Robotic radiosurgery for the treatment of medium and large uveal melanoma

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The aim of the study was to analyze the local efficacy and eye retention rate after frameless, image-guided robotic radiosurgery against uveal melanoma. A total of 217 patients, mostly with medium and large unilateral uveal melanomas (3% small, 62% medium, and 35% large) were treated. The median age was 64 years (range 21–95 years). All patients underwent a single-session procedure beginning with retrobulbar anesthesia, followed by MRI and computerized tomography scanning to generate the treatment plan. The tumor dose was 18–22 Gy (mean, 20.3 Gy) prescribed to the 70% isodose line. Follow-up occurred at 3, 6, 12, and 18 months and yearly thereafter with clinical, ultrasound, and MRI studies. The median follow-up time was 26.4 months. All patients were treated in the frameless setup within 3 h. The actuarial 3- and 5-year eye retention rates were 86.7 and 73%, respectively. Local control at 3 and 5 years was 87.4 and 70.8%, respectively. Serviceable vision was maintained in 30.9% of patients at last follow-up. Treatment-induced glaucoma developed in 33 patients at a median 20.8 months (range, 5.8–54.0 months). Other adverse effects were hemorrhage (26 patients) and macular edema (seven patients). Frameless, single-session, image-guided robotic radiosurgery is an effective and straightforward treatment option for patients with medium and large uveal melanoma that are otherwise difficult to treat. *Melanoma Res* **00:000–000**

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Introduction

Uveal melanoma is a rare disease with an incidence of 6–7/million and is listed by the Office of Rare Diseases of the National Institutes of Health. However, it represents the most common primary intraocular malignancy in adults and is fatal once metastasis has occurred [1]. As the Collaborative Ocular Melanoma Study (COMS) has demonstrated that metastasis and overall survival rates do not differ significantly between patients treated with enucleation and those treated with brachytherapy, eye retention is feasible [1]. Whereas brachytherapy with radioactive eye plaques can only be delivered to patients with uveal melanoma of limited height and transverse diameter, teletherapy approaches such as fractionated proton beam therapy, conventional LINAC radiotherapy, and frame-based radiosurgical techniques can be applied successfully to larger tumor volumes as well as to tumors located close to the posterior pole of the eye [2–15]. Each radiotherapy regimen has its advantages but also brings radiation-specific complications. The aim of this study was to evaluate the treatment outcome of single-fraction robotic radiosurgery in 217 consecutive patients with uveal melanoma. This represents, to our knowledge, the largest published series of uveal melanoma treated by an external radiosurgery technique.

Methods

Patients

A total of 242 consecutive patients with unilateral uveal melanomas were entered into a prospective case–control study and treated with frameless, single-session, image-guided robotic radiosurgery. Of the 242 patients, 217 were included in the analysis and 25 were excluded because of short follow-up (<6 months). None of the excluded patients experienced local failure or required enucleation during this short time.

There were 124 men and 93 women with an age range of 21–95 years (mean, 64 years). Radiosurgery was indicated either because the size and location of the tumor were not amenable for brachytherapy or because the patient wished to avoid primary enucleation. Two patients had undergone prior unsuccessful brachytherapy for the targeted lesion.

All patients were evaluated by an ophthalmologist in the Eye Hospital of the University of Munich Hospital for treatment eligibility. Informed consent was obtained from all patients. According to the WHO criteria, functional vision was defined as a visual acuity over 0.3. This was the cutoff used for follow-up of visual function. All patients underwent a standardized outpatient procedure, which has been described previously [10] and is

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composed of the following steps. Patients underwent standard retrobulbar anesthesia with the goal of complete akinesia of the globe within the orbit. The volume of the anesthetic depended on the volume of the orbit and was 10–15 ml. (Suturing of the rectus muscles was not performed.) Immediately after the injection, a gadolinium-contrast-enhanced MRI of the head with 1-mm slice thickness was performed (T1 and T2 sequences), followed by the planning computed tomography (CT) scan with 1.2-mm slice thickness. On the basis of these two imaging data sets, the target volume was defined by the ophthalmologist and radiation oncologist, and the treatment plan was generated by means of a nonisocentric inverse treatment planning algorithm (MultiPlan; Accuray Inc., Sunnyvale, California, USA). A 1-mm margin, increasing to 2 mm posteriorly, was added to the planning target volume to compensate for potential slight posterior shift of the eyeball during treatment due to resorption of the anesthetic volume. The treatment plan was transferred to the delivery system, followed by immediate treatment. Radiation was delivered in a single fraction with a median dose of 20 Gy enclosing the planning target volume; the dose depended on the size and location of the tumor (Table 1). After the radiosurgery, the patient was discharged home.

