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Impact of tumour volume and treatment delay on the outcome after linear accelerator-based fractionated stereotactic radiosurgery of uveal melanoma

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ABSTRACT

Background/aims Primary radiation therapy is used to treat malignant uveal melanoma (UM). We report our single-centre experience with fractionated radiosurgery (fSRS) with a linear accelerator (LINAC) after specific adaptation for small target volumes with HybridArc.

Methods From October 2014 to January 2020, 101 patients referred to Dessau City Hospital with unilateral UM underwent fSRS with 50 Gy given in five fractions on five consecutive days. Primary endpoints were local tumour control, globe preservation, metastasis and death. Potential prognostic features were analysed. Kaplan-Meier analysis, Cox proportional hazards model and linear models were used for calculations.

Results The median baseline tumour diameter was 10.0 mm (range, 3.0–20.0 mm), median tumour thickness 5.0 mm (range, 0.9–15.5 mm) and median gross tumour volume (GTV) 0.4 cm³ (range, 0.2–2.6 cm³). After a median follow-up of 32.0 months (range, 2.5–76.0 months), 7 patients (6.9%) underwent enucleation: 4 (4.0%) due to local recurrence and 3 (3.0%) due to radiation toxicities, and 6 patients (5.9%) revealed tumour persistence with a GTV exceeding 1.0 cm³. Of 20 patients (19.8%) who died, 8 (7.9%) were tumour-related deaths. Twelve patients (11.9%) suffered from distant metastasis. GTV showed an impact on all endpoints, and treatment delay was associated with reduced odds of eye preservation.

Conclusion LINAC-based fSRS with static conformal beams combined with dynamic conformal arcs and discrete intensity-modulated radiotherapy results in a high tumour control rate. The tumour volume is the most robust physical prognostic marker for local control and disease progression. Avoiding treatment delay improves outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Various radiation techniques have proven their efficacy as a local treatment option for uveal melanoma (UM), with tumour size determining therapeutic outcomes.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that fractionated stereotactic radiosurgery with a linear accelerator after specific adaptation for small target volumes results in a high tumour control rate. The tumour volume is the most robust physical prognostic marker for local control and disease progression.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The tumour volume should be considered in clinical evaluation and staging systems, and immediate access to radiotherapy of UM improves outcomes.

INTRODUCTION

Local treatment of uveal melanoma (UM) comprises different treatment modalities. Historically, enucleation was the treatment of choice. However, strategies towards earlier detection and modern therapies provided the feasibility of ocular globe preservation.[1–4] Hence, primary radiation therapy (RT) became the most common local treatment option for UM, showing comparable long-term survival rates to enucleation for all sizes of tumours.[5–7] Enucleation stays reserved for extended local disease.[4 8 9] RT by brachytherapy or external beam radiation therapy (EBRT) aims to maximise local disease control and improve visual outcomes while retaining an acceptable quality of life.[10–12] Brachytherapy is delivered by episcleral plaque radiotherapy with Iodine-125 (low-dose rate γ radiation) or Ruthenium-106 (β⁻ radiation).[8] EBRT includes charged particle therapy (ie, protons, helium ions) and stereotactic radiotherapy.[9 13] The choice of the appropriate treatment option depends on tumour characteristics, such as size and proximity to vulnerable structures.[14] However, therapy options might be limited due to timely access to experienced radiation clinics. Diagnosis and treatment planning for UM is based on clinical findings, and a histological confirmation for the initialisation of oncological treatment is generally not required.[15–17]

Tumour size often determines therapy, and survival analyses underline its prognostic impact.[13 18–27] Size is usually described as the largest basal diameter (LBD) and tumour thickness (TT).[28] The tumour classification systems for UM used by the Collaborative Ocular Melanoma Study (COMS) Group and the American Joint Committee on Cancer (AJCC) are based on these two tumour parameters.[29 30] However, a better assessment of the actual tumour load is provided by volumetric data, like the gross

Table 1 Patients' characteristics (n=101)

Characteristic	Value
Sex (n)	
Male	55
Female	46
Age (years)	
Median (range)	69.47 (26.48–91.26)
ECOG Performance Status (n)	
0	69
1	22
2	9
3	1
4	0
5	0
Hypertension (n)	
Yes	62
No	39
Diabetes mellitus (n)	
Yes	13
No	88
Follow-up (months)	
Mean (SD)	34.56 (±14.70)
Median (range)	31.97 (2.53–75.99)
Location (n)	
Choroidal	90
Ciliochoroidal	11
Affected eye (n)	
Left	56
Right	45
Affected eye segments (n)[14]	
3 affected eye segments	44
>3 affected eye segments	57
Location specifications (n)	
Juxtapapillary	45
Initial characteristics (n)	
Subretinal fluid at diagnosis	71
Macular oedema at diagnosis	9
Orange pigment at diagnosis	16
Conversion from nevus	9
Tumour thickness (mm)	
Mean (SD)	5.99 (±3.75)
Median (range)	5.03 (0.87–15.52)
Largest basal diameter (mm)	
Mean (SD)	11.06 (±4.03)
Median (range)	10.00 (3.00–20.00)
Gross tumour volume (cm^3) at diagnosis	
Mean (SD)	0.60 (± 0.57)
Median (range)	0.42 (0.18–2.60)
Planning target volume (cm^3)	
Mean (SD)	1.75 (± 1.18)
Median (range)	1.34 (0.33–5.66)
Tumor size (COMS[29]) (n)	
Small	30
Medium	38
Large	33
Clinical Stage Group (AJCC Cancer Staging Manual 8th ed, 2017[30]) (n)	
I	38
IIA	31
IIB	14
IIIA	12
IIIB	6
T category (AJCC Cancer Staging Manual 8th ed, 2017[30]) (n)	
T1	38
T2	33
T3	18
T4	12
Endoresection after radiotherapy (n)	
Yes	19
No	82
Complications (n)	
Cataract progression	71
Neovascular glaucoma	21
Rubeosis iridis	24
Keratopathy	40
Macular oedema	20
Hyphema	3
Vitreous haemorrhage	12
Retinopathy	14
Optic neuropathy	8
Radiation scarring	32
Sicca symptoms	18
Overall survival (n)	
Death	20
Disease-specific death	8
Local recurrence	6
Metastasis	12
Enucleation	7

