Fractionated stereotactic radiotherapy for uveal melanoma: Long-term outcome and control rates

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ABSTRACT.

Purpose: **The aim of our study is to evaluate local tumour control rates, radiation side-effects, visual preservation and disease-free survival (DFS) of uveal melanoma (UM) patients treated with fractionated stereotactic radiotherapy (fSRT).**

Methods: **A retrospective study of UM patients, who were treated with fSRT (N = 189), was performed by the Rotterdam Ocular Melanoma Study group (ROMS), the Netherlands, between 1999 and 2014 with a follow-up of at least 5 years.**

Results: **The 1-, 3-, 5-, 10- and 15-year local tumour control rates were as follows: 99.4%, 92.8%, 92.2%, 89.3% and 89.3%, respectively. Cataract (67.8%) was the most common side-effect of fSRT followed by retinopathy (35.1%), maculopathy (23.8%), vitreous haemorrhage (20.1%), neovascular glaucoma (NVG) (20.0%) and optic neuropathy (12.4%). Patients with anterior located UMs developed cataract more frequently ($p = 0.047$, multivariable analysis). By multivariable analysis, significant factors for secondary enucleation were tumour recurrence ($p < 0.001$) and NVG ($p < 0.001$). In multivariable analysis, risk factors for a worse DFS were larger UM ($p = 0.024$) and tumours with subretinal fluid (SRF) at baseline ($p = 0.038$). The 5-year DFS was 77.0% and the best corrected visual acuity decreased significantly after treatment. After 5 years, 22.0% of patients and after 10 years 17.6% of patients had a visual acuity of ≤0.3 logMAR.**

Conclusion: **Fractionated stereotactic radiotherapy is a good treatment option for small-, medium- and large-sized tumours with 5-year local tumour control of 92.2%. After 5 years, 22.0% of the patients had a good vision. Independently of tumour location, the visual acuity decreased significantly after treatment. Overall, the 5-year DFS was 77.0%.**

Key words: fractionated stereotactic radiotherapy – local tumour control – side-effects – uveal melanoma

Funding: None.

Acta Ophthalmol. 2022: 100: 511–519

doi: 10.1111/aos.15029

Introduction

Uveal melanoma (UM) are rare ocular tumours, but related with significant morbidity and mortality. The treatment of UM depends on the size and the location of the tumour, the secondary effects of the tumour on the eye, the status of the fellow eye and patients' choice. The last decade's eye-preserving therapies have proven to be equally effective regarding overall patient survival and metastasis-free survival compared to enucleation.

Fractionated stereotactic radiotherapy (fSRT) is a treatment for mostly small- and medium-sized UM and some larger UM up to approximately 12 mm in thickness and a diameter smaller than 16 mm. Other radiotherapeutic treatment options for UM of these size are proton beam radiotherapy and brachytherapy. One advantage of fSRT is that fSRT requires no surgical procedures to determine the tumour localization and dimensions. Reported side-effects are similar to those of brachytherapy and proton beam radiotherapy and can lead to visual impairment and secondary enucleation (3–16%) (Shields et al. 2000; Dendale et al. 2006; Damato et al. 2013; van den Bosch et al. 2015). Radiogenic side-effects are cataract, retinopathy, maculopathy, neovascular glaucoma, vitreous haemorrhage and

optic neuropathy (Zehetmayer et al. 2000; Muller et al. 2005; Krema et al. 2009; Dunavoelgyi et al. 2012; Yazici et al. 2017).

The aim of this study was to evaluate the value of fSRT for treatment of UM. Since there are overlapping treatment options depending on the tumour size and location, it is important to know the potential radiogenic side-effects and how to treat them. Awareness of the risk of side-effects can influence the choice of treatment. Since some side-effects develop over the years, we only analysed our treated patients with a follow-up of at least 5 years. For this subset, we report local tumour control rate, (late) radiogenic side-effects (i.e. secondary glaucoma, cataract, vitreous haemorrhage, radiation-induced optic neuropathy, radiation-induced maculopathy and retinopathy), visual preservation and disease-free survival.

Materials and Methods

Patients

A retrospective study by the Rotterdam Ocular Melanoma Study group (ROMS) was performed in 189 patients with choroidal and/or ciliary body UM treated with fSRT at the Radiation Oncology department of the Erasmus MC, Rotterdam, the Netherlands, between 1999 and 2014. We excluded iris melanomas as well as posterior UMs that were larger than 12 mm in thickness and/or had a larger diameter than 16 mm. The latest follow-up date was January first 2020. All patients had a follow-up of at least 5 years. The local medical ethical committee approved the retrospective data analysis for the long-term effects and treatment outcome. The patients were treated in a standardized way and were informed on the treatment and follow-up protocol for this treatment. The study was performed according to the guidelines of the Declaration of Helsinki.

At the time of diagnosis, patients were examined by an ophthalmologist with expertise in ocular oncology. Fundus photography and B-scan ultrasonography were used for follow-up. If necessary, ancillary tests were used, such as fluorescent angiography, indocyanine green angiography and A-scan ultrasonography. All patients underwent full systemic examination and staging evaluation by a specialized oncologist from our institution. All UM patients received primary radiation and were treated by a specialized radiation oncologist. All clinical and follow-up data were collected and processed in a homemade database application based on Filemaker 16 (FileMaker Inc., Santa Clara, CA, USA). UM were categorized according to the Tumour, Nodes, Metastasis (TNM) Classification; the Tumour (T) category of the 8th edition of the American Joint Committee on Cancer (AJCC) staging system of posterior uveal melanoma (Kivelä et al. 2016). The tumour (T) is given a classification of T1–T4 based on its width (largest basal diameter) and height (thickness).

