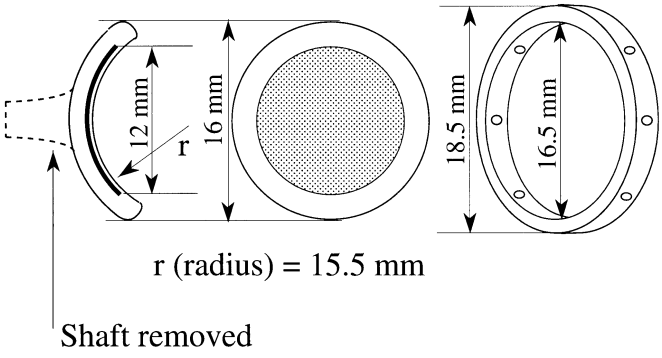

Fig. 1 Our modification of the Amersham SIAQ 7321 strontium-90 applicator. After removing the shaft, we obtain a 16-mm-diameter applicator with a 12-mm radioactive zone. The perforated stainless steel ring to fix the applicator to the sclera is shown at the *right*

Estimation of tumour size

The dimensions of each melanoma were determined by echography and by measuring on fundus photographs. The two methods gave rather similar results. All dimensions mentioned in this paper are determined by a Sonomed B-scan echograph on images showing maximum dimensions of the tumour. Electronic callipers were positioned at the apex of the tumour and at the presumed interface between tumour and sclera, and the computed distance was recorded as the height of the tumour. In order to calculate the radiation dose at the apex of the tumour, 1 mm was added to this figure for the thickness of the sclera. The maximum and minimum diameters of the tumour were also measured with electronic callipers on a B-scan. Tumour volume was calculated by means of the equation: volume=1/6 π h (3/4 d^2 + h^2) where h is the height and d the mean diameter of the tumour as measured by echography.

Patients

Between September 1983 and March 1995, 234 eyes were treated for choroidal malignant melanoma in the Ophthalmology Department of the University Hospital of Leuven. Of these eyes, 48 were treated with one or more applications of the high-dose-rate (HDR) strontium-90 applicator. All patients gave their informed consent for this treatment. This study comprises 46 eyes, with a minimum follow-up of 6 months (mean 45 months). Two eyes were not included because they had tumorectomy prior to the strontium-90 brachytherapy. Tables 1 and 2 give information on the 46 patients who were included, their tumours and their treatment.

The diagnosis of malignant melanoma was made by clinical examination (indirect ophthalmoscopy), A- and B-scan ultrasonography and fluorescein angiography. Small tumours were included in this study only after growth was documented during an observation period of several years (five cases) or when ophthalmoscopic findings such as the presence of obvious lipofuchsin exudation made the diagnosis of naevus unacceptable. The patients were screened for systemic metastasis (liver ultrasound, chest X-ray, CT of the brain, CT of the orbit, technetium scan of the bone, examination of serum parameters, general and dermatological examination). Of the 46 patients, one (no. 4) had liver metastases at the time of initial diagnosis. She was treated with strontium-90 brachytherapy for palliative reasons.

The decision to treat patients with strontium-90 brachytherapy was made on the basis of tumour size and location. Originally only small melanomas, with a maximum diameter of 10 mm and a maximum thickness of 3.5 mm, were considered for this treatment. However, as experience grew, larger tumours, some exceeding 5 mm in height, were treated with the two-step procedure described below. The maximum diameter treatable was limited by the size of the active plaque (12 mm). In three patients tumours with larger diameters, up to 15 mm, were treated. This was done by moving the plaque to a second position (with partial overlap of the two positions) during one intervention. The average size of the tumours treated with strontium-90 brachytherapy was 8.8 ± 2.0 mm (range 4.5–15 mm) in diameter and 3.3 ± 1.3 mm (range 1.4–7 mm) in height.

After treatment, patients were seen regularly during the first year of follow-up (monthly, bimonthly, then after six months), then on a yearly basis. On these follow-up consultations patients were examined by indirect ophthalmoscopy, A- and B-scan ultrasound and fundus photography. The first 15 patients were also followed by fluoroangiography. Fundus photographs and echograms were compared to detect any recurrences.

Dosage

From 1983 to 1990, application time was calculated in order to obtain a dose of 75 Gy to the apex of the tumour. The distance to the plaque was estimated to be equal to the tumour height obtained from A-scan ultrasound with 1 mm added for the thickness of the sclera. In the course of 1990, this procedure was changed for reasons explained in the Discussion. Application time is now calculated to obtain a scleral irradiation of 600 Gy in a single application.

In 1983 the application time needed to deliver 600 Gy to the sclera was approximately 139 min; over the years, due to the decay of the strontium-90 source, this time has increased to slightly over 3 h.