AJCC, American Joint Committee on Cancer; COMS, Collaborative Ocular Melanoma Study; ECOG, Eastern Cooperative Oncology Group; n, number of patients; SD, standard deviation.

tumour volume (GTV). Besides evaluating the efficacy of linear accelerator (LINAC)–based hypofractionated stereotactic radiotherapy, this study emphasises the prognostic impact of the GTV and treatment delay regarding the local and systemic outcomes of patients with UM.

MATERIALS AND METHODS

From October 2014 to January 2020, 263 patients with UM were referred to the Dessau City Hospital, Germany. The patients were treated with brachytherapy (n=151), enucleation (n=3) or fractionated stereotactic radiosurgery (fSRS) (n=109). In total, 101 patients were analysed regarding their clinical outcomes. Patients' characteristics are summarised in table 1.

Inclusion criteria were treatment with 50 Gy delivered within five consecutive working days; metastatic melanomas were excluded. Pretreatment assessment included biomicroscopy, indirect ophthalmoscopy, colour fundus photography, ocular A-scan/B-scan ultrasonography, orbital MRI, best-corrected visual acuity (VA) and eye tonometry; complete tumour staging comprised anamnesis, physical and laboratory examination, chest X-ray and abdominal ultrasonography. Staging was based on the eighth edition of the AJCC Classification of posterior UM.[30] The size was classified according to the COMS staging.[29]

Planning and treatment techniques have been described previously.[14 31] Briefly, four tantalum markers were sutured to the

sclera; three encompassed the tumour, and one was placed on the opposite side of the eye. Planning CT was obtained with a slice thickness of 1 mm. An individualised thermoplastic head mask was used for immobilisation (BrainLAB AG, Munich, Germany). A contrast-enhanced T1-weighted orbital MRI was fused with the planning CT to delineate the GTV for three-dimensional radiation treatment planning. An isotropic margin of 0 to 2 mm was added to the GTV to create the planning target volume (PTV) to compensate for planning and dose delivery uncertainties.[32] A dose of 50 Gy was given in five fractions on five consecutive working days. The dose that covered 98% ($D_{98\%}$) of the PTV was ≥45 Gy. The minimum dose values in the GTV were 98% in 39, ≥95% in 78 and ≥90% in 92 patients. A combination of dynamic conformal arcs, static conformal beams, and intensity-modulated static fields (IMRT), available as HybridArc (BrainLAB AG), was administered by a linear accelerator (Novalis powered by TrueBeam STx) with 5.6 MeV flattening filter-free photons (BrainLAB AG; VARIAN Medical Systems, Palo Alto, CA, USA).[14] Position verification and correction were based on four tantalum markers (ExacTrac 6.0.6 and Robotics 2.0; BrainLAB AG). All patients were additionally trained to minimise eye movements before initiating fSRS. iPlan RT Dose 4.5.3 and 4.5.4 radiation treatment planning systems with the module HybridArc (BrainLAB AG) were used for treatment planning and dose calculation. Steep dose gradients allowed sparing of organs at risk, that is, optic disc, optic nerve, lenses, fellow eye, lacrimal gland and cornea.[33]

Follow-up was performed after 1 week and by 3-month intervals within the first year, then every 6 months, including thoracic and abdominal restaging. Patients were assigned to three groups based on the WHO ICD-11 classification for vision impairment including blindness.[34] Group 1 had a initial decimal visual acuity (VA_{dec}) ≥0.5, group 2 had a VA_{dec} between 0.10 and 0.4, and group 3 had a VA_{dec} ≤0.08. The course of the VA of the three groups was assessed.

