

Local tumor control and morbidity after one to three fractions of stereotactic external beam irradiation for uveal melanoma[☆]

Martin Zehetmayer^{a,*}, Klaus Kitz^b, Rupert Menapace^a, Adolf Ertl^b, Harald Heinzl^d, Irene Ruhsurm^a, Michael Georgopoulos^a, Karin Dieckmann^c, Richard Pötter^c

^aDepartment of Ophthalmology, Oncology Service, University of Vienna, Medical School, Allgemeines Krankenhaus, Währinger Gürtel 18-20, 1090 Vienna, Austria

^bDepartment of Neurosurgery, Gamma Knife Unit, University of Vienna, Medical School, Vienna, Austria

^cDepartment of Radiotherapy, University of Vienna, Medical School, Vienna, Austria

^dDepartment of Medical Computer Sciences/Clinical Biometrics, University of Vienna, Medical School, Vienna, Austria

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Abstract

Background and purpose: To evaluate prospectively local tumor control and morbidity after 1–3 fractions of stereotactic external beam irradiation (SEBI) in patients with uveal melanoma, unsuitable for ruthenium-106 brachytherapy or local resection.

Material and methods: This phase I/II study includes 62 selected patients with uveal melanoma. The mean initial tumor height was 7.8 ± 2.8 mm. With the Leskell gamma knife SEBI, 41 patients (66%) were irradiated with two equal fractions of 35, 30 or 25 Gy/fraction, 14 patients (22%) were treated with three fractions of 15 Gy each, and seven patients (11%) with small tumor volumes below 400 mm^3 were treated with one fraction of 45 Gy. The mean total dose was 54 ± 8 Gy. The minimal follow-up period was 12 months, and the median follow-up was 28.3 months. Data on radiation-induced side-effects were analyzed with the Cox proportional hazards model for possible risk factors.

Results: Local tumor control was achieved in 98% and tumor height reduction in 97%. The mean relative tumor volume reductions were 44, 60 and 72% after 12, 24 and 36 months, respectively. Seven patients developed metastases (11%). Secondary enucleation was performed in eight eyes (13%). Morbidity was significant in tumors exceeding 8 mm in initial height; it was comparable and acceptable in those smaller. In the stepwise multiple Cox model, tumor localization, height and volume, planning target volume (PTV), total dose and patient age were identified as the strongest risk factors for radiation-induced lens opacities, secondary glaucoma, uveitis, eyelash loss and exudative retinal detachment. In this model, the high-dose volume irradiated with more than 10 Gy/fraction was the strongest risk factor for radiation-induced uveitis.

Conclusions: Stereotactic external photon beam irradiation and a total dose of 45–70 Gy delivered in one to three fractions are highly effective at achieving local tumor control in uveal melanoma. Further clinical studies using smaller fraction doses, and consequent smaller high-dose volumes, are justified to optimize dose and fractionation. Fractionated stereotactic irradiation has a challenging potential as an eye-preserving treatment in uveal melanoma. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Intraocular neoplasm; Uveal melanoma; Fractionated stereotactic radiotherapy; Stereotactic radiosurgery; Gamma knife; Outcome results

1. Introduction

Uveal melanoma is the most common primary ocular malignancy in adults and occurs in 6–7 cases/million people per year [12,49]. Although melanoma is traditionally

believed to be radio-resistant, radiotherapy has become the most common form of treatment aimed at conserving the eye and vision [18,43]. Ruthenium-106, iodine-125 and other isotopes are widely used for episcleral plaque brachytherapy [33,37,45]. Proton or helium ion charged particle irradiation and 60–90 Gy delivered in 4–5 fractions has been used successfully for more than 20 years [5,20].

In the last few years, stereotactic external beam irradiation (SEBI) has gained widespread acceptance as an effective method of delivering one or several fractions of high-dose radiation to a small, well-circumscribed target volume. Stereotactic radiosurgery (SRS) refers to a single-fraction

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* Corresponding author.

treatment, whereas fractionated stereotactic radiotherapy (SRT) uses multiple fractions. The effects of radiation on surrounding normal tissue are principally reduced by focussing one or more highly-collimated radiation beams precisely on a small target. Technically, stereotactic irradiation with photon beams is based either on stereotactic linear accelerators, or on the Leksell gamma unit (Gamma Knife[®]) [1,2,30,48]. Gamma knife SEBI is mainly used in neurosurgical centers for non-invasive treatment of a variety of functional, benign and malignant intracerebral and intracranial disorders [1,2].

In 1987, the effects of gamma knife single-dose SRS were studied in a rabbit eye melanoma model. Total destruction of the experimental tumor was reported after a single-fraction irradiation with 60–90 Gy [38]. A preliminary study on 11 uveal melanoma patients, published in 1992, suggested that local tumor control could be achieved with gamma knife single-dose SRS, with doses between 60 and 90 Gy [9]. For uveal melanoma, the minimum dose of SEBI necessary for local tumor control, as well as the effect of fractionation, remained unclear.

In 1993, we initiated a prospective phase I/II study on SEBI for patients with uveal melanoma, unsuitable for local resection or ruthenium-106 brachytherapy. This study describes our experience with selected 62 patients, treated with 1–3 fractions of SEBI and total doses between 45 and 70 Gy.

2. Material and methods

Details of the technique of Leksell gamma knife SEBI were previously published [1,2,50]. Dosimetry studies in a phantom and cadaver head were performed to assess the accuracy of the gamma knife dose distribution for treating intraocular tumors [14].

