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Hypofractionated stereotactic photon radiotherapy of choroidal melanoma: 20-year experience

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ABSTRACT

Background: To evaluate the long-term results after hypofractionated stereotactic photon radiotherapy (SRT) in patients with choroidal melanoma treated between 1997 and 2016.

Material and methods: A total of 335 patients (183 male and 152 female) with choroidal melanoma unsuitable for ruthenium-106 brachytherapy or local resection were treated with linear accelerator-based SRT at the Medical University of Vienna. All patients received five fractions with either 10, 12 or 14 Gy per fraction. A complete ophthalmic examination including visual acuity and measurement of the tumor base and height using standardized A- and B-scan ultrasonography was performed every 3 months in the first 2 years, every 6 months until 5 years and yearly thereafter. Early and late adverse side effects were assessed at every follow-up visit.

Results: The median overall follow-up was 78.6 months (39.1 to 113.7 months). Local tumor control was 95.4% after 10 and 12 years, respectively. Fifty-four patients developed metastatic disease, and 31 died during the follow-up. Mean visual acuity decreased from 0.55 Snellen at baseline to 0.05 Snellen at the last individual follow-up. Ischemic retinopathy (192/335cases) and optic neuropathy (174/335cases) were the most common radiogenic side effects, followed by radiogenic cataract ($n = 127$), neovascular glaucoma ($n = 71$) and corneal epithelium defects ($n = 49$). Enucleation was performed in 54 patients mostly due to neovascular glaucoma ($n = 41$) or tumor recurrence ($n = 10$) during the study period. The eye retention rate was 79.7% after 10 and 12 years.

Conclusion: Hypofractionated stereotactic photon radiotherapy showed a high rate of local tumor control for choroidal melanoma and an acceptable rate of radiogenic side effects.

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Choroidal melanoma; hypofractionated stereotactic photon radiotherapy; local tumor control; long-term survival; adverse side effects

Introduction

Uveal melanoma (UM) is the most common primary intraocular tumor in adults, arising in 90% of cases in the choroid next to the ciliary body and iris [1,2]. Several treatment options exist such as radiation therapy including brachytherapy, proton beam and stereotactic radiation therapy, and surgical approaches in form of endoresection and enucleation [3–6]. Enucleation is usually performed in large tumors only, where there is intensive involvement of the ciliary body or the iris or if extraocular spread is suspected [7]. The main treatment goal of all radiotherapy treatment techniques is local tumor control, to prevent organ and vision, to prevent metastatic spread and increase overall survival. On the other hand, the radiotherapy options for UM depend on tumor localization, size and extension. Peripherally located tumors can be treated using ruthenium-106 or iodine-125 brachytherapy, whereas the preferred options in tumors located posteriorly are proton beam therapy, Gamma Knife radiosurgery and stereotactic hypofractionated radiotherapy (SRT) at a linear accelerator [8–11].

The management of UM also aims to maintain vision and ensure a long metastasis-free interval. Although conserving the eye became achievable with these globe-preserving therapies, they do lead to functional impairment. The Collaborative Ocular Melanoma Study (COMS) reported that more than half of the study patients had a worse visual function of 20/200 3 years after therapy [12]. Researchers have attempted to find reasons for the decrease in vision and describe secondary changes following radiation therapy including radiation retinopathy and optic neuropathy, and radiation-induced cataract impairing visual function [13,14]. Besides the difficulty of vision loss, metastatic disease is a fatal development because no effective therapy exists [15]. Metastases at initial presentation are rare but they can develop in up to 50% of the patients [16]. The risk of metastases is related to increased age, great tumor volume or extrascleral extension [17].

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Apart from side effects and metastatic spread, studies have mainly concentrated on local tumor control to compare the different therapeutic approaches [18,19]. The first 5 years after initial therapy seemed adequate for such a comparison. A tumor control rate of about 97-98% has been achieved 5 years after proton and linac based photon beam therapy [20,21]. However, results of tumor therapy must be considered throughout a patient's life and should, therefore, be presented beyond the initial 5 years after therapy.