IBM SPSS Statistics for Windows, V.28.0 (IBM Corp, Armonk, NY, USA), and MedCalc for Windows, V.20.110 (MedCalc Software, Ostend, Belgium), were used for statistical analyses. R for Windows, V.4.2.1 (R Foundation for Statistical Computing, Vienna, Austria), with the package ggplot2, was used for VA versus months.[35 36] The regression line was based on the linear model. The correlation coefficient and the p value were calculated using the Pearson method. All patients were reviewed for local tumour control (LC), metastatic disease, eye preservation, overall survival (OS) and disease-specific survival (DSS). Descriptive statistics were expressed as mean and standard deviation (SD) and median and interquartile range. Absolute numbers were given for categorical variables. Survival rates and figures were analysed with the Kaplan-Meier method and life tables. For univariate and multivariable analysis, Cox proportional hazards assessment calculated the hazard ratio (HR) with a 95% confidence interval (CI). A p value <0.05 was considered significant. All time-related events were calculated from the last day of treatment to the last follow-up or death. The following clinicopathological parameters were included: age (continuous), sex (dichotomous, female vs male), affected eye (dichotomous, right vs left), diagnosis (dichotomous, choroidal vs ciliochoroidal), GTV (continuous), tumour thickness (continuous), largest basal diameter (continuous), juxtapapillary tumour location (dichotomous, no vs yes), the time between diagnosis and therapy (continuous), and affected eye segments (dichotomous, >3 vs 3 affected segments). The schematic segmentation of the eye was described previously.[14]

RESULTS

In total, 90 (89.11%) of the UM were choroidal melanomas, and 11 (10.89%) were ciliochoroidal melanomas. The eye was divided into eight segments.[14] In 56.44% of the treated cases, the tumour exceeded three segments. In 43.56%, tumour growth was limited to three segments. Forty-five (44.55%) of the UM were located juxtapapillary. At diagnosis, 70.30% of the tumours were accompanied by subretinal fluid and 8.91% by macular oedema. Moreover, 15.84% had orange pigment at diagnosis, and 8.91% UMs converted from nevus. The median LBD was 10.00 mm (range, 3.00–20.00 mm), the median TT was 5.03 (range, 0.90–15.50 mm) and the median GTV was 0.42 cm^3 (range, 0.18–2.60 cm^3). Thirty-eight (37.62%) UMs were staged T1; 33 (32.67%), T2; 18 (17.82%), T3; and 12 (11.88%), T4. The median follow-up was 31.97 months (range, 2.53–75.99 months).

Survival analysis: A summary is depicted in table 2 and illustrated in figures 1 and 2.

The association between variables and survival times is illustrated in table 3.

Local tumour control

The 1-year LC rate was 97.96%±1.43%, and the 2-year LC rate was 95.65%±2.13%, respectively (figure 1A). In six patients, recurrent tumour growth could be detected after a median follow-up time of 17.94 months (range, 10.91–43.66 months). Of these six, metastatic disease occurred in two patients. Four patients with local recurrence (LR) were immediately enucleated, having a bad forecast of vision and complications. One patient's eye was removed in the presence of concomitant side effects of radiation therapy. In one patient, metastatic disease preceded LR. This patient was referred to another hospital to receive systemic therapy; therefore, no eye removal was performed. Histology of the enucleated eyes confirmed high mitotic activity. Two UMs were composed of spindle cells, two of epithelioid cells, and one of a combination of spindle and epithelioid cells. The diagnosis (p=0.002), the GTV (p<0.001), the TT (p=0.012), the LBD (p=0.031) and the time between diagnosis and therapy (p=0.003) were identified as prognostic factors for local recurrence-free survival in univariate analysis. Local failure was observed in UM exceeding an initial tumour volume of 1 cm^3 (figure 1B).

Enucleation-free survival

During follow-up, enucleation was performed in seven patients. Enucleation-free survival (EFS) was 97.94%±1.44% after 1 year and 94.44%±2.42% after 2 years (figure 1C). Four eyes were enucleated due to LR, another two for major radiotoxicity and one as a combination of LR and toxicity. One patient with major side effects of radiation therapy suffered from a corneal ulcer, and the second suffered from corneal necrosis. The third patient had persistent pain due to secondary neovascular glaucoma and vitreous haemorrhage and refused further therapy and preferred the removal of the eye. All enucleations with LR were performed after a median follow-up of 18.14 months (range, 11.27–40.41 months). Enucleation due to radiation toxicity was conducted after a median time of 19.65 months (range, 18.14–55.85 months). The diagnosis (p=0.013), the GTV (p=0.001), the LBD (p=0.033), and the time between diagnosis and therapy (p=0.003) were risk factors for EFS. Histological features of two UMs in eyes enucleated due to radiation toxicity were composed of spindle cells and one of epithelioid cells. Patients'

characteristics, ultrasound and histology of the enucleated eyes are summarised in online supplemental table 1.

Metastasis-free survival

Twelve patients developed metastases after a median follow-up time of 20.67 months (range, 10.28–33.91). Metastasis-free survival (MFS) was 97.98%±1.41% after 1 year and 91.03%±3.04% after 2 years (figure 2A). In 11 patients, only the liver was involved. One patient suffered from metastases in multiple organs. Only 3 of the 12 suffered from concomitant local failure. Five patients with liver metastases received transcatheter arterial chemoembolisation. Of all metastatic patients, two are known to have received immunotherapy in other facilities. The GTV (p=0.002) and tumour thickness (p=0.018) had a statistically significant negative impact on MFS.