SEBI was offered only to patients with uveal melanoma who were deemed unsuitable for ruthenium-106 brachytherapy or local resection. This study includes: (1), melanoma of >7 mm in initial height; or (2), juxtapapillary and/or juxta-macular tumors (height, >3 mm; posterior tumor margin extending to 3 mm of optic disk rim and/or fovea). In these cases, episcleral ruthenium-106 brachytherapy is complicated by a increased rate of local tumor control failures and radiation-induced side-effects [19,24,33,34]. Patients were excluded if they presented evidence of echographic extrascleral tumor extension, neovascular glaucoma, or any form of pretreatment or metastases at baseline. This study was approved by the Medical Ethics Committee of the University of Vienna, and informed consent was obtained from each patient after the nature of the procedure had been fully explained. The study was started in October 1993.

The eye was stabilized by a non-invasive ocular suction system attached to the stereotactic frame [51]. This device fixes the globe and prevents any displacement of the eye and

tumor relative to the stereotactic frame. Before 1997, high-resolution CT-scans with a 2 mm slice thickness were obtained for stereotactic localization and dose planing (34 patients). In four patients with flat melanomas located close to the optic disk, radio-opaque markers had been sutured to the sclera to facilitate accurate CT-delineation [52]. In 1996, a MR-suitable ocular suction system was designed to fit into the magnetic resonance imaging (MRI) head coil. Thereafter, MRI-scans with a 2 mm slice thickness were used for dose planing (28 patients). For obtaining the planning target volume (PTV), a safety margin of 1–2 mm was added to the clinical tumor volume. Spherical or spheroid tumors were treated with one isocenter of an appropriately sized collimator. Irregularly-shaped lesions were treated by combining different collimators and isocenters [15]. By using different weights of the isocenters, various plugging patterns [16] and different gantry positions, dose conformation was achieved (Fig. 1).

Dose calculation was computed in all cases using the treatment planning program KULA 4.4 (Elekta Instruments, Stockholm, Sweden), based on high-resolution CT or MRI images. The PTV was enclosed within the 50% isodose [50]. For each fraction, positioning of stereotactic frame, eye fixation, delineation of the tumor volume and dosimetry were repeated, and, after each fraction, the stereotactic head frame was removed. To study a possible effect of fractionation, the high-dose volume irradiated with 10 Gy or more ($V \geq 10$ Gy/fx) was calculated for each fraction.

2.1. Ophthalmological evaluation

Ophthalmological examination included visual acuity, tonometry, indirect or contact-lens ophthalmoscopy, tundos photography and fluorescein angiography. In patients with ciliary body tumors, gonioscopy and slit-lamp photography were performed. The acoustic properties, vascularity and tumor height were measured with standardized A-scan echography, and the tumor's basal dimensions with B-scan echography [3]. The gross tumor volume (GTV) was calculated using the ellipsoidal solid model [25]. The distance to optic disk and fovea were estimated by ophthalmoscopy and fundus photography. The anterior border of the tumor was examined using transillumination, if appropriate.

Ophthalmic follow-up examinations were performed after 24 h, 7 days, and 2, 4, 8 and 12 weeks after irradiation. Within the first 24 months, patients were seen at 3 month intervals; thereafter they were assessed at 6 months intervals. Examinations included at least visual acuity, tonometry, slit-lamp examination and ophthalmoscopy. Fundus photography, fluorescein angiography, A- and B-scans were performed to evaluate the tumor response and possible side-effects. A metastatic survey was performed in all patients prior to treatment, including blood tests, chest X-ray, abdominal echography and physical examination. This was repeated every 6 months after treatment.