In this evaluation, we extend work we presented previously [10,22,23] and report tumor control, functional outcome and survival 5, 10 and 12 years after hypofractionated linear accelerator-based stereotactic photon radiotherapy. Furthermore, this article presents incidences and the frequency of early and late onset radiogenic side effects.

Material and methods

Between 1997 and 2016, 335 patients with choroidal melanoma unsuitable for brachytherapy or local surgical tumor removal were treated with linear accelerator (LINAC)-based hypofractionated stereotactic photon radiotherapy at the Medical University of Vienna/Vienna General Hospital. Approval of the local ethics committee (EK: 1888/2016) was obtained and the study adhered to the tenets of the Declaration of Helsinki.

Inclusion for hypofractionated SRT treatment comprised choroidal melanomas of 7 mm or more in height, a juxtapapillar or juxtamacular location (defined within 3 mm from the optic disk and/or the macula) and more than 2.5 mm of height, or if other eye-conserving methods were not possible. Patients were not treated with hypofractionated SRT if extrascleral tumor extension was present, neovascular glaucoma was diagnosed before the treatment, any form of other treatment had already been performed or metastatic disease had been detected.

Prior to hypofractionated SRT, a detailed examination was performed including best-corrected visual acuity (BCVA) with Snellen charts, Goldmann applanation tonometry and slit-lamp examination of the anterior chamber including gonioscopy [10]. Ultrasound A- and B-scan echography was performed to assess the quantitative tumor dimensions, base and height. Following the COMS classification of choroidal melanomas, tumors in our patients were divided into four groups according to their dimensions. Tumor volumes were calculated using the ellipsoidal solid model [24].

Metastatic disease was ruled out by a detailed physical examination, blood samples including blood count, renal function variables, transaminases, and inflammatory variables, chest X-ray as well as abdominal ultrasound.

Stereotactic radiotherapy

A detailed description of the treatment planning and dose delivery with head and eye fixation and exe motion surveillance has been published and can be found in literature [10,22,25]. The applied treatment delivery techniques included arc therapy with stereotactic cones or MLC-shaped static conformal fields [26]. All patients were treated with five fractions between 5 to 7 days. In the first 2 years, 24 patients received 14 Gy per fraction prescribed to the 80% isodose. The dose was then reduced twice to 12 Gy per fraction as well as 10 Gy per fraction prescribed to the 80% isodose.

Follow-up was performed in 3-monthly intervals during the first 2 years after therapy, and extended to every 6 months until 5 years and once yearly thereafter. A complete ophthalmic examination including BCVA, tonometry, slit-lamp examination, funduscopy and A- and B-scan echography was performed at each follow-up visit.

The side effects were divided according to the time of appearance into an early or subacute phase and late-onset phase [3]. All side effects were graded according to the Common Terminology Criteria for Adverse Events (CTCAE; U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; latest Version 4.03 published June 14th 2010).

Additionally, all patients were screened for metastatic disease at 6-month intervals. The presence of metastases was ruled out by blood sample tests, chest X-ray, abdominal ultrasound and a detailed physical examination. Follow-up examinations were performed at the Medical University of Vienna (>95%).

Local tumor control was defined as no evidence of tumor recurrence, which was assumed if the tumor volume increased by more than 25% between two follow-up examinations at least 6 months after the radiotherapy. Endpoints were tumor recurrence, metastatic disease, enucleation of the treated eye, death and radiogenic side effects.

Statistical analysis

Statistical calculations were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA; using %cuminc macro). Continuous variables are presented as mean ± standard deviation (SD) if the data are normally distributed and as median and interquartile range (IQR) otherwise, whereas categorical variables as absolute and relative frequencies.