Our fSRT treatment protocol has been described previously. The stereotactic radiation dose is given in 5 fractions of 10 Gray (total 50 Gray), at the 80% isodose over five consecutive days (Muller et al. 2005, 2012).

The following side-effect end-points were counted: neovascular glaucoma, cataract, vitreous haemorrhage (VH), optic neuropathy, maculopathy with or without cystoid macular oedema, retinopathy, subretinal fluid, local recurrence, secondary enucleation and the visual acuity. Neovascular glaucoma can present through either a secondary open-angle or secondary closed-angle mechanism depending on the extent of neovascularization. Cataract was defined as lens opacities that developed after treatment and patients with cataract and/or phacoemulsification before treatment were excluded. Vitreous haemorrhage was counted as a side-effect when a haemorrhage occurred after treatment. Patients with a VH before treatment were excluded. Optic neuropathy was defined as visual loss caused by collateral optic nerve damage and diminished colour vision (using the test of Ishihara) with or without a relative afferent pupillary defect. Presence of maculopathy was defined as haemorrhages, hard exudates and oedema in the macula. Cystoid macular oedema (CME) was noted clinically on fundus examination, on optical coherence tomography (OCT) or on fluorescent angiography when available. CME was counted as maculopathy. We excluded cystoid macular oedema after cataract extraction. After 2007, intravitreal injections of anti-vascular endothelial growth factor (VEGF) became available in our clinic. Retinopathy was marked by damage to retinal blood vessels with bleedings, swelling of the retina or abnormal growth of new blood vessels. Subretinal fluid was counted as a side-effect, when it developed after treatment. Presence of subretinal fluid before treatment was excluded. Local recurrence of UM was determined clinically, with ultrasonography and by comparing fundus photos. We noted the cause of enucleation. From the medical history, we had recorded hypertension and/or diabetes mellitus. The visual acuity was measured with Snellen chart and converted to a logMAR score. We defined mild distance visual impairment as a visual acuity worse than 6/12 (0.3 logMAR) to 6/18 (0.5 logMAR), moderate vision impairment corresponds with a visual acuity worse than 6/18 (0.5 logMAR) to 6/60 (1.0 logMAR) and severe vision impairment corresponds with a visual acuity worse than 6/60 (1.0 logMAR) to 3/60 (1.3 logMAR). Blindness corresponds with a visual acuity worse than 3/60 (1.3 logMAR). Local tumour control was defined as tumour growth after initial treatment; secondary enucleation due to tumour growth; additional treatment due to tumour growth or regrowth after initial regression of the tumour. Disease-free survival (DFS) included time from treatment until metastases or death were diagnosed.

Statistical analyses

General patient and tumour characteristics, and side-effects after treatment were analysed using Mann–Whitney *U*-test and Chi-square statistics. End-points are defined as the time between treatment and a side-effect or in case of survival as the time between treatment and metastases or death. Follow-up duration, used as the time variable, was measured from the date of treatment to the latest visit. The risk of a side-effect caused by a tumour characteristic was analysed by applying Cox proportional hazard models to calculate hazard ratios (HR) with corresponding 95% confidence intervals (CI). Unless explicitly mentioned otherwise, we used univariable analyses for the side-effects. All side-effects were analysed. Multivariable models were estimated by

including variables that were significant in the univariable analyses and, if appropriate, additional covariates based on clinical expertise, while adhering to the rule of thumb of 10 events per variable. If there were no significant variables in the univariable analysis, we added age at diagnosis and sex to the multivariable model.

For the best-corrected visual acuity (BCVA), Wilcoxon signed-rank tests were used to compare the BCVA of the five time-points. We adjusted the significance level for BCVA to the p-value ≤ 0.01 because of multiple testing.

Cox proportional hazard models were performed to assess statistical significance between the curves. Finally, the actuarial rates were calculated at 1, 3, 5 and 10 years of follow-up. We considered a p-value ≤ 0.05 as statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 22.0 for Windows (SPSS inc., Chicago, IL, USA).

Results

Patient and tumour characteristics

Our population included 189 UM patients treated with fSRT with at least a follow-up of 5 years (median 92.9 months, IQR: 55.4–134.7 months). All patients and tumour characteristics are presented in Table 1. One T4 tumour was included and found to be suitable for fSRT, due to a thickness of 9.2 mm and with an oval shape (basal diameter of 12.8 × 18.5 mm). Another factor influencing the choice of treatment was the state of the other eye, as the treated eye had the best visual potential due to an amblyopic fellow eye (visual acuity of 0.70 logMAR/ 0.2 Snellen). Four patients (2.1%) were lost to follow-up for information on side-effects with a median of 104.5 disease-free survival months (IQR: 39.2–149.0 months). One patient died due to other cause, while having metastases of UM. Associations with age, sex and visual acuity at baseline were examined for all tumour characteristics (Table 1). Only a significant association was observed between the T category of the TNM classification and sex (p = 0.048, Pearson Chi-square test). Male patients (49.5%) had the most T3/T4 category UM, while female patients (52.2%) had the most T2

Table 1. General characteristics of the total population at baseline and after treatment with fractionated stereotactic radiotherapy (fSRT) for uveal melanoma.