Overall and disease-specific survival

The 1-year disease-specific survival (DSS) rate was 100.00%±0.00%, and the 2-year DSS rate was 94.16%±2.54%, respectively (figure 2B). Twenty patients died during follow-up. One-year OS rate was 98.00%±1.40%, and 2-year OS rate was 90.16%±3.12%, respectively (figure 2C). Among 20 deaths, 8 were tumour related. The mean DSS was 68.0 months (range, 63.9–72.0 months). The GTV had a statistically significant negative impact on DSS (p=0.021). The mean OS was 58.6 months (range, 52.9–64.3 months). Univariate analysis showed a significant impact of age (p=0.008), GTV (p<0.001), TT (p<0.001), LBD (p=0.002) and the number of affected eye segments (p=0.043).

Toxicity

Secondary neovascular glaucoma was observed in 21 patients, median 15.51 months (range, 2.76–56.31 months) after RT, leading to eye enucleation in one patient. A total of 71 patients had cataract progression leading to cataract surgery in 40 patients. In these 71 patients, the median mean dose (D_{mean}) given to the lens was 3.74 Gy (range, 0.49–50.20 Gy). Retinopathy occurred in 14 patients after a median time of 23.82 months (range, 1.25–48.76 months) and optic neuropathy in 8 patients after a median time of 17.63 months (range, 7.89–37.19 months). The median D_{mean} at the optic disc in patients with optic neuropathy was 42.80 Gy (range, 26.51–49.73 Gy).

VA as a function over time after radiotherapy is shown in figure 3. At baseline, 35 patients had no visual impairment (group 1), 37 mild to moderate impairment (group 2) and 29 severe impairments to blindness (group 3). All patients' VA decreased after fSRS, with no significance in group 3 (p=0.164). Group 1 had a median VA_{dec} of 0.7 at baseline, 0.18 at 12 months, 0.08 at 24 months and 0.01 at 36 months. Group 2 started with a median VA_{dec} of 0.25, altered to 0.15, 0.10 and 0.13 at 12, 24 and 36 months, respectively. The median VA_{dec} of group 3 at baseline was 0.02. At 12 and 24 months, VA_{dec} reduced to 0.01 and slightly increased to 0.03 at 36 months.

DISCUSSION

RT techniques for UM balance between tumoricidal dose, sparing dose in organs to retain the eye and maintaining visual functionality.[2 8 9 37–42] We report an overall local control rate of 94.1% after a median follow-up of 32 months. Photon beam therapy has been increasingly used due to availability and optimised techniques for dose delivery. Eibl-Lindner *et al* analysed 217 patients treated with stereotactic radiosurgery (SRS) using a CyberKnife with a median follow-up of 26.4 months. The actuarial LC was 87.4% at 3 years and 70.8% at 5 years, respectively.[43] Local control rates with Gamma Knife have been reported to range from 91% to 98%.[18 19 44 45] Dunavoelgyi *et al* presented a 5-year local control rate of approximately 95.9% with LINAC-based RT.[25] Size distribution among all studies varies, as different classifications exist.[29 30] Muller *et al* reported 102 patients with T2 tumours (44.1%). T4 tumours were rare (2.0%). The overall LC rate was 96%, with a median follow-up of 32 months.[23] Our cohort included one-third of large UM (COMS), 17.2% T3 tumours and 11.9% T4 tumours, respectively.

Eye removal is rarely indicated.[3] The enucleation rate of 6.93% in the present series compared favourably with the enucleation rate of 14.71% observed by Muller *et al*.[23] Damato *et al* reported 25 eyes (7.16%) undergoing secondary enucleation in a cohort of 349 patients treated with proton beam radiation therapy (PBRT).[20] Neovascular glaucoma or local recurrence are the main reasons for enucleation, and size and tumour location are the major risk factors.[20 23 25 46]

Metastatic disease is a primary reason for death.[8] Median survival in patients with distant metastasis ranges from 4 to 15 months, mostly due to cytogenetic characteristics.[28 47 48] In our series, 12 patients (11.88%) developed metastatic disease after a median time of 28.16 months after fSRS. Muller *et al* reported metastatic progression in 13.7% of102 patients. Dunavoelgy *et al* presented a 5-year metastasis-free survival of 84.6% and 74.9% after 10 years. OS and DFS were 82.4% and 90.2% after 5 years and 65.5% and 76.1%, respectively.[23 25] In our study, 20 patients (19.8%) died from any cause during follow-up. Only eight deaths (7.9%) were tumour related.

Basal diameter and thickness are prognostic characteristics.[28 49] Shields *et al* reviewed 8033 eyes and showed that tumour thickness was associated with a higher risk of metastasis. Regarding toxicity, the larger the UM, the more toxicity was observed, and more enucleations had to be performed.[28] Notably, the impact of the tumour volume on all outcome parameters was

Table 2 Summary of event calculation and life tables

Event	Number of events	Mean survival (months)	Cumulative proportion surviving at the time		
			12 months (%)	24 months (%)	36 months (%)
Overall death	20 patients	58.63±2.92	98.00±1.40	90.16±3.12	84.76±4.22
Disease-specific survival	8 patients died of disease	67.96±2.06	100.00±0.00	94.16±2.54	94.16±2.54
Local tumour control	6 local failures	69.22±1.95	97.96±1.43	95.65±2.13	95.65±2.13
Metastasis-free survival	12 metastasis (11 liver, 1 multiple organs)	65.79±2.22	97.98±1.41	91.03±3.04	83.94±4.45
Eye retention	7 enucleations (4 local recurrences, 1 corneal ulcer and local recurrence, 1 corneal necrosis, 1 persistent pain)	67.86±2.41	97.94±1.44	94.44±2.42	94.44±2.42

Numerical values are mean values with a SD.