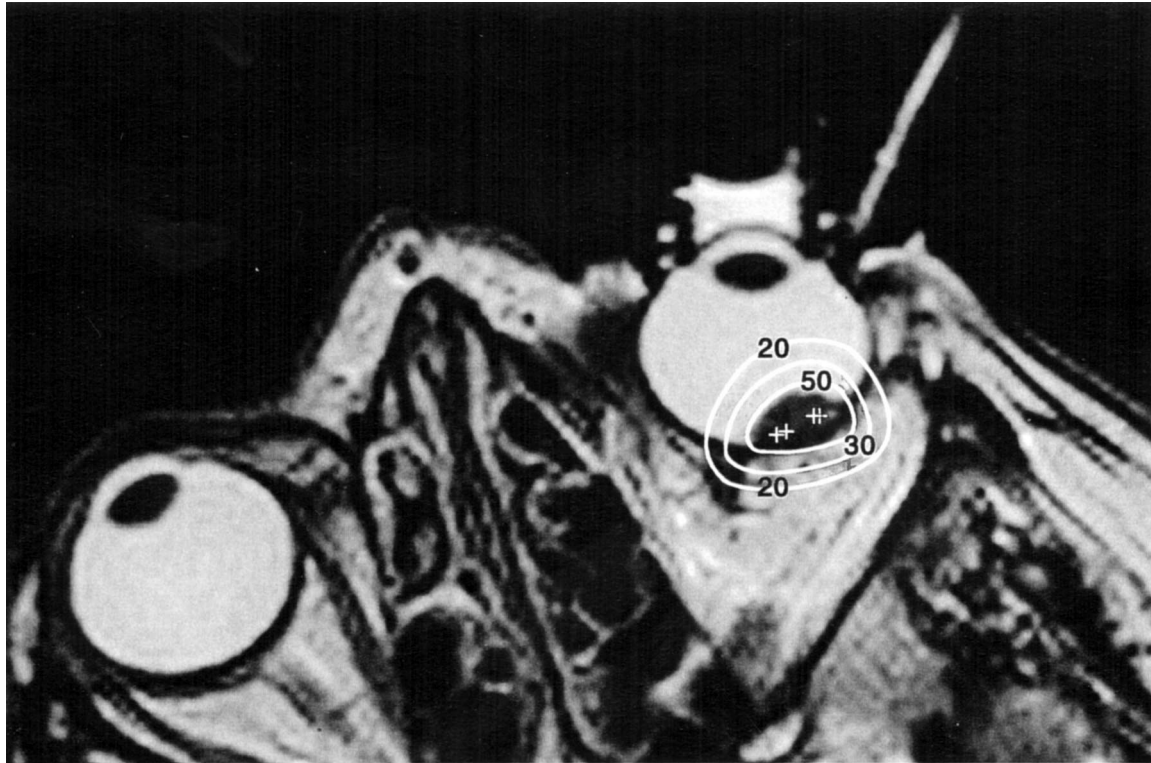


Fig. 1. Axial MRI scan of choroidal melanoma located under the central fovea of retina. The 20, 30 and 50% isodose line, as well as the four isodose centers (+) are shown. Anterior to the eye, the vacuum fixation device is visible being placed on the corneal limbus to immobilize the eye during delineation and treatment.

2.2. Patient data

Between October 1993 and April 1997, 62 patients were treated. The age at treatment was 61 ± 13 years (mean \pm one standard deviation). We treated 32 right and 30 left eyes. Fourteen patients (23%) presented with melanomas involving the ciliary body, all of them exceeding 8.7 mm in height. Two of them had tumor extension into the chamber angle. Forty-eight tumors (77%) were located in the choroid. In 45 of them, the central tumor margin extended to 3 mm of the optic disk rim and/or fovea. In 19 patients, the tumor touched or involved the fovea. Forty-three patients presented with juxtapapillary tumors (distance to optic disk rim, <3 mm). In 17 patients, the central tumor margin touched the optic disk rim. In a subgroup of patients with tumors of <8 mm in initial height, all 32 patients presented with a central tumor margin within a 3 mm distance to the optic disk rim or macula, and 31 of them (97%) presented with juxtapapillary tumors. In 18 patients (56%), the tumor touched or involved the fovea.

The initial tumor height, largest and smallest tumor diameters, GTV and TNM classification are listed in Table 1. The mean distance between the posterior tumor margin and the fovea was 2.5 mm, and the mean distance to the rim of the optic disk was 2.8 mm. Eight patients presented with collar-stud tumors and 54 with dome-shaped tumors. Forty-six patients presented with a visual acuity of

0.1 or better. At baseline, secondary serous retinal detachment was seen in 37 patients, with vitreous hemorrhage in five cases.

2.3. Total dose and fractionation

We initially used two fractions of 35 Gy (ten cases). After observing local tumor control in all cases, we subsequently lowered the dose to 2×30 Gy (17 cases) and to 2×25 Gy (14 cases). In all except one patient, the two fractions were delivered with 1 week apart. In the remaining case with a large ciliary body tumor (11.4 mm thickness), a total retinal detachment developed after the first fraction of 28 Gy, and therefore, the second fraction was delayed until day 59. During 1995, seven consecutive patients with small melanomas below a 400 mm^3 tumor volume were treated with one fraction of 45 Gy. Since September 1996, three fractions, of 15 Gy each, were used for the remaining 14 patients. Treatment with the three fractions was completed within 11 days. The last patient was treated in April 1997.

2.4. Dose planning

The mean PTV was $1960 \pm 1318 \text{ mm}^3$. The number of isocenters/fraction ranged from 1 to 5, (2.3 ± 1.2). The volume irradiated with 10 Gy or more/fraction ($V \geq 10 \text{ Gy/fx}$) had a median of 13.2 cm^3 (lower and upper quartile, 5.8 and 21.9 cm^3 ; range, 0.7–53 cm^3). The ratio between

Table 1
Tumor characteristics

	Mean (mm)	SD (mm)	Range (mm)
Height	7.8	2.8	3.3–14.3
Largest tumor diameter	14.2	3.5	7.7–23.0
Smallest tumor diameter	12.4	3.2	7.2–20.7
	Median (mm ³)	Lower/upper quartile (mm ³)	Range (mm ³)
GTV	640	330/1100	100–3260
	<i>n</i> (%)		
Tumor height			
>5 mm	50 (81)		
>8 mm	30 (47)		
>10 mm	12 (19)		
Largest tumor diameter			
>15 mm	24 (39)		
TNM classification			
T2	12 (19)		
T3	50 (81)		

echographically noticed GTV and PTV had a median of 0.36 (lower quartile, 0.28; upper quartile, 0.55; range, 0.19–1.04). The median of the maximal dose to the crystalline lens, as measured at the point of the crystalline lens closest to the tumor, was 16.5 Gy (lower quartile, 9.5 Gy; upper quartile, 42.1 Gy; range, 3–115 Gy). In tumors exceeding 8 mm in height, the median of the maximal lens dose was 43 Gy. In the 14 patients with ciliary body tumors, the maximal lens dose had a median 63 Gy. The mean total dose to the optic disk was 29 ± 16 Gy.

2.5. Evaluation for local tumor control, radiation-induced side-effects and metastases

Local tumor control was defined as freedom from local progression as noticed by A- and B-scan, and ophthalmoscopy at the last follow-up examination.