Application technique

Patients were admitted to hospital for treatment. The application of the strontium-90 plaque is carried out under retrobulbar anaesthesia using a long-acting agent such as bupivacaine (Marcaine). The sclera is prepared (usually a rectus muscle disinsertion is required). The tumour location is determined by transcorneal transillumination. An applicator ring made of stainless steel, designed to fix the

Table 1 Tumour characteristics, treatments with HDR strontium-90 brachytherapy and outcome

Patient	Age (years)[a]	Tumour characteristics				Treatment					Results			
		Diameter		Height	Volume (mm^3)	Date of first treatment	Brachytherapy[b]				Vision[c]	Local control[d]	Follow-up (years)	General condition[e]
		Mean	Max				First	Second	Third					
1	39	9.0	9.0	1.9	72	Sep 83	400				1.0	Scar	12.2	Normal
2	76	4.5	4.5	3.0	29	Dec 84	650				0.8	Scar	11.0	Normal
3	72	8.0	8.0	2.8	84	Jan 85	490				–	Enucleated	8.4	Dead other cause
4	68	12.0	12.0	5.4	366	Dec 85	532				–	Involution	0.7	Dead with metastases
5	78	7.0	9.0	2.0	46	May 86	299				0.1	Scar	5.6	Dead other cause
6	56	9.5	9.5	2.3	98	Apr 87	355	C 400	400		0.7	Involution	8.7	Normal
7	44	8.0	8.3	2.6	78	May 88	441				1.0	Scar	7.5	Normal
8	74	12.7	12.7	3.3	251	Jun 88	710				0.4	Scar	7.4	Normal
9	65	6.0	6.0	3.0	51	Nov 88	539				0.2	Scar	7.0	Normal
10	78	11.7	11.9	5.2	335	Aug 89	670	P 659			0.3	Scar	6.3	Normal
11	50	5.5	7.0	2.5	36	Sep 89	424				0.8	Scar	5.8	Normal
12	57	6.0	6.0	1.5	25	Feb 90	232	C 233			0.8	Scar	5.7	Normal
13	53	5.0	5.0	2.2	26	Mar 90	337			X	0.8	Scar	5.7	Normal
14	34	8.5	9.5	3.2	109	May 90	574			X	0.8	Scar	5.5	Normal
15	55	8.3	8.7	3.0	97	Jun 90	600				CF	Scar	5.5	Normal
16	58	11.2	12.4	4.6	272	Oct 90	600	C 600	600		CF	Involution	5.2	Normal
17	55	10.4	11.2	2.5	127	Dec 90	632	C 400			0.3	Scar	4.9	Normal
18	62	10.5	10.8	4.6	239	May 91	706				CF	Scar	4.6	Normal
19	63	9.2	9.5	5.3	211	May 91	600	P 617			0.08	Scar	4.5	Normal
20	29	6.8	6.8	2.3	50	Jun 91	619				0.4	Scar	4.4	Normal
21	70	10.7	11.5	2.3	124	Jul 91	600				–	Enucleated	0.7	Dead with metastases
22	45	8.6	8.8	3.2	111	Jul 91	600				HM	Scar	4.4	Normal
23	69	7.7	7.9	2.8	78	Oct 91	600				0.8	Scar	4.1	Normal
24	68	9.3	10.3	2.3	94	Nov 91	600				0.8	Scar	4.1	Normal
25	61	9.6	9.7	4.2	182	Nov 91	616	P 600			0.16	Scar	4.0	Normal
26	44	7.2	8.1	1.6	39	Nov 91	600				1.0	Scar	4.0	Normal
27	68	11.0	13.1	3.4	194	Mar 92	S 800	C 600		X	0.8	Involution	3.7	Normal
28	73	7.8	8.4	1.6	46	Mar 92	600			X	0.12	Involution	3.7	Normal
29	66	10.9	12.1	4.8	269	Jun 92	600				0.2	Scar	3.4	Normal
30	60	12.8	14.8	4.8	370	Jul 92	S 1000			X	0.2	Involution	3.4	Normal
31	59	10.1	11.3	5.1	245	Nov 92	600	P 600		X	–	Enucleated	3.0	Normal
32	72	9.9	10.2	3.0	138	Dec 92	600	C 600			0.1	Scar	3.0	Normal
33	61	9.8	10.5	4.5	204	Feb 93	600	P 600	600	X	0.6	Involution	2.8	Normal
34	64	10.4	11.3	4.9	250	Apr 93	600				0.8	Involution	2.6	Normal
35	42	7.1	7.4	1.7	40	May 93	600				HM	Involution	2.6	Normal
36	61	7.9	8.0	2.5	73	Jul 93	600				LP	Involution	2.4	Normal
37	55	9.0	9.2	4.9	187	Oct 93	600				0.7	Involution	2.1	Alive with metastases
38	55	9.0	15.0	3.5	134	Nov 93	S 800				0.5	Scar	2.0	Normal
39	64	7.0	9.0	4.0	92	Feb 94	600				0.8	Involution	1.8	Normal
40	85	10.0	10.0	7.0	330	Mar 94	675				HM	Involution	1.7	Normal
41	53	6.5	6.9	3.4	68	Aug 94	600				CF	Scar	1.3	Normal
42	76	6.9	6.9	1.6	36	Dec 94	600				HM	Scar	0.9	Normal
43	46	5.6	5.6	1.6	24	Dec.94	600				0.8	Scar	0.9	Normal
44	74	10.1	10.2	4.6	221	Jan 95	600				CF	Scar	0.9	Normal
45	81	7.2	6.9	1.4	34	Feb 95	600				0.2	Involution	0.7	Normal
46	86	11.0	9.8	2.9	165	Mar 95	600				0.07	Involution	0.7	Normal