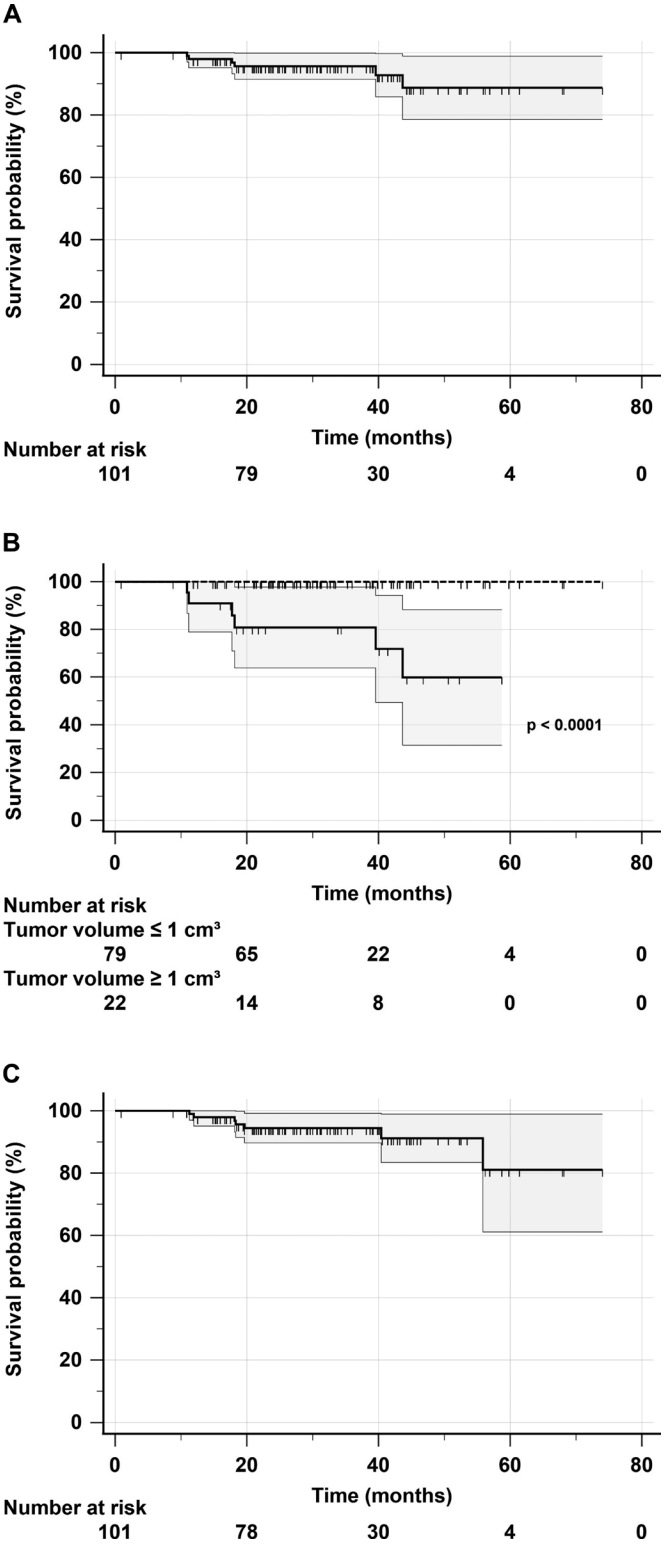

Figure 1 Local treatment outcomes. (A) Local control. (B) Local control: tumour volume ≤1 cm³ (dotted line) vs ≥1 cm³ (full line). (C) Enucleation-free survival.