The reverse Kaplan-Meier method was applied for estimation of median follow-up time based on overall survival data [27]. For each side effect, for tumor recurrence, as well as the event that visual acuity falls below 0.1 Snellen, the time until the event of interest is computed using Cumulative Incidence Functions (CIF) to account for competing events [28,29]. The following competing events accounted for: death from other causes for the time until disease related death ('disease-specific survival'); death from any cause for time until metastasis ('proportion metastasis-free'), time until enucleation ('eye retention'), and all subacute and early side effects; death from any cause and enucleation for late side effects, death from any cause and enucleation without previous recurrence for enucleation after previous recurrence (and analogously for enucleation after previous neovascular glaucoma).

For comparability, overall survival (without competing event) is presented as 1 minus Kaplan-Meier (1-KM)

Table 1. Summary of patient and tumor characteristics.

Characteristics	Value
Sex	
Male	183 (54.6%)
Female	152 (45.2%)
Follow-up (months)	78.6 (IQR 39.1–113.7)
Age (in years)	61.4 ± 13.4 (range: 20.9 to 93.0)
Shape	
Dome	285 (85.1%)
Collar	50 (14.9%)
Quadrant	
Q1	91 (27.2%)
Q2	78 (23.2%)
Q3	75 (22.4%)
Q4	91 (27.1%)
Tumor thickness (in mm)	4.67 (IQR 3.64–6.28)
<5mm	184 (54.9%)
>=5-<8mm	122 (36.4%)
>=8-<10mm	25 (7.5%)
>=10mm	4 (1.2%)
Initial volume (in mm^3)	261.44 (IQR 138.51–441.93)
Initial visual acuity (> 0.1Snellen)	
Yes	283 (84.5%)
No	52 (15.5%)
Distance to the center of the macula (in mm)	
0mm	109 (32.5%)
>0-≤3mm	184 (55.2%)
>3mm	41 (12.2%)
Distance to the rim of the optic nerve (in mm)	
0mm	90 (26.9%)
>0-≤3mm	189 (56.4%)
>3mm	56 (16.7%)
Total radiation dose	
70 Gray	24
60 Gray	159
50 Gray	147

IQR: Inter-quartile range.
Quantitative tumor dimensions (base, height) were performed by two experienced ophthalmologists (M.Z. and R.D.) using an ultrasound A- and B-scan.

estimates. Percentages of patients free from an event of interest after 3 months, 1,351,012 years as well as 95% confidence intervals (CIs) are based on CIF and 1-KM estimates, respectively.

Results

Patient data

This study with a median potential follow-up was 78.6 months (IQR 39.1–113.7) included 335 patients with a mean age of 61.4 ± 13.4 years (range: 20.9 to 93.0 years). See Table 1 for patient and tumor characteristics.

Local tumor control and loss of eye

Local tumor control was 95.4% [CI 92.8 − 98.1] at 10 as well as 12 years after SRT. Recurrent tumor growth was seen in 12 patients. After 10 years 96.3% [CI 94.0–98.7] did not yet have the event 'enucleation after recurrence'. Secondary enucleation of the affected eye was performed in 10 cases, whereas two patients received brachytherapy with Ruthenium-106 after 26 and 65 months after initial stereotactic photon therapy. Figure 1 shows the continuous decrease in median tumor dimensions. Eye retention rate was 79.7% [CI 74.7–84.7] after 10 as well as 12 years. In total, 54 eyes underwent secondary enucleation during the follow-up