[a] Age at time of first brachytherapy

[b] Scleral dose (Gy) of strontium-90 applications: *S* plaque shifted during first application to cover a large-diameter tumour, *P* brachytherapy planned in two sessions, *C* second or third session given to correct incomplete treatment, *X* Xenon arc photocoagulation added to treatment

[c] Last known visual acuity in decimal units: *CF* counting fingers, *HM* hand movements, *LP* light perception

[d] Condition of tumour at last visitor at time of patient's death: *scar* local atrophy has progressed to point where local recurrence seems impossible, *involution* present condition satisfactory but tumour remnant still requires supervision

[e] At last visit in 1995

Table 2 Summary of observations on brachytherapy with HDR strontium-90 for malignant melanomas of the choroid

Number of patients in study:	46
Age of patients: (mean±SD)	61.4 ± 13 years
Tumour characteristics	
Mean diameter	8.8 ± 2.0 mm
Maximal diameter	9.4 ± 2.4 mm
Height	3.3 ± 1.3 mm
Volume	143 ± 111 mm
Dose at first treatment	558 ± 126 Gy (range 232–1000)
Follow-up duration	4.1 years (range 6 months to 12 years)
Additional treatments	
Planned second brachytherapy	5
Corrective additional brachytherapy	6
Xenon arc photocoagulation	7
Final results	28
Complete scarring of tumour	
Involution of tumour	15
Inadequate control and enucleation	3
General condition:	2
Dead with metastases	
Alive with metastases	1
Death from other causes	2

radioactive plaque onto the sclera, is positioned on the sclera exactly over the area of the tumour base and sutured to the sclera. After verification of the correct position by means of transillumination, the strontium-90 plaque is placed in the applicator ring (afterloading technique). In this way the manipulation time of the HDR emitter is reduced to a few seconds. The plaque is kept in close contact with the sclera by means of a 5/0 thread, placed over the applicator and knotted along a grand circle around the eye. At the end of the application time, the plaque is removed. During application, the patient remains in the operating suite (2–5 h). No special precautions for the environment need to be taken. After application, the patient stays a few days in hospital for post-operative follow-up and care (anti-inflammatory drugs, mydriatics).

In some patients the brachytherapy was completed by photocoagulation. A Zeiss xenon arc light source with Fankhauser delivery system in combination with a 90-D field lens is used after retrobulbar anaesthesia. The light intensity is progressively increased over 1 min or more by gradually opening the aperture diaphragm, until a faint coagulation mark is obtained. This method is used to obtain deep penetration of the thermal energy in the tissues [19].

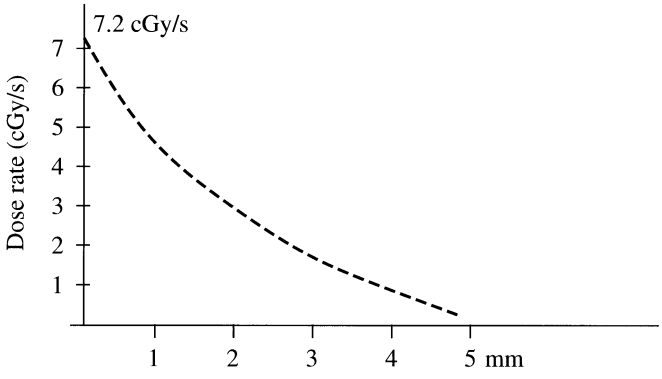

Fig. 2 The depth-dose curve of the strontium-90 applicator, measured by lithium borate transluminescent dosimetry (in 1983)

Results

All 46 patients treated with HDR strontium-90 brachytherapy for choroidal malignant melanoma were followed up to the time of writing or until death. Duration of follow-up ranges from 6 months to 12 years (6 patients with less than 1 year, 24 patients with 1–4 years, 16 patients with more than 5 years of follow-up). Table 1 gives detailed information on all cases and Table 2 summarizes our observations.

Thirty-five of the 46 eyes were treated with a single application of the strontium-90 plaque.