Clinical and imaging follow-up was performed after treatment at 3, 6, 12, and 18 months and annually after that, using standardized A-scan and B-scan ultrasound and a 1-mm slice MRI (T1 and T2 sequences) for evaluation of local control. Tumor control was defined as either continuous regression of the tumor or no further progression. All patients received clinical oncologic tumor staging with at least an ultrasound evaluation of the liver before stereotactic radiosurgery (SRS). Most patients underwent a thoracic and abdominal CT scan. For oncologic follow-up, a thoracic and abdominal scan was run at least annually.

System description

The robotic radiosurgery device (CyberKnife; Accuray Inc.) used in this study consists of a 6-MV compact linear accelerator (LINAC) mounted on a computer-controlled six-axis robotic manipulator [8,14] that allows beam delivery from more than 2000 directions around the patient. Integral to the system is a dedicated image-guidance mechanism that consists of two X-ray sources and two flat-panel detectors, which acquire orthogonal images of the target area. Exact patient positioning is done through an automated patient couch. During treatment, the robotic manipulator automatically corrects for translational and rotational motion of the target within a range of 0.5–10 mm based on periodically acquired images. For cerebral indications, this is accomplished through the co-registration of the acquired X-ray images of the bony structures with digitally reconstructed radiographs from the planning CT; offsets from the setup position are compensated by adjusting the direction of the treatment beam.

Table 1 Tumor size and percentage of patients according to COMS classification

Size of treated tumors according to COMS	Height (mm)		Transverse diameter (mm)	Percentage of patients
Small	1–2.4	And	5–16	3.3%
Medium	2.5–10	And	≤16	66.9%
Large	>10	And/Or	>16	29.8%

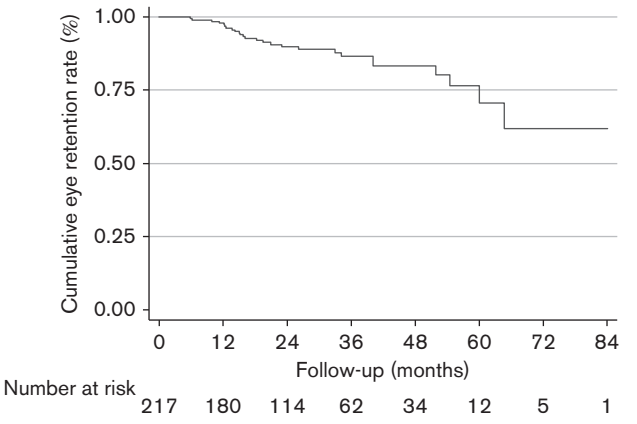
COMS, Collaborative Ocular Melanoma Study.

Results

Mean prescription dose enclosing the tumor was 20.3 Gy (range 17–22 Gy, median 20 Gy) at the 69% (range 60–75%, median 70%) isodose. Mean follow-up was 29.6 months (range 5.9–84.0 months, median 26.4 months). Sixty-seven patients (30.6%) were followed up for at least 3 years after treatment.

The Kaplan–Meier-predicted eye retention rate is shown in Fig. 1. Actuarial eye retention was 86.7% [95% confidence interval (CI): 79.9–91.3%] at 3 years and 73.0% (95% CI: 58.1–83.3%) at 5 years. Out of the 26 patients requiring enucleation, tumor size before treatment was large in 35% and medium in 65% according to COMS (Table 2). No small tumors required enucleation during follow-up. The mean time from treatment to enucleation was 24.9 months (range, 5.7–64.6 months; median, 17.2 months). Reasons for enucleation were suspected recurrence (69%), neovascular glaucoma (19%), or tumor necrosis syndrome (12%). Suspicion of local recurrence was defined as an increase in maximal height on a standardized ultrasound A-scan examination of more than 0.3 mm associated with a decrease in internal reflectivity on two occasions within 3–6 months of follow-up after stereotactic radiosurgery and/or extrascleral growth on a standardized ultrasound B-scan verified by cMRI. In all, 26 of the 217 patients were enucleated. Histological

Fig. 1



Eye retention: Kaplan–Meier-calculated eye retention rate following radiosurgery for uveal melanoma.

Table 2 Comparison of age, location, tumor size, and reflectivity of all uveal melanoma patients treated with CyberKnife compared with those enucleated

Uveal melanoma treated with CyberKnife	All patients treated	Patients requiring subsequent enucleation	*P*
Age at treatment (years)			
Mean	63.4	59.9	0.24*
Median (range)	64.9 (20.9–94.5)	61.3 (35.7–80.1)	
Location			
Posterior pole	31.1%	25.0%	0.41†
Periphery	59.9%	58.3%	
Periphery including ciliar body	9.0%	16.7%	
Height (mm)			
Mean	6.6	7.1	0.40*
Median (range)	6.4 (1.5–13.9)	7.2 (3.1–12.1)	
Base (mm)			
Mean	11.9	13.4	0.024*
Median (range)	11.6 (5.9–20.5)	14.1 (6.0–19.9)	
Reflectivity (%)			
Mean	52.3	50.8	0.61*
Median (range)	52.0 (20–90)	50.0 (28–74)	

*Two-tailed Student's *t*-test, 95% confidence interval.
†Fisher's exact test.