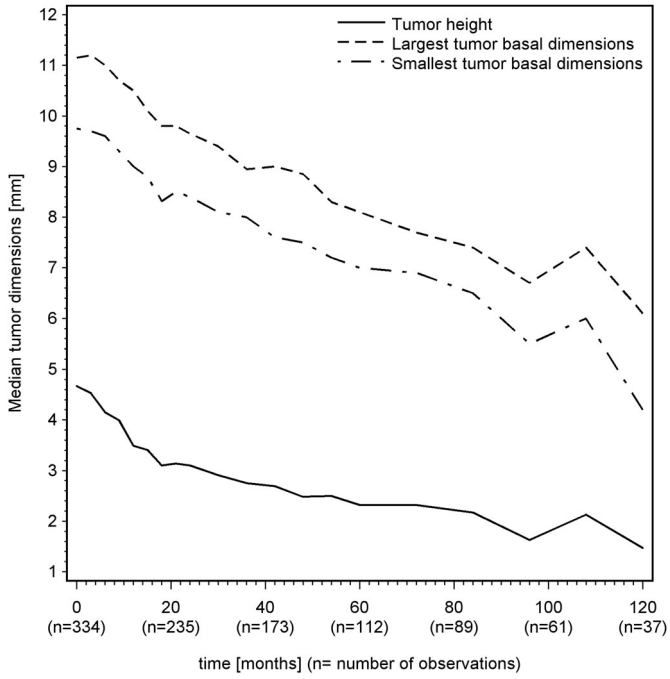

Figure 1. Median tumor base dimensions (dashed) and height (solid) decreased over the follow-up period. Numbers of patients remaining in the sample are given in brackets below the horizontal axis. Note that the length of observation time varies between patients and missing values at later time points might be informative.

period, mostly due to neovascular glaucoma ($n = 41$) and corneal ulcers ($n = 3$).

Metastatic disease and long-term survival

In total, metastatic disease was discovered in 54 patients, in 31 of whom it deceased during the study period. The frequency to be free of metastatic disease was 77.3% [71.4-83.2] after 10 years and 70.5% [CI 61.2–79.8] after 12 years. After 10 years 85.8% [80.7–90.9] and after 12 years 83.8% [77.6–90.1] of the patients were free from disease-related death, respectively.

In total, 55 patients died during the follow-up. Twenty-four patients died due to other reasons (age, second cancer or other). Overall survival was 74.7% [68.1–81.2] after 10 years and 68.9% [58.8–79.0] after 12 years. Supplemental material 1 and Figure 2 show detailed information on metastatic disease and long-term survival.

Visual acuity

At baseline the median BCVA was 0.55 Snellen (IQR 0.30 − 0.80), which dropped to 0.05 (IQR 0.001 − 0.4) at 2 years after SRT. Before SRT, 283 patients (84.5%) had a BCVA of 0.1 Snellen or better, whereas 52 (15.5%) had a BCVA of 0.1 Snellen or worse. A severe decrease in BCVA was observed from 6 months on. Only 56.8% of the patients reached a BCVA of 0.1 Snellen or better after 1 year, whereas 5.4% after 5 years, 0.6% after 10 years and no patient after 12 years. BCVA development is in shown in supplemental material 2.

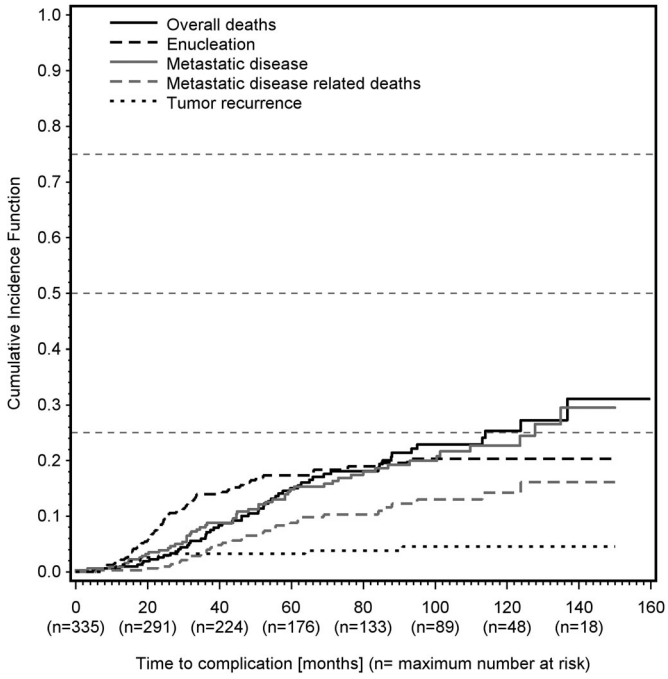

Figure 2. Cumulative incidence functions for late radiotherapy side effects: cataract, neovascular glaucoma, optic neuropathy and retinopathy.