In eight eyes two applications, separated in time by 5–24 months, were necessary. Five of these second applications were planned in advance, when the distance from the apex of the tumour to the plaque exceeded 5 mm, because in these cases radiation penetration was considered insufficient to eliminate all malignant cells by a single application (Fig. 2). Additional applications became necessary in other cases when initial treatment proved insufficient during follow-up (usually insufficient treatment of the edge of a lesion or inadequate positioning of plaque). Three eyes received three applications each.

Seven patients received additional xenon arc lamp coagulations.

Three of the 46 eyes treated were enucleated, 30 eyes have non-evolutive scars and in 13 eyes complete involution of the tumour is not yet certain.

Involution of the tumour

During the first few days after the application a faint retinal oedema marks the site of the irradiation, and soon small retinal haemorrhages appear in that area. At 2 weeks after the application of 600 Gy to the sclera, fluoroangiography shows that all perfusion has stopped in all

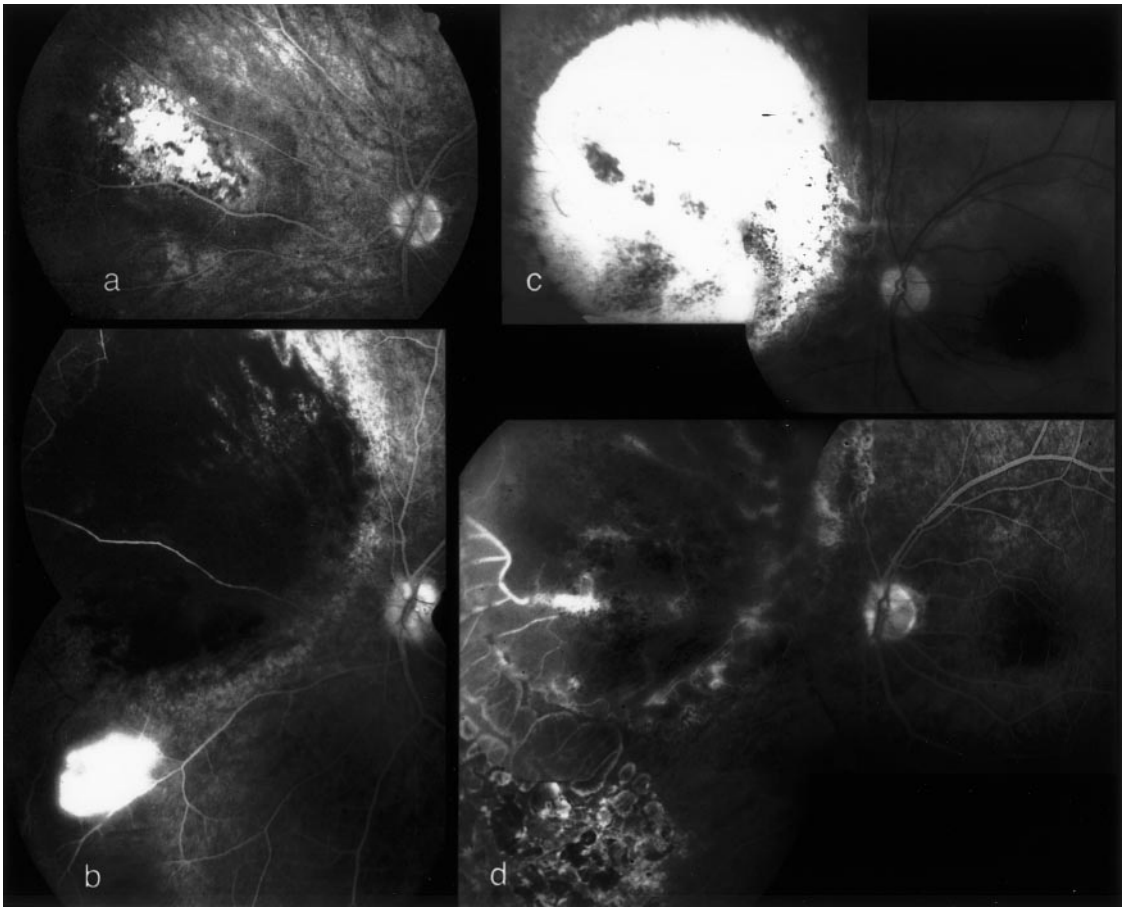

Fig. 3a–d Patient 12. In 1987 a suspect lesion was first noticed in the left eye of this 56-year-old woman during a routine examination. In July 1989, the diagnosis of malignant melanoma of the choroid was made. The size of the lesion was 7×5.5 mm, thickness 2.5 mm. **a** A fluoroangiogram, late phase, of the lesion. It was treated in September 1989 by a strontium-90 application of 424 Gy on the sclera, delivered in 1 h 55 min. **b** A fluoroangiogram taken 5 months after treatment. All vessels in the irradiated area, except one retinal vein, are obliterated. This has resulted in an ischaemic area in the retina at the peripheral edge of the scar, inducing the formation of a neovascular tuft. This ischaemic area was treated by laser coagulations. **c** The lesion 7 years later: the scar is white and flat and has sharp limits. **d** Fluoroangiography shows some revascularization in the scar; the retinal neovascularization has regressed and the optic disc and macular area appear normal. Vision is 10/10