Patient characteristics	Population fSRT (*N* = 189) *N* (%)	Median and IQR *in mm or months*
Age (mean ± SD) *in years*	62.1 ± 11.1 range (28.1–84.0)	
Sex (*N* = 189)		
Female	92 (48.7)	
Male	97 (51.3)	
Affected eye (*N* = 189)		
OD	89 (47.1)	
OS	100 (52.9)	
Tumour characteristics		
Shape (*N* = 189)		
Dome	145 (76.7)	
Mushroom	38 (20.1)	
Diffuse	3 (1.6)	
Unknown	3 (1.6)	
Tumour Pigmentation, Yes (*N* = 187)	165 (88.2)	
Orange Pigment, Yes (*N* = 177)	75 (42.4)	
Vitreous haemorrhage pre-treatment (*N* = 188)	11 (5.9)	
Drusen, Yes (*N* = 180)	56 (31.1)	
Subretinal fluid pre-treatment (*N* = 186)		
Grade 1	57 (30.7)	
Grade 2	46 (24.7)	
Grade 3	13 (7.0)	
TNM class, T category (*N* = 189)		
1	28 (14.8)	
2	83 (43.9)	
3	77 (40.7)	
4	1 (0.5)	
Margin to fovea ≤3 mm (*N* = 189)	102 (54.0)	
Margin to fovea *in mm*		Median: 3.0 (IQR: 1.0–6.0)
Margin to optic disc ≤3 mm (*N* = 189)	94 (49.7)	
Margin to optic disc *in mm*		Median: 3.0 (IQR: 2.0–5.1)
Metastases		
Metastases and development of metastases (*N* = 189)	54 (28.6)	
Disease-free survival overall (*N* = 189) *in months*		Median: 91.6 (IQR: 41.9–132.5)
Disease-free survival in metastases-group (*N* = 54) *in months*		Median: 30.0 (IQR: 19.3–51.3)
Status at the end of the study		
Alive without metastases, Disease-free survival *in months*	88 (46.6)	Median: 115.6 (IQR: 84.4–164.0)
Alive with known metastases	3 (1.6)	Median: 163.7
Death through UM, Disease-free survival *in months*	49 (25.9)	Median: 28.9 (IQR: 20.0–48.0)
Death other cause, Disease-free survival including 1 patient with metastases *in months*	33 (17.5)	Median: 89.1 (IQR: 41.1–104.5)
Lost to follow-up, Disease-free survival *in months*	4 (2.1)	Median: 60.8 (IQR: 16.1–95.2)
Medical history pre-treatment		
Diabetes mellitus (*N* = 189)	16 (8.5)	
Hypertension (*N* = 189)	58 (30.7)	

SD = standard deviation, TNM = primary tumour (T), regional lymph nodes (N), distant metastases (M), IQR = interquartile range.

category UM. The side-effects after fSRT are shown in Table 2.

Local tumour control

In the study population (N = 185), local tumour control was achieved in 91.4% (Fig. 1). Some patients had a follow-up of 19 years. The 1-, 3-, 5-, 10- and 15-year cumulative local tumour control rates were as follows: 99.4%, 92.8%, 92.2%, 89.3% and 89.3%, respectively. Of the 185 patients, only 16 UM recurred with a median time of 19.8 months (IQR: 15.3–37.1 months). Of the 16 (8.7%) tumour recurrences (Table 3), ten eyes (5.4%) were enucleated due to tumour progression and six (3.2%) tumours received only transpupillary thermotherapy (TTT).

Table 2. Side-effects after fractionated stereotactic radiotherapy (fSRT) for uveal melanoma.

Side-effects	Study population fSRT N = 185 (%)	Median and IQR *in months*
Neovascular glaucoma, (N = 185)	37 (20.0)	Median: 21.1 (IQR: 14.3–42.3)
Cataract, (N = 149) excluded due to pre-treatment cataract (N = 36)	101 (67.8)	Median: 24.3 (IQR: 8.3–42.5)
Vitreous haemorrhage (VH), (N = 174) excluded due to pre-treatment VH (N = 11)	35 (20.1)	Median: 24.8 (IQR: 10.5–41.6)
Optic neuropathy, (N = 185)	23 (12.4)	Median: 23.6 (IQR: 14.0–36.9)
Maculopathy, (N = 185)	44 (23.8)	Median: 29.3 (IQR: 11.3–54.0)
Retinopathy, (N = 185)	65 (35.1)	Median: 26.3 (IQR: 16.7–48.2)
Subretinal fluid (SRF) (N = 151) excluded due to pre-treatment SRF (N = 34)	10 (6.6)	Median: 12.1 (IQR: 2.1–96.1)

IQR = interquartile range.