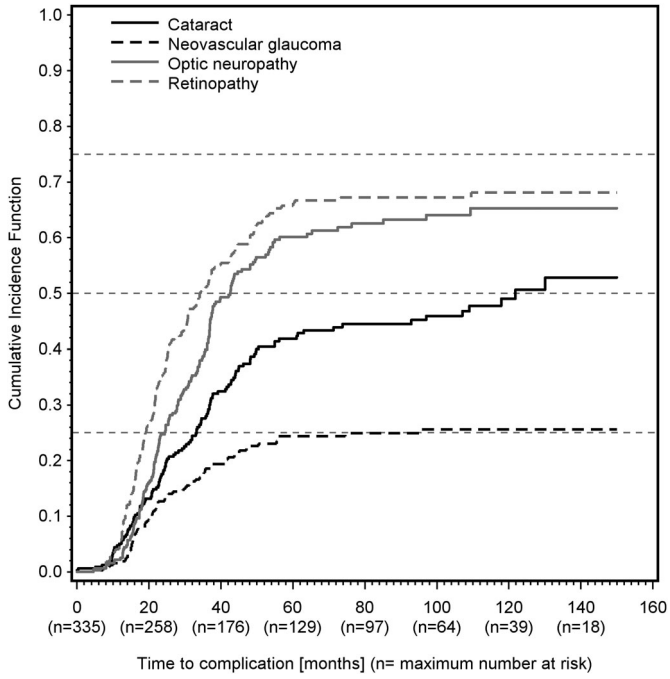

Figure 3. Subacute, early and late side effects of the radiotherapy according to the applied irradiation dosage: 50 Gy-group and 60/70 Gy-group.

Radiotherapy related side effects

As all our patients had posteriorly located tumors, the doses calculated with the treatment planning system (TPS) at the organs at risk were lower in the anterior eye segment (10-20% of dose prescribed for the planning target volume (PTV) per fraction) than in the posterior eye segment (50-100% of dose prescribed for the PTV per fraction). Figure 3 illustrates the occurrence of the late side effects cataract, neovascular glaucoma, optic neuropathy and ischemic retinopathy. Overall numbers of all side effects including early and late side effects, and the percentage of patients free of these events are shown in Table 2.

49 patients had corneal epithelium problems, of whom the percent without corneal changes was 99.4% [CI 98.6 – 100] during the first 3 months, but decreased to 86.4% [CI 82.5–90.3] after 36 months. A corneal ulcer was found in 23 patients one to three months after treatment. After 3 months, no patient had a corneal ulcer. After 36 months 94.2% of the participants remained free from this side effect [CI 91.5 – 96.9].

Ischemic retinopathy (192 cases) and optic neuropathy (174 cases) were the most common radiogenic side effects in this study, followed by radiogenic cataract (127 cases) and neovascular glaucoma (71 cases). The 12-year probability to remain free of ischemic retinopathy was 31.9% [CI 26.1 – 37.6] and of optic neuropathy was 34.7% [CI 28.5 – 41.0].

Panretinal laser photocoagulation was performed in 168 patients because of ischemic retinopathy, optic neuropathy or neovascular glaucoma. 37.8% [CI 31.8 – 43.8] of the patients did not require laser photocoagulation 10 as well as 12 years after radiotherapy.

For the 127 patients with cataract, mean age at cataract was 60.2 ± 12.1 years. The probability to develop no cataract was 51.0% [CI 44.2 – 57.7] after 10 years and dropped to 47.2% [CI 39.3 – 55.1] after 12 years. In total, 73 patients required cataract surgery. 65.9% [CI 57.4 – 74.3] of the patients did not require surgical removal of radiogenic cataract 12 years after the treatment.