layers in the irradiated area. At about 6 months atrophy of the tumour and surrounding tissues becomes evident, and in about 2 years the involution progresses to a deep scar (Fig. 3). The scar itself is yellowish-white in colour. In the irradiated area the choroid and retinal pigment epithelium have completely disappeared. No vessels can be seen in the scar during the first years. Later on, in some scars, vessels reappear in the sclera. On ophthalmoscopy one sees complete atrophy of all retinal and choroidal structures within the area of the scar. Most melanomas have completely disappeared, leaving only faint areas of pigment granules in the scar. In some eyes a remnant of the tumour remains visible as a dark clump of pigment, in others some pigmentation is visible outside the edge of the scar. In these eyes the permanent destruction of the tumour is still uncertain; in Table 1 the outcome of the treatment in these cases is marked as "involution".

The scars after strontium-90 brachytherapy are characterized by sharp delineation from the surrounding viable retina and choroid without signs of radiation vasculitis or neuritis outside of the scar. In 10 eyes the scar was within 1 disc diameter of the fovea or optic disc, yet still these eyes retained visual acuity of 0.2 or better.

Recurrence and additional treatments

Additional treatments were needed in 15 eyes. These were either planned in advance (marked P in Table 1) or corrective (marked C in Table 1) because of insufficient effect of the primary brachytherapy or for tumour recurrence.

Planned two-step irradiation

In six eyes (patients 10, 19, 25, 31, 33 and 40) strontium-90 brachytherapy in two applications was planned in advance, because tumour height exceeded 5 mm. In a first step, 600 Gy to the sclera resulted in marked flattening of the tumour. In a second session, 4-10 months later, another 600 Gy applied to the same scleral area was expected to destroy all the remaining viable cells of the tumour. In three of these eyes this resulted in complete local control of the tumour; one eye (patient 31) was finally enucleated, and one eye (patient 33) needed a third application 19 months after the second planned application. This tumour seems to be under control. In one patient (no. 40) the second brachytherapy had not yet been carried out at the time of writing. In this only functional eye a mushroom-shaped tumour of 7 mm height was situated close to the macula. Strontium-90 brachytherapy was preferred in order to reduce the radiation damage to the fovea. In 12 months after the first treatment the tumour shrank to 3 mm height and remained stable 24 months after the first application.

Lateral shifting

In three eyes (patients 27, 30 and 38) the tumour had an oblong shape with the long axis exceeding 12 mm, the active area of the plaque. In these eyes the plaque was first fixed over one part of the tumour and left in place until 400 or 500 Gy had been delivered to the sclera, and then shifted in such a way as to irradiate the other part with 400 or 500 Gy on the sclera. In the central overlap zone, a total dose of 800 or 1000 Gy was administered. In one of these eyes (patient 38), a favourable result was obtained without further treatment. Patient 27 received an additional strontium-90 application 10 months later. Patient 30 received additional xenon arc photocoagulation of a border of the lesion 8 months later. These three eyes had useful vision (20/100 or better) at the patients' last visit.

Corrective additional brachytherapy

In six eyes (patients 6, 12, 16, 17, 27 and 32), additional brachytherapy treatment was given because there was doubt concerning the efficacy of the initial treatment (part of tumour out of irradiation area, doubt about border of lesion). Recurrence or suspicion of recurrence starting in the centre of the irradiated area was not seen in these eyes. Two of these eyes each received two additional applications (cases 6 and 16). All six eyes retained useful vision. In three eyes the tumour was completely destroyed, in the others the involution of the tumour is still being monitored.

Additional photocoagulation

Seven eyes received one (patients 14, 27, 28, 30, 31 and 33) or two (patient 13) additional treatments with xenon arc photocoagulation of an insufficiently treated border or offshoot of the tumour. None of these patients was known to have metastases at the end of this study, and six of them had useful vision in the treated eye.

Two eyes (patient 9 and 35) were treated with xenon arc photocoagulation before the brachytherapy. In one patient (no. 35) a small malignant melanoma close to the macula was initially treated with xenon arc photocoagulation 5 years before a recurrent melanotic growth was detected around the scar. In the other (no 20) an attempt at photocoagulation seemed to give insufficient results.

Enucleation

Three eyes were enucleated during follow-up. The eye of patient 3 was enucleated 42 months after strontium-90 brachytherapy because of tumour recurrence. She died of cerebrovascular disease 106 months after the initial treatment. At that point there was no evidence of metastases.

Patient 31 received two consecutive strontium-90 applications (initial tumour diameter 11 mm, height 5.1 mm, situated in posterior pole). Thirteen months after the initial treatment the eye was enucleated because there was clinical evidence of another tumour mass in the ciliary body. Histology showed two separate foci of spindle cell malignant melanoma. This patient was free of metastases at the end of this study.