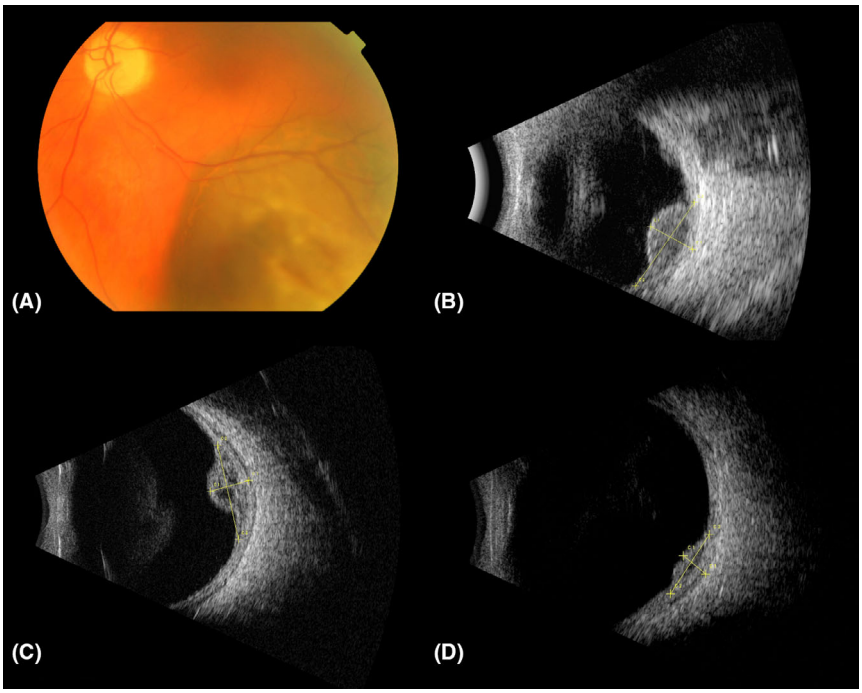

Fig. 1. A 66-year-old woman with an uveal melanoma was treated with fractionated stereotactic radiotherapy. At presentation, a T2 tumour is visible temporal inferior of the macula of the right eye (A) and with a tumour thickness of 5.7 mm and a largest basal diameter of 12.1 mm on ultrasound (B). After treatment, ultrasound images showed tumour regression: with a thickness of 4.4 mm after one year (C) and a thickness of 2.7 mm after 2 years (D). Yellow lines show the points of the tumour measurements.

Two of the ten enucleated patients due to tumour progression received TTT before enucleation. Two additional enucleations occurred due to later developed neovascular glaucoma (Table 3). After additional treatment, no recurrence was observed. Twelve tumours with recurrences were treated before 2007 with a median time to recurrence of 21.4 months versus tumours treated after 2007 with a median time to recurrence of 17.6 months ($p = 0.055$). Tumours with subretinal fluid at baseline were more likely to recur (HR: 4.81, 95% CI 1.08–21.31, Cox proportional hazard models), while larger UM did not recur more. Eyes with tumour recurrence were significantly more enucleated (HR: 14.35, 95% CI 4.62–44.50). This applies to univariable analysis and multivariable analysis with enucleation and subretinal fluid at baseline in the model; significant more eyes were enucleated ($p < 0.001$; Table S1a).

Ocular side-effects

Radiation-induced side-effects after fSRT vary from very mild to severe. Thirty-six patients (19.5%) did not develop any radiogenic side-effects after a median follow-up of 39.3 months (IQR: 21.3–86.1 months). Of these 36 patients, eight patients were still alive and had no metastases at the end of the study after a median follow-up of 93.4 months (IQR: 77.5–139.0 months). The following late side-effects after fSRT (Table 2) were observed:

Neovascular glaucoma

Of the 37 patients, who developed neovascular glaucoma (NVG), significantly more patients had larger UM ($p = 0.030$). T3 and T4 tumours were 3.8 times more likely to develop NVG compared to T1 tumours alone (HR: 3.82, 95% CI 1.14–12.84). NVG was controlled with medication and/or laser treatment in 22 eyes and treated with anti-VEGF intravitreal injections in 13 eyes. Often combinations of those treatments were given. Sixteen eyes were eventually enucleated due to uncontrollable NVG, resulting in a blind eye. Eyes with NVG had significantly (HR: 7.15, 95% CI 3.73–13.71; $p < 0.001$) more enucleations. After multivariable analysis with the following variables: age at diagnosis, enucleation and TNM classification; this

effect between NVG and enucleation remained significant ($p < 0.001$; Table S1b). The median period for an enucleation after NVG was 31.5 months (IQR: 16.3–69.5 months).

Cataract

Thirty-six (19.5%) of the 185 patients were excluded, because they already had pre-treatment cataract. In total, 101 of the 149 patients (67.8%) developed cataract after fSRT. The degree and associated symptoms of the cataract varied. Therefore, of the patients with cataract ($N = 101$), only 42 patients (41.6%) were treated with phacoemulsification after a median period of 21.7 months (IQR: 13.7–48.1 months). Larger UM within categories T3/T4 (versus category T1 UM (HR: 2.35, 95% CI 1.23–4.50)) and tumours further from the fovea developed significantly more cataract than tumours closer to the fovea ($p = 0.025$; HR: 1.09, 95% 1.01–1.17). Eyes with T2 tumours did not develop more cataract. We estimated a multivariable model with the following covariates: tumour T(NM) classification, margin to the fovea, margin to the disc, age at diagnosis and sex. By multivariable analysis, only UM further from the fovea developed significantly more cataract ($p = 0.047$; Table S1c).