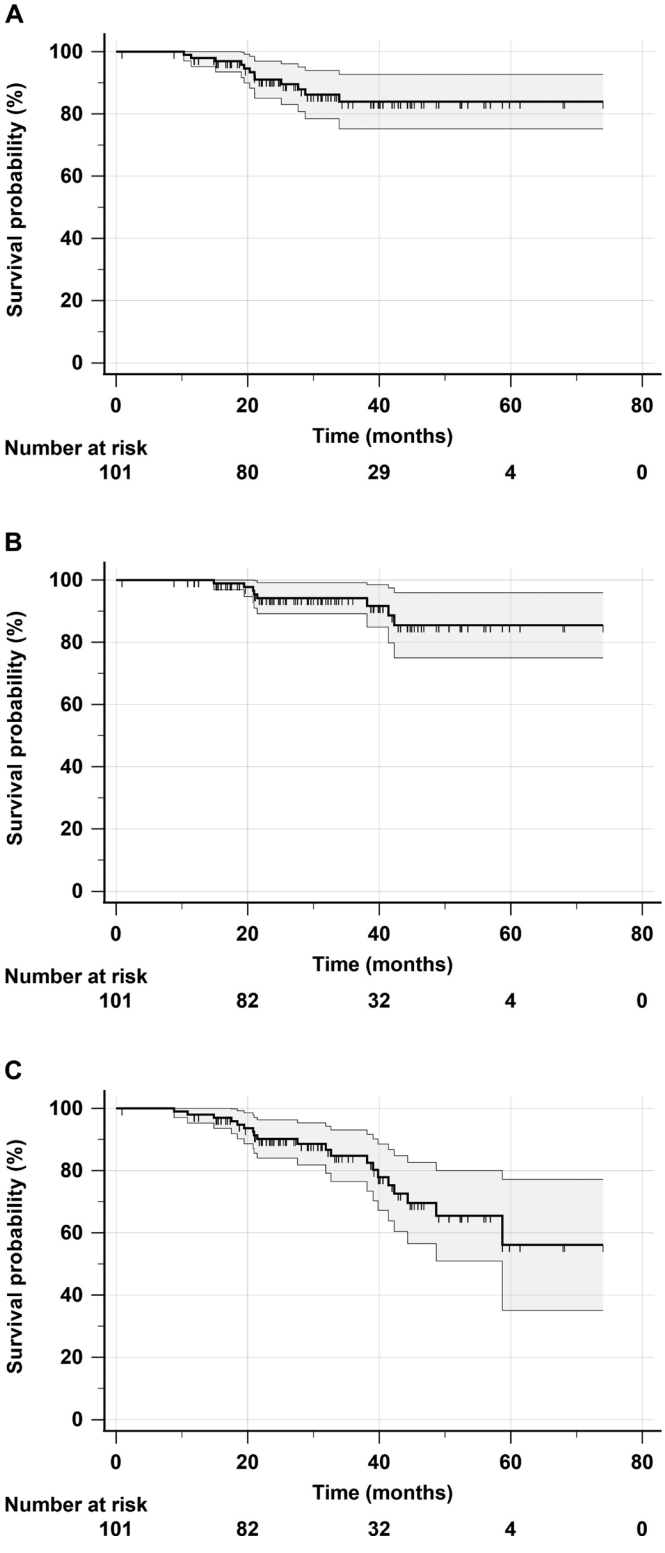

Figure 2 Oncological outcomes. (A) Metastasis-free survival. (B) Disease-specific survival. (C) Overall survival.

more sensitive than thickness and diameter in the present series (table 3). Local recurrences were observed only for GTVs >1 cm³. Ten of the 12 patients with metastatic progression had a GTV >0.8 cm³. Consequently, the larger the tumour volume, the more likely radiation toxicity occurred. The median GTV leading to secondary neovascular glaucoma was 0.6 cm³. Our data confirm the nature of the volume-dependent therapeutic outcome.

Combined modality treatment might lead to better LC, as suggested by Suesskind *et al*.[46] In their study of 78 patients, eyes treated with radiation followed by resection had a local control rate of 100% after 3 years, compared with patients receiving radiation monotherapy with a 3-year LC rate of 85%.

Table 3 Risk factors associated with treatment outcome: univariate Cox proportional hazard analysis