During follow-up, the presence or absence of the following side-effects was noticed: eyelash loss, uveitis (anterior chamber flare, > Tyndall 0), new asymmetric lens opacities (grade 3+ and 4+ cortical or posterior subcapsular lesions), secondary glaucoma (intraocular pressure, >21 mmHg and/or need for antiglaucomatous medication in a previously normotensive eye), neovascular glaucoma (secondary glaucoma plus iris or chamber angle neovascularization), corneal epithelial defects, radiation-induced exsudative retinal detachment (de novo or increase of a pre-existing detachment), optic neuropathy (hyperemia, hemorrhages, narrowing of optic disk vessels, partial or total atrophy), ischemic retinopathy (intraretinal hemorrhages, cotton wool spots and lipid exudates distant of the tumor base) and vitreous hemorrhage. Metastases and cause of death

were confirmed by biopsy or autopsy. Data entered until 31 June 1998 were analyzed.

2.6. Risk factors and statistical evaluation

Risk factors studied included patient's age, initial ultrasound tumor height, GTV, tumor localization (ciliary body to choroidal), total dose, PTV, total dose to the lens and to the optic disk, the high-dose volume irradiated with 10 Gy or more/fraction ($V \geq 10$ Gy/fx), and the ratio between GTV and PTV. For radiation-induced optic neuropathy and retinopathy, the distances of the central tumor margin to the optic disk and fovea were included as additional factors.

Variables of interest with symmetrical or skewed distributions were described by means (\pm SD) or medians (lower and upper quartile, minimum and maximum), respectively. Probabilities for retaining the eye, remaining free from metastasis, preserving useful vision, as well as overall and cause-specific survival were calculated by the product limit method of Kaplan and Meier. For treatment complications with more than ten events observed, the Cox proportional hazard model [10] was used to assess the univariate effects of potential risk factors on complication times. Prior to analysis, risk factors with skewed distributions were logarithmically (base 2) transformed. The Bonferroni–Holm correction [23] was applied to adjust *P*-values for the multiple testing carried out. To identify potentially independent risk factors in an exploratory manner, stepwise selection multiple Cox proportional hazards models were used. All reported *P*-values are the results of two-sided tests. A *P*-value of less than 5% was considered statistically significant. The SAS statistical software system (SAS Institute, Inc., Cary, NC) was used for calculations.

3. Results

The median follow-up of our study was 28.3 months, ranging from 12 to 51 months. All patients, except for one case, attended for scheduled ophthalmological follow-up examinations. This patient, a 70-year-old man was irradiated in January 1995, and last seen in July 1996. In June 1998, the patient was reached by phone and found to be alive without ocular complaints.

3.1. Tumor control and tumor shrinkage

Local tumor control was achieved in 61 patients (98%). In 60 cases (97%) with local tumor control, a reduction of tumor height corresponding to partial response was seen. The mean relative tumor height reductions were 33% at 12 months, 45% at 24 months ($n = 32$), and 53% at 36 months ($n = 15$). The mean relative tumor volume reductions were 44, 60 and 72% at 12, 24 and 36 months, respectively. Relative tumor volume reductions were similar between patients presenting with initial heights of <8 mm

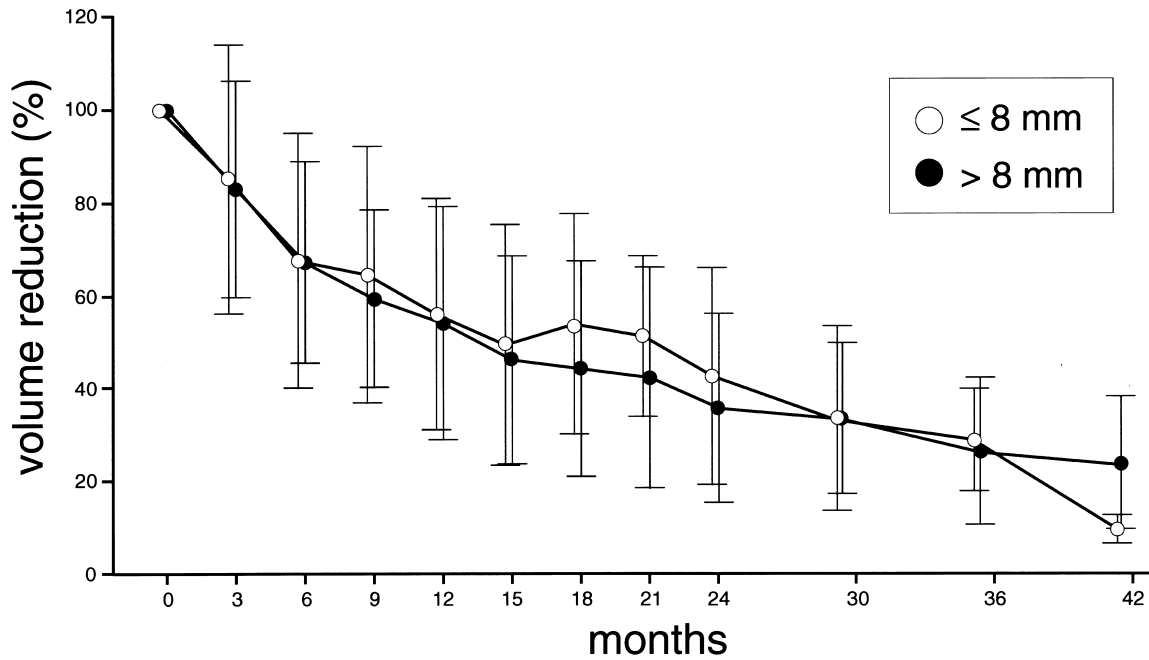


Fig. 2. Relative tumor volume reduction vs. time for the subgroups of tumors ≤ 8 mm ($n = 32$) and tumors > 8 mm in initial height ($n = 30$).