Dose-dependent results

Two groups were created for the analysis of the dose-dependent results and the follow-up is presented up to 5 years. The first group comprised patients received 50 Gy (50 Gy group; $n = 147$) and the second group patients received either 60 or 70 Gy (60/70 Gy group; $n = 159/24$), prescribed to the 80% isodose. Comparability of these two groups is limited due to the different follow-up periods. Therefore, the results are presented descriptively.

Local tumor control as well as the eye retention rate did not differ in both groups (local tumor control: 50 Gy group: 96.9% [92.9 – 99.0]; 60/70 Gy group: 96.7% [93.4 – 98.7]; eye retention rate was in the 50 Gy group 88.3% [81.2 – 93.6] and in the 60/70 Gy group: 80.0% [73.9 – 85.5]) after 5 years.

No significant difference of metastatic free disease in the 50 Gy group 85.5% [76.3 – 92.5] and in the 60/70 Gy group 84.8% [79.2 – 89.7] after 5 years. The proportion of metastatic-free survival was higher in the 50 Gy group (94.5% [87.23 – 98.3]) than in the 60/70 Gy group (89.7% [84.7 – 93.7]) as was the overall survival (50 Gy group: 92.3% [84.5 – 97.0]; 60/70 Gy group: 81.8% [75.7 – 87.11]) after 5 years.

The analysis of the subacute and early as well as late radiogenic side effects showed similar results for both groups. See Table 3 for radiogenic side effects regarding the dose-dependent results.

Table 2. Early and late radiotherapy side effects in the total study population.

Subacute and early radiotherapy side effects							
Events	Number	After 3 months	CI	After 12 months	CI	After 36 months	CI
Alopecia	12	96.4%	94.4 – 98.4	96.4%	94.4 – 98.4	96.4%	94.4 – 98.4
Dermatitis	9	97.9%	96.3 – 99.4	97.6%	95.9 – 99.2	97.2%	95.4 – 99.0
Corneal Epithelium Problems	49	99.4%	98.6 – 100.0	95.0%	92.7 – 97.4	86.4%	82.5 – 90.3
Eyelash Loss	13	98.2%	96.7 – 99.6	97.2%	95.5 – 99.0	96.3%	94.2 – 98.3
Corneal Ulcer	23	100.0%	n.a.	98.7%	97.5 – 100.0	94.2%	91.5 – 96.9
Diseases of the Lacrimal Drainage System	10	97.0%	95.2 – 98.8	97.0%	95.2 – 98.8	97.0%	95.2 – 98.8
Uveitis	16	99.7%	99.1 – 100.0	98.7%	97.5 – 100.0	94.9%	92.4 – 97.4
Late radiotherapy side effects							
Events	Number	After 5 years	CI	After 10 years	CI	After 12 years	CI
Cataract	127	57.6%	51.7 – 63.6	51.0%	44.2 – 57.7	47.2%	39.3 – 55.1
Neovascular Glaucoma	71	75.7%	70.6 – 80.7	74.4%	69.2 – 79.7	74.4%	69.2 – 79.7
Optic Neuropathy	174	39.9%	34.0 – 45.8	34.7%	28.5 – 41.0	34.7%	28.5 – 41.0
Retinopathy	192	33.8%	28.1 – 39.4	31.9%	26.1 – 37.6	31.9%	26.1 – 37.6
Cataract Surgery	73	77.4%	72.3 – 82.4	70.4%	64.2 – 76.5	65.9%	57.4 – 74.3

CI: confidence interval.
Percent give proportions of patients still free from the specified side effect at the specified time after SRT.

Table 3. Subacute, early and late side effects of the radiotherapy according to the applied irradiation dosage: 50 Gy-group and 60/70 Gy-group.