Vitreous haemorrhage

In total, 35 (20.1%) of the 174 patients developed a vitreous haemorrhage (VH). We excluded 11 patients with a VH at baseline. Diabetes mellitus did not influence the occurrence of VH. Patients with hypertension developed significantly less VH ($p = 0.026$), while patients with a lower age ($p = 0.006$, HR: 0.96, 95% CI: 0.94–0.99) developed more VH. In multivariable analyses with age at diagnosis and sex added to the model; hypertension was not a significant protective factor, while age at diagnosis remained a significant factor for the development of VH ($p = 0.031$; Table S1d). The mean age at diagnosis in the group with VH was 57 years and in the group without VH was 63 years.

Optic neuropathy

Patients with a lower age (HR: 0.96, 95% CI 0.93–1.00) and tumours with less pigment (HR: 0.29, 95% CI: 0.12–

Table 3. Clinical characteristics of 16 uveal melanoma patients with tumour recurrence.

N	Sex	Age (years)	TNM class, T category	Margin to fovea ≤3 mm or >3 mm	Margin to optic disc ≤3 mm or >3 mm	Year of treatment	Time to metastasis (months)	DFS (months)	Time to tumour recurrence (months)	Time to TTT (months)	Time to secondary enucleation (months)	Time to NVG (months)	Cause of enucleation
1	F	65	1	<3 (1 mm)	<3 (0 mm)	2001	–	217.2	83.7	–	84.8	–	Tumour progression
2	M	61	3	≤3 (3 mm)	<3 (0 mm)	2003	–	193.5	16.4	16.4	42.6	26.7	Tumour progression
										20.4			
										23.4			
3	M	44	3	<3 (0 mm)	<3 (0 mm)	2002	–	198.7	23.6	23.6	63.4	–	Tumour progression
4	M	56	2	>3 (5 mm)	>3 (5 mm)	2003	–	133.1	81.8		82.3	–	Tumour progression
5	M	79	3	>3 (8 mm)	>3 (8 mm)	2003	25.4	25.4	15.3	–	15.3	–	Tumour progression
6	M	83	2	≤3 (3 mm)	≤3 (3 mm)	2006	35.7	35.7	14.0	–	14.0	–	Tumour progression
7	F	67	2	<3 (0 mm)	<3 (1 mm)	2006	–	158.8	40.4	–	40.4	–	Tumour progression
8	M	66	3	>3 (8 mm)	>3 (6 mm)	2010	–	103.0	79.9	–	80.1	42.8	Tumour progression
9	M	57	3	>3 (4 mm)	>3 (4 mm)	2012	32.8	32.8	19.8	–	21.2	–	Tumour progression
10	F	54	3	≤3 (3 mm)	>3 (4 mm)	2012	27.9	27.9	15.4	–	15.8	–	Tumour progression
11	M	50	2	<3 (1 mm)	≤3 (3 mm)	2001	–	202.1	15.3	15.3	44.5	40.7	NVG
12	M	77	3	≤3 (3 mm)	>3 (6 mm)	2003	–	136.7	22.8	22.8	74.5	70.3	NVG
13	F	66	2	>3 (6 mm)	≤3 (3 mm)	2001	32.4	32.4	27.2	27.2	–	–	–
14	M	53	2	<3 (0 mm)	<3 (1 mm)	2002	–	106.9	19.9	19.9	–	–	–
15	M	48	1	<3 (1 mm)	<3 (2 mm)	2002	–	188.8	9.0	9.0	–	–	–
16	F	51	1	<3 (0 mm)	<3 (1 mm)	2011	–	93.7	13.2	13.2	–	–	–

TNM = primary tumour (T), regional lymph nodes (N), distant metastases (M); DFS = disease-free survival; TTT = transpupillary thermotherapy; NVG = neovascular glaucoma.

0.70) developed more optic neuropathy. Additionally, tumours closer to the optic disc were significantly associated with optic neuropathy (HR: 0.82, 95% CI: 0.68–1.00). In multivariable analysis with age at diagnosis, pigmentation of the UM and margin to the disc added to the model: only UM with less pigment developed significantly more optic neuropathy ($p = 0.008$; Table S1e).

Radiation maculopathy

Of the 44 eyes with maculopathy, 35 eyes had cystoid macular oedema and nine eyes developed an ischaemic maculopathy without oedema. UM treated after the year 2007 developed more and significantly earlier maculopathy (median 29.3 months) than before 2007 ($p = 0.003$) (median 37.4 months). Tumours closer by the optic nerve or to the fovea were not associated with maculopathy. After multivariable analysis with age at diagnosis and sex added to the model, treatment after 2007 remained a significant factor for the development of maculopathy ($p = 0.003$; Table S1f).

Radiation retinopathy

Younger patients (HR: 0.97, 95% CI: 0.95–0.99) developed more radiation retinopathy. The mean age at diagnosis in the group with retinopathy was 59 years and in the group without retinopathy was 64 years.

Only T1 tumours were associated with retinopathy in univariable analysis (HR: 1.95, 95% CI: 1.00–3.78) compared to other T category tumours. A multivariable model with the covariates, age at diagnosis, TNM classification, margin to the fovea and to the disc, was estimated. In this model, lower age at diagnosis ($p = 0.007$) and TNM classification, T1 tumours compared to T3/T4 UM, were significantly independently associated with radiation retinopathy ($p = 0.021$; Table S1g). We found no evidence that diabetes mellitus or hypertension influenced the occurrence of retinopathy, maculopathy or neovascular glaucoma.