Covariate	Univariate		
	HR	95% CI	p Value
Overall survival			
Age (continuous; median 69.47 years)	**1.056**	**1.015 to 1.100**	**0.008**
Sex (dichotomous; female (n=46) vs male (n=55))	0.402	0.146 to 1.108	0.078
Affected eye (dichotomous; right (n=45) vs left (n=56))	0.964	0.398 to 2.331	0.934
Diagnosis (dichotomous; choroidal (n=90) vs ciliochoroidal (n=11))	1.465	0.487 to 4.410	0.497
Gross tumour volume (continuous; median 0.42 cm^3)	**2.650**	**1.556 to 4.512**	**<0.001**
Tumour thickness (continuous; median 5.03 mm)	1.197	1.072 to 1.336	**<0.001**
Largest basal diameter (continuous; median 10.00 mm)	**1.185**	**1.063 to 1.321**	**0.002**
Affected eye segments (dichotomous; >3 (n=44) vs 3 (n=57) affected segments)	**2.846**	**1.032 to 7.849**	**0.043**
Juxtapapillary tumour location (dichotomous; no (n=56) vs yes (n=45))	0.819	0.337 to 1.988	0.659
Time between diagnosis and therapy (continuous; median 35.00 days)	0.991	0.963 to 1.020	0.531
Disease-specific survival			
Age (continuous; median 69.47 years)	1.055	0.990 to 1.125	0.098
Sex (dichotomous; female (n=46) vs male (n=55))	0.732	0.175 to 3.063	0.669
Affected eye (dichotomous; right (n=45) vs left (n=56))	1.254	0.313 to 5.019	0.749
Diagnosis (dichotomous; choroidal (n=90) vs ciliochoroidal (n=11))	0.885	0.108 to 7.223	0.909
Gross tumour volume (continuous; median 0.42 cm^3)	**3.152**	**1.352 to 7.346**	**0.008**
Tumour thickness (continuous; median 5.03 mm)	1.171	0.987 to 1.338	0.070
Largest basal diameter (continuous; median 10.00 mm)	1.123	0.948 to 1.329	0.178
Affected eye segments (dichotomous; >3 (n=44) vs 3 (n=57) affected segments)	0.966	0.241 to 3.867	0.961
Juxtapapillary tumour location (dichotomous; no (n=56) vs yes (n=45))	0.338	0.068 to 1.693	0.187
Time between diagnosis and therapy (continuous; median 35.00 days)	1.004	0.979 to 1.030	0.739
Local recurrence-free survival			
Age (continuous; median 69.47 years)	1.010	0.951 to 1.073	0.738
Sex (dichotomous; female (n=46) vs male (n=55))	0.563	0.103 to 3.083	0.508
Affected eye (dichotomous; right (n=45) vs left (n=56))	0.018	0.000 to 13.128	0.232
Diagnosis (dichotomous; choroidal (n=90) vs ciliochoroidal (n=11))	**15.108**	**2.764 to 82.587**	**0.002**
Gross tumour volume (continuous; median 0.42 cm^3)	**5.911**	**2.161 to 16.163**	**<0.001**
Tumour thickness (continuous; median 5.03 mm)	**1.303**	**1.061 to 1.600**	**0.012**
Largest basal diameter (continuous; median 10.00 mm)	**1.244**	**1.020 to 1.518**	**0.031**
Affected eye segments (dichotomous; >3 (n=44) vs 3 (n=57) affected segments)	5.024	0.582 to 43.390	0.142
Juxtapapillary tumour location (dichotomous; no (n=56) vs yes (n=45))	0.204	0.024 to 1.766	0.149
Time between diagnosis and therapy (continuous; median 35.00 days)	**1.021**	**1.007 to 1.036**	**0.003**
Distant metastasis-free survival			
Age (continuous; median 69.47 years)	1.024	0.978 to 1.073	0.308
Sex (dichotomous; female (n=46) vs male (n=55))	0.612	0.184 to 2.033	0.423
Affected eye (dichotomous; right (n=45) vs left (n=56))	1.176	0.379 to 3.646	0.779
Diagnosis (dichotomous; choroidal (n=90) vs ciliochoroidal (n=11))	2.320	0.627 to 8.577	0.207
Gross tumour volume (continuous; median 0.42 cm^3)	**3.052**	**1.505 to 6.191**	**0.002**
Tumour thickness (continuous; median 5.03 mm)	**1.182**	**1.029 to 1.357**	**0.018**
Largest basal diameter (continuous; median 10.00 mm)	1.136	0.993 to 1.299	0.063
Affected eye segments (dichotomous; >3 (n=44) vs 3 (n=57) affected segments)	1.733	0.521 to 5.759	0.370
Juxtapapillary tumour location (dichotomous; no (n=56) vs yes (n=45))	0.382	0.103 to 1.415	0.150
Time between diagnosis and therapy (continuous; median 35.00 days)	0.997	0.970 to 1.024	0.825
Enucleation-free survival			
Age (continuous; median 69.47 years)	1.031	0.968 to 1.098	0.338
Sex (dichotomous; female (n=46) vs male (n=55))	0.401	0.076 to 2.107	0.281
Affected eye (dichotomous; right (n=45) vs left (n=56))	0.017	0.000 to 7.399	0.188
Diagnosis (dichotomous; choroidal (n=90) vs ciliochoroidal (n=11))	**7.693**	**1.550 to 38.193**	**0.013**
Gross tumour volume (continuous; median 0.42 cm^3)	**5.763**	**2.130 to 15.590**	**0.001**
Tumour thickness (continuous; median 5.03 mm)	1.192	0.988 to 1.437	0.066
Largest basal diameter (continuous; median 10.00 mm)	**1.219**	**1.017 to 1.461**	**0.033**
Affected eye segments (dichotomous; >3 (n=44) vs 3 (n=57) affected segments)	1.359	0.299 to 6.180	0.692
Juxtapapillary tumour location (dichotomous; no (n=56) vs yes (n=45))	0.706	0.151 to 3.303	0.658
Time between diagnosis and therapy (continuous; median 35.00 days)	**1.020**	**1.007 to 1.034**	**0.003**

Bold values are significant (p value <0.05).
95% CI, 95% confidence interval; HR, hazard ratio; n, number of patients.

In our study, 19 (18.81%) patients received tumour endoresection after a median time of 45.3 days after RT. Patients undergoing endoresection had a median GTV of 0.87 cm^3, while two (10.53%) still developed local recurrence and four (21.05%) suffered from distant metastasis. Tumour-related death occurred in four (21.05%) patients. Three (15.79%) had a GTV greater than 1.0 cm^3. Only one eye (5.26%) had to be removed due to LR. However, survival analysis showed no significant differences in PFS and OS or the development of radiation toxicities (all p values exceeded 0.05). The increased investigations regarding cytogenetics and emerging targeted therapies might lead to further developments. In summary, the main advantage of PBRT seems to be the physical characteristics of the dose distribution. PBRT can spare sensitive structures using a simple beam geometry even if the UM is large.[50] The advantage of PBRT for small and medium-sized tumours remains unproven, as results with SRS yield comparable LC.[13]

In our study, light perception was preserved in 86 of the 101 patients, 78 identified hand motions and 62 could count fingers. Papakostas *et al* reported on 336 patients after PBRT.[50] They reported a visual acuity of 20/200 of less than 20% after PBRT, compared with 35.64% after fSRS. However, Papakostas *et al* treated large choroidal melanoma.