Patient 21 developed a vitreous haemorrhage after treament of a relatively large tumour (diameter 11.5×9.8 mm, height 2.3 mm, extensive retinal detachment). Ultrasonography suggested that the tumour had responded poorly to treatment and after 3 months the eye was enucleated. Histology revealed an epitheloid type of malignant melanoma with invasion of the sclera and of the ocular vessels. This patient died of metastases 8 months after the initial treatment with the strontium-90 plaque.

Complications

In two patients (nos. 16 and 18) a haemorrhage collected between the strontium-90 plaque and the sclera during the application. This haemorrhage may have reduced the penetration of beta-radiation to the tumour (enlargement of plaque-tumour distance). In patient 16 two additional strontium-90 application were necessary. No metastases were detected in these two patients. The surgical procedure was changed in 1991. Nowadays the plaque is pulled tightly against the sclera by a thread placed around the

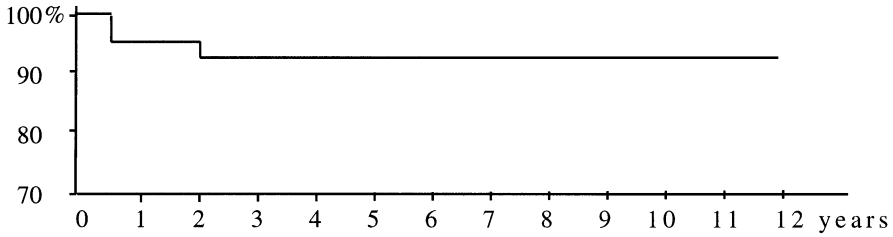

Fig. 4 Kaplan-Meier disease-free survival curve of all 46 patients treated with HDR strontium-90 brachytherapy

eye, thus preventing the accumulation of blood between the plaque and the sclera.

Six eyes developed extensive retinal detachment within a week after treatment (patients 6, 19, 26, 33, 36 and 37). Four detachments resolved spontaneously, resulting in functional eyes with good vision. Two needed surgery, one with success; the other patient (no. 96) who had previously had a retinal detachment in the other eye, failed to recover vision.

One patient (no 42) developed preretinal fibrosis in the central retina. She was treated with vitreoretinal surgery but failed to recover good vision.

When the tumour is situated near the optic disc, large retinal vessels passing over the tumour become obliterated, resulting in a non-perfusion area peripherally. Here new vessel formation may occur, as in retinal branch occlusion. In five eyes (cases 1, 11, 15, 23 and 28) a treatment by argon laser photocoagulation was needed. One of these patients (no 28) had proliferative diabetic retinopathy.

In five patients strontium-90 application was followed by transient double vision, which regressed spontaneously.

Radiation effect on the sclera

The inner face of the sclera appeared normal by ophthalmoscopy in all eyes, including those that had 1000–1800 Gy radiation delivered to the same area of the sclera. At the occasion of the 14 reinterventions the outer surface of the scleral wall could be inspected 2–24 months after the preceding brachytherapy. The sclera had an almost normal appearance: white with a few adhesions to Tenon's capsule as seen in reinterventions after retinal detachment surgery. No deleterious effects of the radiation were seen, even in the scleras that had previously received 1200 Gy.

Histopathological examination of the three enucleated eyes gave more information about the condition of the sclera. In patient 3 the sclera was examined 42 months after the application of 490 Gy, the eye of patient 21 was examined 4 months after the application of 600 Gy and in patient 31 two applications of 600 Gy each preceded the enucleation by 13 and 2 months respectively. In all three cases the results were similar: the sclera in the area of irradiation consisted of the same collagen fibres with the same staining properties, the same texture and the same arrangement in lamellae as in other non-irradiated areas. Fibrocytes were totally absent in the irradiated area in patient 31 and reduced in number to about 5% of the normal values in the other two patients. The episclera in all cases was normal.

Patient survival

Figure 4 gives a Kaplan-Meier diagram of patient survival. Four of the 46 patients died, two from metastases of malignant melanoma, two from other causes. One of the two patients who died from metastases of malignant melanoma, patient 4, was treated for palliative reasons; liver metastases had already been diagnosed before the strontium-90 application.

Two patients died of cardiovascular disease. Patient 5 died 67 months after initial treatment. At the time of his death the choroidal tumour was cicatricial, and no evidence for metastases was found. In patient 3 the eye was enucleated 42 months after brachytherapy because of a recurrence. When she died, 64 months later, there was no evidence of tumour metastases.

One patient (no. 37) is ill with liver metastases found 25 months after brachytherapy of 600 Gy. Her eye had a malignant melanoma of moderate size, diameter 9 mm and height 4.9 mm, which had responded well to the brachytherapy.

The other 41 patients were alive and without evidence of metastases at their last control examination in 1995.