Subretinal fluid

Of the 116 UM with subretinal fluid (SRF) at baseline (Table 1), in 82 of these UM, the fluid resolved after treatment. SRF remained in 34 UM and these 34 patients were, therefore, excluded for analyses about the post-treatment side-effect of SRF (Table 2). Only 10 (6.6%) UM of the remaining 151 UM developed SRF. The development of SRF was not influenced by any patient characteristic nor by any side-effect. One eye was enucleated, due to untreatable extensive SRF after several vitrectomies and additional bleeding of the tumour.

Indications for the 32 *secondary enucleations* were NVG in 16 patients and tumour recurrence in 10 patients (Table 3). Two eyes with 'toxic tumour syndrome' were enucleated and three eyes with severe inflammation (of which one endophthalmitis after cataract surgery). In one of these three patients, this severe inflammation contained necrotic cell debris and no vital tumour cells. The last enucleated eye was in a patient with recurrent retinal detachments and this resulted in a painful blind eye. Larger (T3/T4) tumours were significantly more enucleated (HR: 5.39, 95% 1.25–23.20) compared to smaller tumours. In UM with SRF at baseline (HR: 5.40, 95% CI: 1.87–15.47), in eyes with tumour recurrence (HR: 7.97, 95% CI: 3.84–16.51) and NVG (HR: 6.74, 95% CI: 3.29–13.79) occurred more enucleations. With multivariable analysis and the variables, TNM classification, SRF at baseline, tumour recurrence and NVG in the model, the only significant factors for enucleation were: NVG ($p < 0.001$) and tumour recurrence ($p < 0.001$; Table S1h). The median time after treatment for an enucleation was: 41.5 months (IQR: 15.9–69.3 months). We observed no phthisis, hyphema or scleral melting in eyes with UM after treatment of fSRT.

Visual acuity

At the time of diagnosis, the median best corrected visual acuity (BCVA) was 0.15 logMAR (IQR: 0.00–0.51) (Fig. 2). The visual acuity decreased after treatment: in the first year after diagnosis, the median BCVA in logMAR increased from 0.15 to 0.40 (IQR: 0.10–1.00) after 3 months, 0.45 (IQR: 0.10–1.30) after 6 months, 0.52 (IQR: 0.15–1.30) after 9 months and 0.49 (IQR: 0.15–1.52) after 12 months, respectively. The BCVA in logMAR observed at diagnosis was significantly lower and subsequently better vision than 1 year after fSRT ($p < 0.001$, Wilcoxon signed-rank test), than 5 years after fSRT ($p < 0.001$), than 10 years after fSRT ($p < 0.001$) and, finally, than 15 years after fSRT ($p = 0.004$), respectively. Five years after treatment, 22.0% of patients and 10 years after treatment, 17.6% of patients have visual acuity of ≤ 0.3 logMAR.

Disease-free survival

The cumulative incidence of disease-free survival at 1, 3, 5, 10 and 15 years

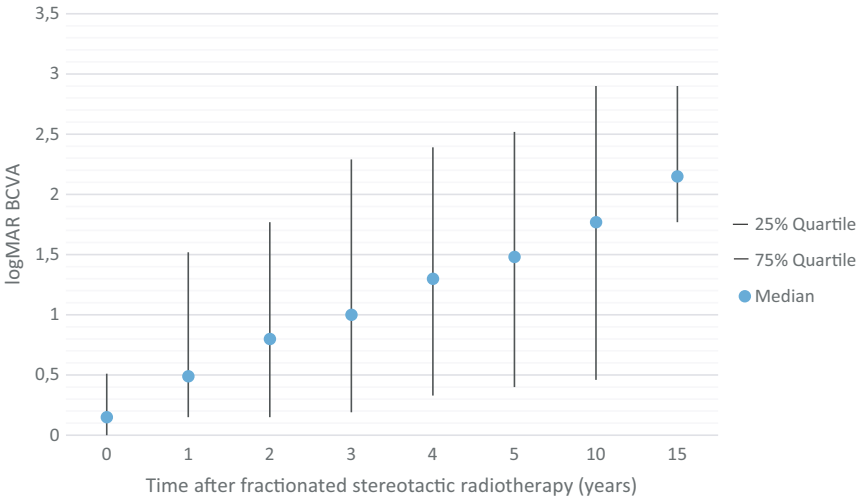

Fig. 2. The visual acuity decreases for uveal melanoma patients after fractionated stereotactic radiotherapy treatment. The median Best Corrected Visual Acuity (BCVA) measured in LogMAR increases over time.

was 96.3%, 81.5%, 77.0%, 69.9% and 61.9%, respectively. Univariable analyses showed the development of vitreous haemorrhage (HR: 0.35, 95% CI: 0.14–0.87) and retinopathy (HR: 0.53, 95% CI: 0.29–0.97) as protective risk factors for death due to UM or for development of metastases. Additionally, SRF at baseline (HR: 3.33, 95% CI: 1.62–6.84) and larger tumours (T3/T4) compared to T1 tumours (HR: 6.62, 95% CI: 2.04–21.53) were risk factors for worse disease-free survival. Independent risk factors after multivariable analysis (in a model with the variables: SRF at baseline, retinopathy, TNM classification and VH) with death due to UM or metastases as end-point were as follows: SRF at baseline ($p = 0.038$) and larger tumours (T3/T4) compared to T1 tumours ($p = 0.024$; Table S1i).