($n = 32$), or those of > 8 mm ($n = 30$), as well as between subgroups of patients treated with different total doses and fractions (Figs. 2 and 3).

Marginal recurrence was seen in one patient (2%). This patient, a 79-year-old man, was treated in July 1994 with two fractions of 35 Gy for a large anterior choroidal tumor. During follow-up, the tumor height had diminished from 8.7 to 1.7 mm. Forty-two months after treatment, a deeply pigmented, flat extension at the central margin was noticed

on the ophthalmoscopy. The patient refused re-treatment or enucleation.

Over a period of 6 months, this marginal recurrence extended for about 2 mm, remaining flat.

In the one patient with a large ciliary body melanoma (11.4 mm thickness) who had developed total retinal detachment after a first fraction of 28 Gy, mentioned above, the tumor height remained unchanged. Despite an attempt to re-treat the patient 9 months after the initial treatment, the eye

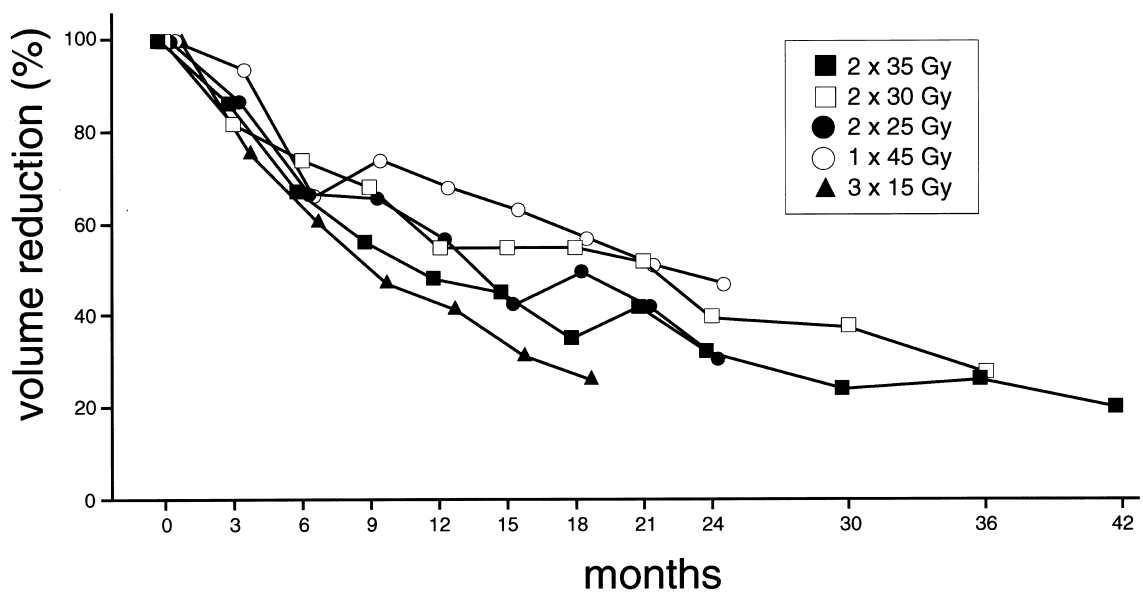


Fig. 3. Relative tumor volume reduction vs. time for the subgroups of tumors irradiated with 2×35 ($n = 10$), 2×30 ($n = 17$), 2×25 ($n = 14$), 1×45 ($n = 7$) and 3×15 Gy ($n = 14$).

Table 2
Radiation-induced side effects and enucleations for tumors^a

	≤8 mm ^b	>8 mm ^b	P-value ^c
Acute and subacute side-effects			
Eyelash loss	2 (6)	14 (47)	0.0001
Exsudative retinal detachment	7 (22)	16 (53)	0.026
Uveitis	4 (13)	14 (47)	0.0003
Late side-effects			
Lens opacities	8 (25)	19 (63)	0.0001
Secondary glaucoma	2 (6)	11 (37)	0.0004
(Neovascular glaucoma)	1 (3)	9 (30)	
Retinopathy	4 (13)	10 (33)	0.19
Optic neuropathy	10 (31)	6 (20)	0.32
Corneal epithelial defects	0	8 (27)	n.t.
Vitreous hemorrhage	3 (9)	2 (7)	n.t.
Secondary enucleation	0	8 (27)	n.t.

^a Numbers in parentheses are in percentages.

^b Tumors of sizes <8 mm ($n = 32$) and >8 mm ($n = 30$) in initial height.

^c P-values are taken from the univariate Cox model to test if tumor height has a significant impact on various side-effects. Only side-effects with more than ten events have been tested.

was enucleated because of angle closure glaucoma due to total exsudative retinal detachment.

3.2. Radiation-induced side-effects enucleations and metastasis

Table 2 lists all acute, subacute and late side-effects for tumors of ≤8 mm (5.5 ± 1.4 mm) and >8 mm (10.0 ± 1.4 mm) in initial height. Median follow-up periods for these subgroups were 25.5 and 31.7 months, respectively. Regarding radiation-induced exsudative retinal detachment, all but six had resolved by June 1998.