Final visual results

In our study group of 46 eyes, 3 were enucleated, 12 had poor vision of less than 20/400, 13 had visual acuity between 20/200 and 20/50, and 18 had visual acuity equal to or better than 20/40 on their last visit.

In 17 patients (37%) the final visual acuity was equal to or better than that before treatment. Ten patients (22%) had a slight deterioration of visual acuity (up to two Snellen lines). Nineteen patients (41%) had marked deterioration of visual acuity (three or more Snellen lines).

Discussion

With a few exceptions, all choroidal malignant melanomas we treated were small to medium-sized (diameter up to 12 mm, height up to 5 mm). Until mid-1990 we calculated the dosage to obtain 75 Gy at the apex of the tumour and adjusted the application time accordingly. However, two observations made us change that policy. First, we had more problems of incomplete treatment with small tumours that received small irradiation doses of 250–350 Gy to the sclera (cases 6, 12 and 13, see Table 1) than with those who were given 600 Gy to the sclera. Secondly, we did not observe any structural damage to the sclera with the high doses. In addition, the timely occlusion of all vessels in the irradiated area produced by 600 Gy to the sclera appeared desirable.We therefore decided to apply a minimum of 600 Gy to the sclera in all subsequent cases.

This resistance of the sclera to high doses of irradiation (up to 1800 Gy in patient 33) came as a pleasant surprise, as problems with the sclera are known with the use of other applicators. This suggests that the duration of the contact with the sclera is more deleterious than the intensity of the radiation. There is some logic in this observation: even a low dose of radiation, for example 75 Gy, will kill all cells in the sclera, and collagen itself seems to be unaffected.

Additional brachytherapy was needed for definitive tumour control in 11 eyes, most of them containing larger tumours. Among the 22 eyes with tumours less than 100 mm^3 in volume, additional brachytherapy sessions were needed only twice (patients 6 and 12), in eyes treated with 355 Gy or less in the first session. In contrast, among the 24 tumours larger than 100 mm^3, 9 needed additional brachytherapy. In five of these eyes this additional brachytherapy was planned in advance, in the other cases it was a correction of our initial not completely successful treatment. However, as this treatment is simple and not much of a burden for the patient or the surgeon, it is generally well accepted.

One would expect that the maximum tumour height treatable is determined by the penetration of the radiation into the ocular tissues. The depth-dose curve shows that less that 5% of the scleral dosage emitted by strontium-90 penetrates to a distance of 5 mm in tissues. However, slightly higher tumours were treated successfully as well, in some cases with just one application of 600 Gy to the sclera (patients 18, 29 and 44) or with two planned consecutive applications at an interval of no more than 1 year. One may object that a planned two-step procedure is unsound, because viable malignant cells might metastasize before the second application. The obliteration of all irradiated choroidal vessels within 2 weeks after the first application should reduce the likelihood of metastasis formation. For the individual patient the advantage of the reduced radiation damage to adjacent retina has to be weighed against this potential risk. Longer follow-up of the patients treated is needed to settle this controversy.

None of the recurrences started from the apex of the tumour, where the irradiation dosage was smallest. This may be due to the enhanced cytocidal effect of HDR irradiation or may support the hypothesis that irradiation achieves its result in part by interference with the vascularization of the base of the tumour. All recurrences originated from the border of the irradiated area, presumably because the lateral spread of the tumour cells exceeded the irradiated area. This is a drawback inherent to the use of a method with a very localized effect.

The maximum treatable diameter was limited by the 12 mm diameter of the active plaque. As experience grew, we also treated lesions with larger diameters. In these cases the plaque was shifted to a second position during the procedure. We obtained good results with this modified procedure. We hope that larger strontium-90 plaques will become available, facilitating the brachytherapy of choroidal malignant melanomas with apparent diameters of more than 10 mm. Our experience with shifting the plaque suggests that strontium-90 plaques with active zones of up to 15 mm diameter could be well tolerated by the eye.

Follow-up of patients after strontium-90 application is very important (as with the other types of brachytherapy). Recurrences or insufficiently treated lesions can be treated with consecutive applications or with xenon arc photocoagulation. Enucleation was performed in three cases (6.5%) after strontium-90 therapy had been shown inadequate.

The survival rate in our group of 46 eyes treated with strontium-90 brachytherapy was good, comparable to results published in other studies, as should be expected for small tumours. At least 5 years of follow-up are required before one can draw any significant conclusions [13]. We have 16 patients with follow-up of more than 5 years. However, the results in the study group as a whole are very similar to those in this subgroup of 16 eyes with longer follow-up.

One of the major advantages of brachytherapy of choroidal malignant melanomas is the possibility of preserving useful vision in the treated eyes. In our group 55% of the eyes treated retained visual acuity of 20/100 or better. Three out of every five eyes treated with strontium-90 brachytherapy had relatively stable visual acuity (maximum drop of two lines on the Snellen chart) at their last visit compared with their visual status before treatment. Two out of every five eyes treated had a major drop in visual acuity (three or more lines on the Snellen chart).