Discussion

This study describes local tumour control, radiation-induced side-effects, visual preservation and disease-free survival after a follow-up of at least 5 years of UM treated with fSRT. The local tumour control was excellent with cumulative control rates of 99.4%, 92.2%, 89.3% and 89.3% after 1 year, 5, 10 and 15 years, respectively.

Our 5-year local tumour control is higher than the 5-year local progression-free survival of 82% after fSRT reported by Akbaba et al. and than the 2-year local tumour control of 82% after stereotactic radiosurgery/fSRT reported by Yazici et al. (Yazici et al. 2017; Akbaba et al. 2018). On the other hand, our local tumour control was lower than 95.9% after 5 years and 92.6% after 10 years after hypofractionated SRT (Dunavoelgyi et al. 2011). In this study, tumour recurrence was observed after a median follow-up of 53.2 months. Tumour recurrence was assumed if an increase in tumour volume of more than 25% was observed over two examinations intervals at least 6 months after radiotherapy (Dunavoelgyi et al. 2011). Within our study, tumour recurrence was observed much earlier at a median follow-up of 19.8 months, and this difference may be due to the used definition for tumour recurrence. In our study, we classified tumour recurrence as tumour growth after initial regression after treatment. Overall the 3-year tumour control rate of our study was 92.8% and therefore comparable with other SRT studies with a tumour control rate of 94% at approximately 3 years after SRT (Krema et al. 2009), and 93.3% after Gamma Knife radiosurgery with a median time of 29.4 months (Modorati et al. 2020). A higher tumour control rate of 98% has been described after stereotactic external beam radiation with a total study period of 4.5 years (Zehetmayer et al. 2000). However, in this study, the median follow-up was only 28.3 months and when compared to our study considerably shorter. Although in our study the median time of a recurrence was 19.8 months, the percentages of tumour control are in general difficult to compare as mentioned before, due to differences in tumour characteristics, definitions of tumour recurrence and follow-up. The overall local tumour control of fSRT (84–98%) (Zehetmayer et al. 2000; Dieckmann et al. 2003; Muller et al. 2005; Akbaba et al. 2018) is comparable to brachytherapy (82–98%) (Gündüz et al. 1999; Damato et al. 2005; Wagner et al. 2014; Pagliara et al. 2018).

Radiation induces (late) side-effects, depending on the area treated as well as the radiation dose that was used. The five most common side-effects in our cohort were cataract followed by retinopathy, maculopathy, VH and neovascular glaucoma. The median time to develop a side-effect ranges between 12.1 months for the development of SRF and 29.3 months for the development of maculopathy. This implies that frequent follow-up of the patient is necessary, even after 2 years of treatment.

The lens is sensitive for radiation and cataract is a well-known long-term consequence of radiotherapy. Of the anterior located tumours, 85% develop cataract due to the proximity of the lens (Collaborative Ocular Melanoma Study 2007). In our cohort, we also observed that patients with anteriorly located tumours developed a cataract more frequently. A greater cumulative radiation dose has a direct effect on the development of cataract. However, even after a small dose of 10–18 Gy, cataract has been reported. Our study population has a comparable percentage of cataract (66.5%) compared to other studies that reported 41–75% cataract (Krema et al. 2013; Modorati et al. 2020).

The second and third causes of a side-effect are radiation retinopathy and maculopathy. Radiation retinopathy gives an altered retinal vascular physiology and shows similarity with diabetic retinopathy. After radiation of the eye, high doses of vascular endothelial growth factor (VEGF) are found, which promotes the growth of new blood vessels (Boyd et al. 2002). In general, the factors that increase the likelihood of developing radiation retinopathy are comorbidities, such as diabetes mellitus or hypertension, high radiation dose and proximity of the tumour to the fovea and optic disc (Gunduz et al. 1999; Bianciotto et al. 2010). UM with posterior margin <3 mm of the fovea are noted to have early on set and increased severity of retinopathy. We could not confirm that these factors had an effect on the observed retinopathy. This may be due to the fact that the number of cases was too small to reach significance. In addition, diabetes mellitus and hypertension did not increase the risk of radiation maculopathy and retinopathy in our patient population. An explanation might be that our prevalence of diabetes mellitus was low, only 16 patients. Previously, retinopathy was only treated when patients demonstrated proliferative retinopathy, VH or tractional retinal detachment (Murray et al. 2019). Nowadays, treatment starts earlier to retain visual acuity and anatomical structures in the macula, and includes laser photocoagulation, intravitreal anti-VEGF, intravitreal steroids or a combination of those. UM treated after the year 2007 developed more and significantly earlier maculopathy than before 2007. This could be explained by the increasing quality or higher resolution of the spectral domain (SD) OCT scan and therefore a better detection of this side-effect. Radiation maculopathy is, on average, detectable on OCT at 12 months, and as early as 4 months after treatment (Murray et al. 2019). After the introduction of anti-VEGF intravitreal injections, maculopathy became treatable and even preventable. In a randomized clinical brachytherapy study in UM patients with radiation maculopathy injections of Aflibercept every 6 weeks, it appears to limit vision loss and reduced central retinal thickness after 1 year (Murray et al. 2019). And

another plaque radiotherapy study with prophylactic anti-VEGF injections of Bevacizumab every 4 months for 2 years reported a reduction in maculopathy and better visual acuity compared to a cohort between 2007 and 2009 without intravitreal injections (Shields et al. 2019).