Subacute and early radiotherapy side effects						
	50Gy group			60 and 70Gy group		
Events	Number of events	Free after 1 year	CI	Number of events	Free after 1 year	CI
Alopecia	2	98.6%	95.5–99.7	10	94.5%	90.6–97.2
Dermatitis	0	100.0%	n.a.	9	95.6%	92.0–98.0
Corneal Epithelium Problems	14	96.4%	92.2–98.7	35	94.0%	89.9–96.8
Eyelash Loss	0	100.0%	n.a.	13	95.1%	91.3–97.6
Corneal Ulcer	8	98.5%	95.2–99.7	15	98.9%	96.4–99.8
Diseases of the Lacrimal Drainage System	4	98.6%	95.3–99.7	0	100.0%	n.a.
Uveitis	5	99.2%	96.2–99.9	11	98.9%	96.4–99.8
Late radiotherapy side effects						
	50Gy group			60 and 70Gy group		
Events	Number of events	Free after 5 years	CI	Number of events	Free after 5 years	CI
Cataract	46	52.1%	41.4–63.6	81	58.1%	50.8–65.6
Neovascular Glaucoma	29	70.8%	61.2–79.9	42	77.8%	71.8–83.6
Optic Neuropathy	65	36.7%	27.2–48.2	109	41.9%	35.0–49.6
Retinopathy	77	26.5%	18.3–37.6	115	38.3%	31.5–43.2

Percent give proportions of patients still free from the specified side effect at the specified time after SRT.

Discussion

During the last decades hypofractionated SRT has become an effective treatment option to preserve the eye and achieve local tumor control in choroidal melanoma unsuitable for brachytherapy [10,30]. In this study, we present our 20-year experience with hypofractionated SRT relating to local tumor control, functional outcome and side effects for the treatment of UM located close to the optic nerve and/or the macula.

The main finding, local tumor control, is an important parameter to describe the efficacy of a therapy. Several researchers have published similarly high rates of local tumor control of 96% after 5 years, 81.9% after 5 years and 100% after two years in proton beam therapy, stereotactic radiosurgery with Gamma Knife and hypofractionated SRT, respectively [21,30–33]. In our study, we present long-term results of the local tumor control rate (95.4%) 10 as well as 12 years after SRT treatment and thus, even after reducing the single and total dose during the study period.

Another interesting aspect of tumor therapy is the eye retention rate. In brachytherapy high rates of 95.6% or 90.2% are reported five to ten years after treatment [34,35]. However, enucleation is commonly performed due to tumor recurrence, which is related to tumor size, height or proximity to the posterior pole, or secondary glaucoma. In proton beam therapy, the eye retention rate is about 95.0%, within the first two to three years after treatment [36]. But afterwards a decrease to 83.7% is observed after 15 years, which similar to our results of 79.7% after 12 years [37].

The development of metastases is still associated with a pronounced decrease in survival rates as no beneficial or established treatment is available. In our study, 55 patients died during the follow-up interval, of whom 31 died of uveal-melanoma-related disease. The tumor-related survival was highest 5 years (91.2%) after SRT. Afterwards a decrease to 83.8% was observed during the 12-year follow-up. Nevertheless, our results are comparable to proton beam

centers publishing survival rates of 79.0% after 5 years to 62.7% after 15 years [31,38].

Most of our patients experienced major vision loss 6 months after initial therapy (our results: BCVA >0.1 Snellen: 56.8% after 1 year). This was mainly related to the unfavorable localization of the tumor within 3 mm proximity to the optic disk (83.3%) and macula (87.7%). Due to this fact, the optic nerve and the macula received BED (biological equivalent dose) above 80 Gy, which produces damages at the vessels of the optic nerve and macula. Nevertheless due to the low radiation sensitivity of UM high radiation doses are required to achieve good local tumor control [39,40].

Vision-sensitive areas are located close to the radiation field and are therefore irradiated, thus causing radiogenic side effects. Our functional results were as unsatisfactory as reported in several other studies reporting vision loss in up to 56% within 5 years after proton beam therapy or 63.6% within 6 to 24 months after Gamma Knife radiosurgery [20,31,41]. Furthermore, to minimize these effects, the dose was reduced twice in our patient cohort. Initially, five fractions of 14 Gy were applied, thereafter from June 1998 5 fractions of 12 Gy were applied and from February 2006 in 5 fractions of 10 Gy. All fractional doses were prescribed to the 80% isodose, which was optimized during treatment planning to fully encompass the PTV. This did not result in a lesser degree of local tumor control or lower eye retention rate. Also, no difference was seen in metastasis development. Therefore it has to be concluded that even the minimum tumor dose of 50 Gy (BED of around 100 Gy ($\alpha/ß = 10$ for tumor) is still too high and further studies might be necessary de-escalating the tumor dose without compromise to the local control.