An important observation in the present series was the negative impact of treatment delay on LC. The observation needs to be confirmed, but as access to PBRT is limited,[51] LINAC-based fSRS can be used safely as a primordial treatment option, leaving PBRT amenably to selected cases. To estimate the advantages of PBRT over fSRS, the dose gradients at the target volume's boundary can be compared by means of the anisotropic dose gradient measures, like the superficially averaged dose gradient.[52] Due to existing comparative data of PBRT and photon beam therapy, it remains reasonable to accept photons as an equipotent oncological treatment.[13 53]

Furthermore, image acquisition by MRI can provide more accurate measurements for treatment planning than ultrasound. Functional scans substantiate clinical diagnosis and treatment response.[16 54 55]

The main limitation of our study is the retrospective design, affecting statistical reliability due to referral and treatment biases. The cases were heterogeneous, and a biopsy prior to radiation was not required. The median follow-up of 32 months after the end of therapy was relatively short, and due to the small number of events, an investigation of the influencing variables using multivariate Cox regression analysis was not sensible.[56] VA comparisons are subjected to bias, RT toxicity and interventions after definitive RT. A prospective randomised trial needs to confirm our results.

In summary, the present series highlights the efficacy of LINAC-based fSRS for UM using the combination of dynamic conformal arcs, static conformal beams, and discrete intensity-modulated radiotherapy. The gross tumour volume, GTV, should be considered as a prognostic factor in staging systems. Early diagnosis and treatment are beneficial, and access to photon treatment facilities should reduce the waiting times for rare technologies.

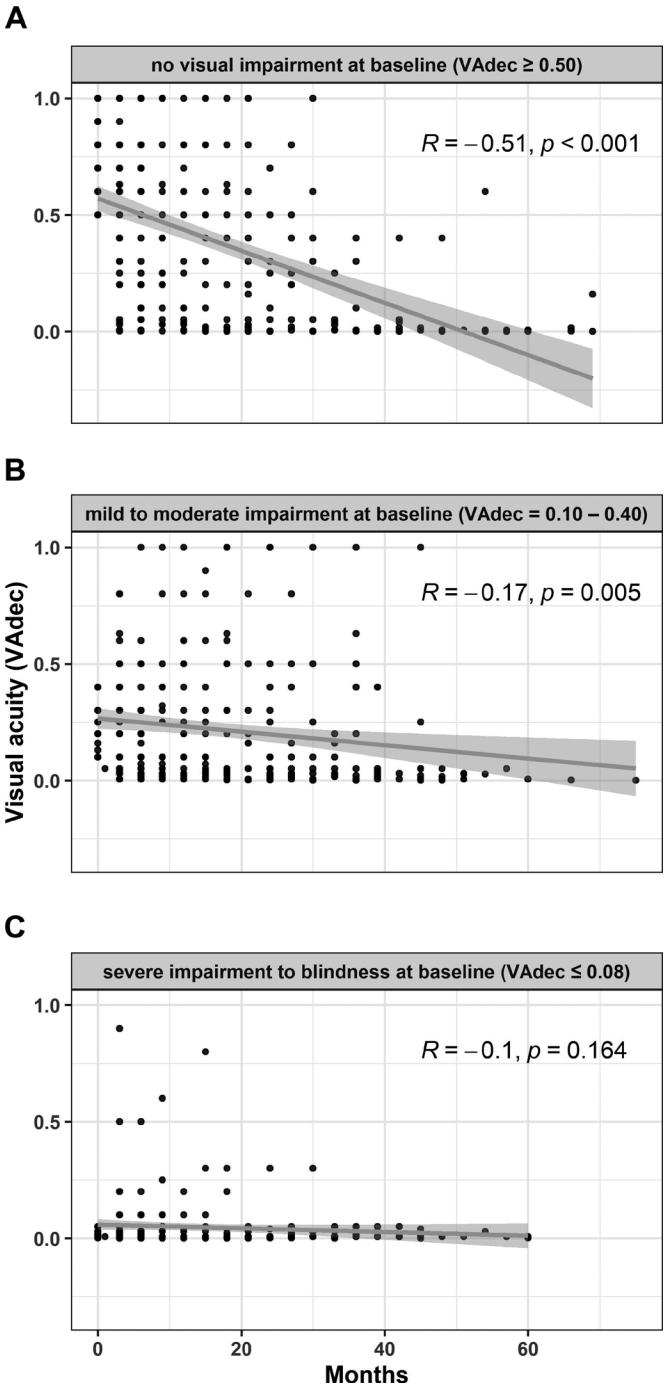

Figure 3 Evolution of visual acuity over time after radiotherapy with photons. (A) Patients with a visual acuity ≥0.5 before radiotherapy. (B) Patients with a visual acuity of 0.10–0.4 before radiotherapy. (C) Patients with a reduced visual acuity ≤0.08 before radiotherapy.

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