Due to the weak penetration of strontium-90 beta radiation there is little irradiation of the ocular tissues in the environment of the plaque. This is probably the major reason for the infrequency of intra-ocular side effects of the treatment despite the HDR irradiation. We did not see radiation retinopathy in the area surrounding the treated le-

sion. A narrow transition zone separated the yellowish-white scar from normal tissue. In four eyes the irradiation scar came to within 1 disc diameter or less of the fovea, with good visual outcome of 20/30 or better. In 10 eyes the scar almost touched the optic disc without inducing radiation neuritis. This shows that tumours close to vital structures can sometimes be treated by strontium-90 brachytherapy without inducing severe functional loss.

Pre- and subretinal neovascularization at the edge of an ischaemic area was seen and required treatment in five eyes. Two eyes needed surgery for retinal detachment. One eye was treated by vitrectomy for a preretinal fibrosis in the macular area. There were no cases of radiation cataract or keratoconjunctivitis sicca.

The weak penetration of strontium-90 beta rays makes this therapy safe to perform, with almost no radiation hazard for staff performing the procedure or working in the operating theatre. The plaque is handled by means of a simple needle holder and manipulation lasts only a few seconds with our afterloading method. No special precautions have to be taken to protect the surgeon's hands.

We attempted to compare our results with those of other means of brachytherapy described in the literature. The first large study was published in 1966 by Stallard [22], who reported a series of more than 100 eyes treated with cobalt-60 brachytherapy. Lommatzsch [17] reported good results with ruthenium-106 applicators. More recent publications [12, 18, 23] confirm the value of this technique. There have been many publications on the use of iodine-125 [7, 8, 10, 14, 20] and more recently on the use of palladium-103 brachytherapy [4–6]. The newer sources of irradiation have the advantage of fewer complications, in contrast with the sometimes devastating effects of Cobalt-60 on irradiated eyes (high incidence of radiation retinopathy, cataract, keratoconjunctivitis sicca, punctate occlusion with epiphora, scleral necrosis) [3, 12, 21].

Treatment with the gamma emitter iodine-125 is the most popular type of brachytherapy for malignant melanoma in the United States today [11]. The iodine-125 seeds can be incorporated in plaques of different sizes and shapes, adapted to the individual tumour [9]. Most studies report average application times of 7–10 days [7, 20]. Iodine-125 has a short half-life of 60 days, so the iodine-125 seeds require frequent renewal.

The results after ruthenium-106 plaque radiotherapy do not differ greatly from those with iodine-125 brachytherapy [12, 17, 18, 23]. Ruthenium-106 is a beta emitter with a half-life of 366 days. Ruthenium-106 therapy requires average application times of 4–5 days or more.

Recently palladium-103 brachytherapy has been advocated as an even more effective method with even fewer side effects [4–6]. Palladium-103 is a weak gamma emitter. More of its photons are absorbed within the tumour and slightly fewer reach the surrounding tissues than with iodine-125. It is to be expected that complications will be uncommon, but this has not yet been demonstrated.

HDR High Dose Rate strontium-90 brachytherapy has three major advantages over iodine-125, ruthenium-106 or palladium-103 therapy:

1. Owing to the very high dose rate of the strontium-90 plaque, very short treatment times can be obtained (2–5 h in our patients). This contrasts with treatment times of several days for applications of iodine-125, ruthenium-106 and palladium-103. The short application time with strontium-90 greatly simplifies the procedure. Patients remain in the operating theatre. No special precautions for hospitalization of patients with radioactive material in situ are needed. Application and removal of the strontium-90 plaque are carried out within the time span of one administration of retrobulbar anaesthesia.
2. The weak penetration of the strontium-90 beta rays produces sharply delineated scars with abolition of all vascular perfusion in the treated area and no radiation damage to the surrounding tissues, despite the use of HDR radiotherapy.
3. Because of the long half-life of strontium-90 (28.5 years), repeated use of the same plaque over many years is possible. This reduces the cost of the procedure considerably. All 46 eyes in our study were treated with the same plaque. In contrast, the shorter half-lives of iodine-125 (60 days), ruthenium-106 (366 days) and palladium-103 (17 days) make frequent replacement of the applicators necessary.

Although still preliminary, this study shows that the use of HDR strontium-90 brachytherapy is a valuable and safe means of treating small (up to 100 mm^3 volume) choroidal malignant melanomas. Larger tumours with volumes up to 350 mm^3 and height up to about 5 mm have been treated with acceptable results, but longer follow-up of these patients is needed to evaluate this procedure. HDR strontium-90 brachytherapy is a safe method for the treated eye and its surrounding structures and for the medical personnel performing the treatment. In addition it is fast, convenient for the patient and relatively inexpensive. We hope that further follow-up will confirm our encouraging findings.

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