Tumour necrosis, proliferative radiation retinopathy and posterior vitreous detachment have been suggested as a presumed aetiology for VH (Bianciotto et al. 2012). Risk factors for development of VH after plaque radiotherapy are the presence of diabetic retinopathy at first visit, shorter tumour distance to the optic disc, greater initial tumour thickness and break in the Bruch membrane (Bianciotto et al. 2012). We could not confirm the relation between these risk factors and VH.

Painful eyes with NVG are an indication for secondary enucleation. Of the 16 eyes that had to be enucleated due to NVG, nine developed NVG before the start of intravitreal anti-VEGF injections and seven after diverse treatments. Compared with a study population that started in 1993 that had a 27.3% NVG, our NVG rate is lower (Modorati et al. 2020). Other studies report 20–42% of NVG (Gragoudas et al. 2002; Krema et al. 2009; Dunavoelgyi et al. 2012). Larger tumours are associated with neovascular glaucoma and have a higher risk of secondary enucleation (Gragoudas et al. 2002; Damato & Lecuona 2004). In larger tumours, the volume of the irradiated eye is larger, which may increase the risk of side-effects. Ischaemic changes that end up in neovascularization, especially in larger UM, are a risk for NVG (Fernandes et al. 2011). Transscleral resection of a large UM or with a thickness < 6 mm could be considered to reduce NVG (Bechrakis et al. 2002; Kivelä et al. 2003), or endoresection of the tumour in selected patients (tumour diameter >10 mm and thickness >5 mm) after proton beam radiotherapy showed less NVG and secondary enucleation (Cassoux et al. 2013). However, in the historical cohort in our study, these treatment options had not yet been available in our institute.

The median BCVA rises from pre-treatment 0.15 logMAR to 0.49 logMAR at 12 months after fSRT. After 4 years, the median visual acuity became worse than 1.3 logMAR in 61 patients. Eleven of these 61 patients already started with a higher BCVA in logMAR. In total, in 50 patients (42.7%) the BCVA became worse after 4 years after treatment. This was mainly due to cataract, maculopathy, retinopathy, optic neuropathy, vitreous haemorrhages or neovascular glaucoma. Visual acuity is most effectively preserved in eyes with small tumours outside a radius of 5 mm from the optic disc and fovea (Shields et al. 2000).

The cumulative incidence of disease-free survival of 77.0% after 5 years is lower than Yazici et al. and Gallie et al. report, however, comparable with the study of Cohen et al. (Cohen et al. 2003; Ophthalmic Oncology Task Force 2016; Yazici et al. 2017). In our cohort, patients with large tumours and UM with SRF at baseline had a worse disease-free survival. The risk for metastasis and death increased twofold with each increasing tumour category, and the 10-year metastatic rate was 15% for T1, 25% for T2, 49% for T3 and 63% for T4 tumours (Shields et al. 2013).

Every retrospective study has its flaws, and we had to exclude four patients due to incomplete medical records. On the other hand, our study comprises a period of 15 years after treatment of fSRT and all patients had a follow-up of at least 5 years. In this period treatment options alter, especially intravitreal injections with anti-VEGF for (the prevention of) ischaemic side-effects, such as maculopathy, retinopathy and NVG are now standard care. Some patients develop side-effects after 10 years of follow-up and studies with a shorter follow-up do not monitor these side-effects. This is probably one reason why the incidence of side-effects, such as retinopathy, shows wide differences of 2.9% to 41.7% among 12 studies with a follow-up ranging from 6 months to 67 months (Modorati et al. 2020).

In conclusion, this study presents a long follow-up of the radiation-induced side-effects of UM treated with fSRT in a tertiary referral centre in the Netherlands. The cumulative 5-year local tumour control was 92.2% and the most common side-effects were cataract (67.8%) followed by retinopathy (35.1%), maculopathy (23.8%), vitreous haemorrhage (20.1%), neovascular glaucoma (20.0%) and optic neuropathy (12.4%). By multivariable analysis, risk factors for a worse DFS were larger UM ($p = 0.024$) and tumours with SRF at baseline ($p = 0.038$). The 5-year DFS was 77.0% and visual acuity decreased significantly after starting the treatment. After 5 years, 22.0% of patients and after 10 years 17.6% of patients had a good vision.

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Received on May 7th, 2021.
Accepted on August 31st, 2021.

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The authors have no conflict of interest to report.

Funding: None.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1a. Multivariable analysis of the side effect: Tumour recurrence.
Table S1b. Multivariable analysis of the side effect: Neovascular glaucoma.
Table S1c. Multivariable analysis of the side effect: Cataract.
Table S1d. Multivariable analysis of the side effect: Vitreous haemorrhage.
Table S1e. Multivariable analysis of the side effect: Optic neuropathy.
Table S1f. Multivariable analysis of the complication: Radiation maculopathy.
Table S1g. Multivariable analysis of the side effect: Radiation retinopathy.
Table S1h. Multivariable analysis of secondary enucleation.
Table S1i. Multivariable analysis of disease-free survival.