Eight eyes (13%) were enucleated. The Kaplan–Meier probabilities to retain the eye after 1, 2 and 3 years were 94, 87 and 83%, respectively. The reason for enucleation was neovascular glaucoma in six patients. Other reasons

included angle closure glaucoma due to total exsudative retinal detachment and stable tumor dimensions in one patient, and persisting total retinal detachment with amaurosis in another. Four of the patients requiring enucleation had ciliary body tumors. All patients requiring enucleation had presented with tumors larger than 9 mm in height. In all enucleated patients, the mean initial tumor height was 11.7 mm.

Seven patients (11%) developed metastases. Six of them had presented with initial tumor heights exceeding 8 mm. In all patients, local tumor control had been achieved. The 1, 2 and 3 year Kaplan–Meier estimates to remain free from metastasis are 98, 93 and 85%, respectively. Eight patients (13%) died during follow-up. The 1, 2 and 3 year Kaplan–Meier estimates for overall survival are 100, 88 and 84%, respectively. Six patients (19%) died of metastatic melanoma, approximately 4 months after the diagnosis of tumor dissemination. The 1, 2 and 3 year Kaplan–Meier estimates for cause-specific survival are 100, 91 and 86%, respectively.

3.3. Visual results

At baseline, 46 patients presented with a visual acuity of 0.1 or better. The 1 and 2 year Kaplan–Meier estimates for retaining this level of vision are 41 and 21%, respectively. In the subgroup with tumors of <8 mm in height, 25 patients presented with a visual acuity of 0.1 or better. For this subgroup, the 1 and 2 year Kaplan–Meier estimates for retaining visual acuity of 0.1 or better are 56 and 19%, respectively.

3.4. Analysis of risk factors for radiation-induced side-effects

The results of the univariate and the multivariate Cox analyses are listed in Tables 3 and 4. In the stepwise multiple Cox proportional hazards models (Table 4), tumor loca-

Table 3
P-values of the univariate Cox model for radiation-induced side-effects with more than ten events

	Lens opacities	Sec. glaucoma	Uveitis	Eyelash loss	Retinal detachment	Optic neuropathy	Retinopathy
Age	0.055	0.47	0.34	0.28	0.0061	0.99	0.66
Tumour height	0.0001 ^a	0.0004 ^a	0.0003 ^a	0.0001 ^a	0.026	0.32	0.19
GTV ^b	0.0001 ^a	0.0007 ^a	0.0001 ^a	0.0001 ^a	0.036	0.48	0.62
Localization (CB, CH) ^c	0.0001 ^a	0.0062	0.0004 ^a	0.0001 ^a	0.031	0.50	0.83
Total dose	0.16	0.0038	0.013	0.049	0.20	0.57	0.21
PTV	0.0001 ^a	0.012	0.0001 ^a	0.0001 ^a	0.18	0.74	0.86
Dose to lens ^b	0.0001 ^a	0.022	0.0001 ^a	0.0001 ^a	0.11	0.85	0.15
Dose to optic disk	0.18	0.34	0.32	0.11	0.85	0.60	0.86
Volume ≥10 Gy/fx ^{b,d}	0.0001 ^a	0.0026	0.0001 ^a	0.0035	0.38	0.34	0.36
GTV/PTV ^b	0.022	0.034	0.17	0.029	0.095	0.039	0.78
Distance to optic disk	n.t.	n.t.	n.t.	n.t.	n.t.	0.20	0.47
Distance to fovea	n.t.	n.t.	n.t.	n.t.	n.t.	0.46	0.79

^a Values indicate the significance after Bonferroni–Holm correction (global significance level, 0.05).

^b Log values (base 2).

^c Localization (ciliary body, choroid).

^d Volume >10 Gy/fx, volume irradiated with 10 Gy or more/fraction.

Table 4
Significant covariates of stepwise multiple Cox model for radiation-induced side-effects with more than ten events, with estimated risk ratios (RR) and their 95% confidence intervals (CI)

	RR	Lower CI	Upper CI	P-value
Lens opacities				
Localization (CH to CB) ^a	6.782	2.486	18.501	0.0002
Age (years)	1.095	1.044	1.149	0.0002
PTV (cm ³)	2.263	1.449	3.535	0.0003
Secondary glaucoma				
Tumor height (mm)	1.354	1.097	1.670	0.0048
Total dose (Gy)	1.095	1.009	1.189	0.030
Uveitis				
Volume ≥ 10 Gy/fx ^{b,c}	2.150	1.041	4.440	0.039
Tumor volume ^c	2.081	1.020	4.246	0.044
Eyelash loss				
Tumor volume ^c	4.317	2.274	8.198	0.0001
Exudative retinal detachment				
Age (years)	0.952	0.919	0.987	0.0061
Optic neuropathy				
GTV/PTV ^c	0.472	0.230	0.970	0.039

^a CH, choroidal; CB, ciliary body localization.

^b Volume ≥ 10 Gy/fx, volume irradiated with 10 Gy or more/fraction.

^c Log values (base 2), RR corresponds to a doubling of the corresponding covariate.

lization, height and volume, PTV, total dose and patient's age were identified as the strongest risk factors in predicting radiation-induced lens opacities, secondary glaucoma, uveitis, eyelash loss and exudative retinal detachment. In this model, the influence of fractionation, represented by the high-dose volume irradiated with 10 Gy or more/fraction, could be demonstrated for radiation-induced uveitis ($P = 0.039$). In the univariate Cox proportional hazards models (Table 2), this high-dose volume irradiated with 10 Gy or more/fraction was significantly associated with lens opacities and uveitis ($P = 0.0001$).