In this study radiogenic side effects were divided according to the time of appearance. Our patients experienced seldom early radiogenic side effects such as dermatitis, alopecia or eyelash loss after 3, 12 and 36 months and showed reversible manner. Only problems of the corneal epithelium occurred more often in the late phase of follow up after 36 months. 23 out of the 49 patients with corneal epithelium effects concomitantly developed corneal ulcers. In most patients local therapy was sufficient, except in three patients who received enucleation due to therapy-resistant corneal ulcer. Radiogenic keratitis with or without corneal ulcers was observed in up to 11.5% after radiation therapy of the eye [31]. The etiology of corneal damage following irradiation is yet unknown but irreversible long-term damage to corneal endothelium or innervation resembling neurotrophic ulcer is being discussed [42].

Ischemic retinopathy and optic neuropathy are commonly found after radiotherapy, especially for UM located near the optic disk and fovea. Next to the tumor localization, high radiation dose rate is a key predicator for radiation neuropathy [43–45]. Both were the main late-onset side effects in our study cohort, already affecting more than 50% of the patients 5 years after SRT. Dendale *et al.* found maculopathy in 66.5% of patients but only 23.4% optic neuropathy 5 years after proton beam therapy, but in this cohort tumor localization was 4.3 to 3.5 mm from the optic disk [31]. Muller *et al.* observed ischemic retinopathy in 5% and optic neuropathy in 9% of patients, however within 2 years after fractionated stereotactic RT [30], but follow-up time was to short, that the whole dimension cannot be estimated. Lane *et al.* showed that increasing distance from the optic nerve results in less vision loss after 10 years [46].

Our long-term results for ischemic retinopathy and optic neuropathy were comparable to literature for stereotactic radiotherapy and proton beam radiotherapy, suggesting no major difference between the different treatment modalities [30,31,47,48].

Further late-onset radiogenic side effects were cataract and secondary glaucoma, which developed in 58% and 27% of the patients, respectively. Other studies reported the high variability in development of cataracts of 35% to 61.8% and in secondary glaucoma of 4.7% to 28.6% two to five years after therapy [4,31,49]. Regarding these late radiogenic side effects, ischemic retinopathy, optic neuropathy and neovascular glaucoma developed mainly within the first 5 years after initial therapy and remained rather unchanged thereafter, whereas cataracts developed progressively during follow-up which is also attributable to aging. Kim *et al.* reported a similar observation, 68% of patients developed optic neuropathy after a median interval of 17.7 months after proton beam therapy [48]. This shows that except for cataracts the probability of developing 'late' side effects drops around 5 years after initial therapy.

The dose was reduced twice during the last 20 years, from 70 Gy to 60 Gy and from 60 Gy to 50 Gy. The radiogenic side effects showed a distribution according to the dose used. Subacute and early side effects were more pronounced with the 60 Gy and 70 Gy dose and late side effects with the 50 Gy dose. Thus, the reduction of fraction size revealed a good tumor response rate, even in lower irradiation doses. The proportion of metastatic free survival and overall survivals as well as the early radiogenic side effects seemed to show a more favorable outcome with the 50 Gy dose. But the influence of the localization and volume was not specifically analyzed in the dose-dependent statistics. Further, the comparability of the two groups, and subsequently the results, are limited due to the shorter follow-up of the 50 Gy group.

In our 20-year experience, hypofractionated stereotactic photon radiotherapy shows a high rate of local tumor control for choroidal melanoma and moderate rate of radiogenic side effects.

Disclosure statement

The authors declare no conflict of interest.

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