4. Discussion

This study represents the largest series of uveal melanoma patients treated with SEBI. In all other studies, the number of patients was smaller and follow-up periods were shorter [27,35,36,39,47].

In our study, SEBI resulted in effective local tumor control. Local tumor control was achieved in 98%, with tumor height reduction being demonstrated in 97%. After other forms of eye-preserving treatment modalities, the local tumor control ranges between 82 and 98% [4,7,21, 41,42]. Local tumor control was found in all 43 juxtapapillary tumors. In a study on 93 juxtapapillary tumors treated with rutheniums106 brachytherapy and followed-up for a mean 41 months, the local tumor control failure rate was 15% [34].

Since the initiation of our work, other studies have been published using gamma knife single-fraction SRS with

doses between 38 and 70 Gy. Local tumor control rates ranged between 97 and 100% [27,35,36,39].

It is widely accepted that rates of radiation-induced side-effects after different forms of radiotherapy for uveal melanoma are influenced by various factors, including tumor size, tumor localization and total dose. After helium ion therapy, larger tumors and those in the vicinity of the optic nerve and fovea had a higher incidence of most side-effects and visual loss [6]. In this study, we treated a highly selected group of patients with large tumors, as well as tumors in close vicinity to the optic disk or fovea. All patients were unsuitable for local resection or ruthenium-106 brachytherapy. All tumors presenting with an ultrasound height between 3 and 7 mm, and a distance of more than 3 mm between the central tumor margin and the optic disk rim or fovea, were excluded from this study and treated with ruthenium-106 brachytherapy. Our exclusion criteria were based on the decision of our study group not to offer gamma knife SEBI to patients with tumors which could safely be treated with other available techniques of established eye-preserving modalities. However, comparison of our results is limited by these selection criteria.

In tumors exceeding 8 mm in initial height, local tumor control was evident in all but one. However, in this subgroup, the radiation-induced morbidity was significant. This seems to be related to significantly larger PTVs, as well as to a high amount of ciliary body tumors (47%). In most of these cases, treatment had been performed alternatively to primary enucleation. Eight eyes in the study (13%) were enucleated, mainly due to neovascular glaucoma. After various radiation techniques, secondary enucleation ranges between 6% at 2 years and 19% at 8 years, mainly depending on the time of follow-up, radiation modality and study population [4,6,7, 13,42]. A study on proton beam irradiation found ciliary body involvement, tumor heights of greater than 8 mm and the proximity of the tumor to the fovea as leading risk factors for enucleation [13]. For us, the comparably high number of large tumors is the major factor for the relatively high overall enucleation rate. In our study, all eyes with secondary enucleations presented with an initial height exceeding 9 mm. The second reason for the high overall enucleation rate is the amount of ciliary body tumors. In our study, the 14 ciliary body tumors presented with a median height of 10.1 mm, and were followed for a mean period of 38 months. We observed four cases with neovascular glaucoma and four enucleations (each 29%). In another study, 54 slightly smaller ciliary body tumors (median height, 9.2 mm) were treated with helium ion therapy. At 3 years, the authors noticed a 40% change of developing neovascular glaucoma, and a 20% change of losing the eye [11]. Especially in our patients with tumors exceeding 11 mm in initial height, the clinical outcome was poor. At present, it is questionable whether stereotactic irradiation should be offered to patients presenting with these extra-large tumors. Seven of 12 eyes, presenting with 11 mm or more in initial height, were consequently

enucleated, with the remaining cases developing significant side-effects.

In the subgroup of 32 patients with initial tumor heights of 8 mm or less and consecutively smaller PTVs, side-effects were less frequent. Anterior eye segment complications were relatively rare. Eyelash loss was observed in two patients and uveitis in four. Secondary glaucoma was seen in two patients, with neovascular glaucoma in only one of them (3%). New asymmetric lens opacities developed in eight of 32 patients (25%). In a study on ruthenium-106 brachytherapy for uveal melanoma, the 2 and 3 year cumulative probabilities of developing asymmetric lens opacities were 21 and 27%, respectively [46]. In a study on proton beam irradiation for uveal melanoma, new posterior subcapsular opacities were found in 42% at 3 years [22]. However, both of the latter studies included ciliary body tumors. In the subgroup of patients with initial tumor heights of 8 mm or less, optic neuropathy developed in ten patients (31%). Optic neuropathy and/or retinopathy developed in 12 (38%) patients. Almost all patients (97%) had presented with juxtapapillary tumors. In a study on helium ion irradiation on 82 patients, radiation vasculopathy of the nerve or fovea developed in 18% [5]. In this study [5], only 19 patients (23%) presented with a central tumor margin extending to 3 mm of the optic disk rim and/or fovea. After ruthenium-106 brachytherapy for juxtapapillary tumors, the change of developing partial or total optic nerve atrophy at 2 and 5 years was 40 and 66%, respectively [34].

It is well known that the amount of radiation delivered to the anterior segment will influence anterior eye segment side-effects. To represent the anterior segment exposure to radiation, we investigated if the maximal dose to the lens, as measured at the point of the crystalline lens closest to the tumor, might be related to anterior eye segment complications. In tumors exceeding 8 mm in height, and especially in ciliary body tumors, this total lens dose exceeded average values. In the univariate Cox proportional hazards model, this total lens dose was a significant factor for lens opacities, uveitis and eye lash loss. However, in the multivariate analysis, we were not able to demonstrate a significant effect of the total lens dose on major complications. In a prospective study on helium ion therapy, 29% of 86 patients developed neovascular glaucoma after a mean observation time of 53 months [7]. However, only 5.5% had presented with a tumor height of 8 mm or more. In another study on proton beam therapy for uveal melanoma, 34% of 127 patients developed rubeosis iridis after a median follow-up period of 36 months. A major predictive factor for the development of rubeosis iridis was a large tumor size unsuitable for plaque therapy [17]. After a mean follow-up period of 28 months, we noticed 13 cases with secondary glaucoma (20%), including ten cases with iris or chamber angle neovascularizations (16%). Almost all of these cases were found in the large tumor subgroup.

In our study, 41 and 21% of eyes with initial good visual acuity of 0.1 or better maintained this level of vision over a

period of 1 and 2 years, respectively. Permanent loss of visual acuity was mainly attributed to radiation-induced retinopathy, optic neuropathy, serous retinal detachment and neovascular glaucoma. Studies on the visual results after charged particle treatment suggest that an overall of 54–65% of uveal melanoma patients maintained an initial visual acuity of 0.1 or better over a period of 1.6–2.1 years [31,40]. Patients with tumors exceeding 5–6 mm in height, and those with tumors located close to the optic disk and fovea, are known to have a greater risk for visual loss [6,40], and these formed a significant proportion in our sample.

We have taken into account the large body of experience underlining the positive correlation between dose/fraction and the incidence and severity of adverse side-effects. During the study period, we changed the dose and fractionation from 2×35 to 2×30 , 2×25 and 3×15 Gy, while prospectively monitoring local tumor control and observing in detail the different ocular side-effects. However, the total dose was not reduced below 45 Gy. After a total dose of 48 Gy (4 fx) of helium ion irradiation, the local tumor control failures increased to about 13%, compared with 3–5% local failures after irradiation with a total dose of 50–80 Gy [4]. A study on proton beam irradiation with total doses below 50 Gy had to be discontinued because of a higher failure rate [8].

Fractionation with the gamma knife is difficult to obtain, since the application of the skull-fixed stereotactic head frame, ocular fixation and CT- or MRI-delineation had to be repeated prior to each treatment fraction. Theoretically, fractionated SRT must be regarded as potentially superior to radiosurgery even for small malignant tumors, especially if complications are mainly caused by radiation damage to adjacent healthy critical structures [28,29]. In a rat glioma model, histological changes after SRS were found to be greater than those achieved with biologically equivalent doses of fractionated radiation therapy [26].

Compared to studies on gamma knife single-dose SRS for uveal melanoma, we have obtained more favorable results. In a study [39] delivering a single fraction of 70 Gy, 13 of 14 treated patients developed significant complications after a median follow-up period of 24 months. Retinopathy was found in 78%, and neovascular glaucoma in 43% of patients. Three of 11 patients (27%) with an initial visual acuity of 0.1 or better have maintained this level. In another study, ten patients were treated with single-dose SRS and a mean dose of 58 Gy. After a 24 month follow-up period, severe complications, such as neovascular glaucoma, radiation retinopathy and/or optic neuropathy, were observed in five of ten patients [36].

Our data demonstrate the influence of high-dose volume and fractionation on certain side-effects. In the univariate Cox analysis, the volume irradiated with 10 Gy or more/fraction was a significant risk factor for radiation-induced uveitis and new asymmetric lens opacities. In the multivariate Cox analysis, this high-dose volume was the strongest predictor for radiation-induced uveitis. This volume effect

directly corresponds to the dose/fraction, and thus to fractionation.

Although no definite evidence is provided in this study that increased fractionation will have a beneficial effect on the major complications, like neovascular glaucoma, lens opacities, retinopathy and optic neuropathy, our results are encouraging and justify further clinical investigations with an increased number of fractions. However, a gamma knife treatment of uveal melanomas with more than three fractions is limited by the patient's tolerance to the repeated application of a neurosurgical head frame and the ophthalmic fixation device, as well as by the availability and expense for stereotactic CT- or MRI-scans prior to each fraction.

Using a stereotactic linear accelerator, we have started a new clinical study addressing 5–7 fractions of SRT for uveal melanoma. This device offers the advantages of real non-invasiveness and unlimited fractionation. Our ongoing study addresses the issue of dose and fractionation necessary for local tumor control of uveal melanoma in relation to radiation-induced morbidity [53]. In vitro studies have shown the relative radio-resistance of human uveal melanoma cells to be virtually unaffected by low-dose fractionated radiotherapy with single doses below 4.2–6 Gy, and indicated that high-dose fractions of at least 7–8 Gy should be prescribed [32,44]. Recently, a preliminary study on the use of a 6-MeV linear accelerator and 48 Gy in eight fractions for uveal melanoma has been published. The majority of 16 patients remained free from relapse and major complications. However, morbidity was not discussed in detail [47].

In summary, our study clearly proves that stereotactic external photon beam irradiation (SEBI) and a total dose of 45–70 Gy, delivered in 1–3 fractions, is highly effective at achieving local tumor control in uveal melanoma. Morbidity is influenced by various patient-, tumor- and treatment-related factors, including the high-dose volume irradiated with more than 10 Gy/fraction. Further clinical studies using smaller fraction doses, and consequent smaller high-dose volumes, are necessary to optimize dose and fractionation. For uveal melanomas, fractionated SRT with linear accelerators has a challenging potential as an available eye-preserving treatment in general radiation oncology.

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