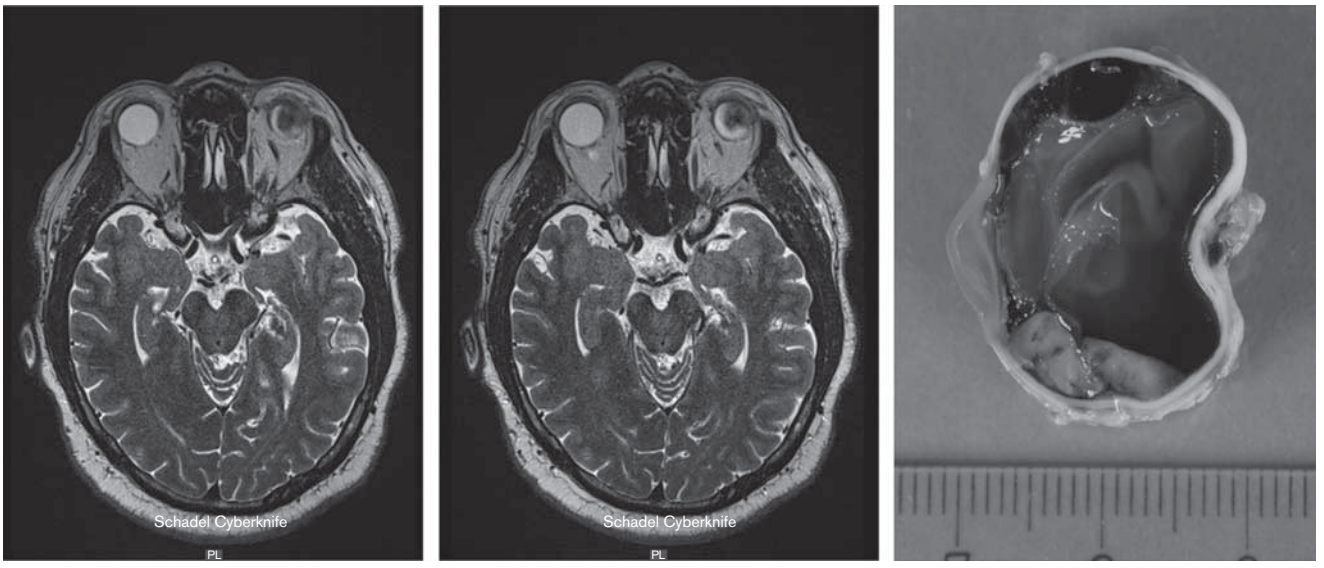
analysis was performed for 24 patients and showed extrascleral growth in 11 cases, uncontrolled secondary glaucoma such as optic nerve atrophy but no signs of uncontrolled tumor growth in six cases, and large exudative retinal changes with retinal detachment and subretinal hemorrhage in seven specimens (Fig. 2).

The Kaplan–Meier-predicted local tumor control rate (Fig. 3) was similar to eye retention, with an actuarial local control of 87.4% (95% CI: 80.1–92.2%) at 3 years and 70.8% (95% CI: 54.8–82.0%) at 5 years. Excluding patients who underwent enucleation, maximum apical tumor height and mean base diameter were measured with a standardized A-scan ultrasound before treatment and during follow-up. Figure 4a and b compare boxplots of tumor height and base diameter from before treatment with the last available follow-up. Decrease in the maximum height was highly significant, from a median value of 6.4 mm (mean, 6.7 ± 2.9 mm) before treatment to 4.0 mm (mean, 4.8 ± 2.6 mm) at the last available follow-up examination ($P < 4 \times 10^{-22}$, paired Student's *t*-test). Base diameter also decreased significantly, from a median value of 11.5 mm (mean, 11.8 ± 3.0 mm) before treatment to 10.4 mm (mean, 10.8 ± 3.1 mm) at the last available follow-up examination ($P < 2 \times 10^{-7}$, paired Student's *t*-test) (Fig. 5). Reflectivity increased significantly from a median value of 52.0% (mean, $51.7 \pm 13.6\%$) before treatment to 70.0% (mean, $69.0 \pm 13.9\%$) at the last available follow-up examination ($P < 7 \times 10^{-30}$, paired Student's *t*-test) (Fig. 6).

One of the strengths of this analysis is the significant number of patients with large uveal melanoma as defined by COMS (29.8%; Table 1). Therefore, we decided to perform a subgroup analysis of these patients (Table 3). Large tumors were mainly located in the periphery of the eyes (78.2%), which might have been one of the reasons for the late clinical diagnosis. In all patients, maximal tumor height as measured by the standardized ultrasound A-scan decreased significantly after robotic radiosurgery. Vision of more than 0.3 (if present before treatment) was preserved in almost all patients.

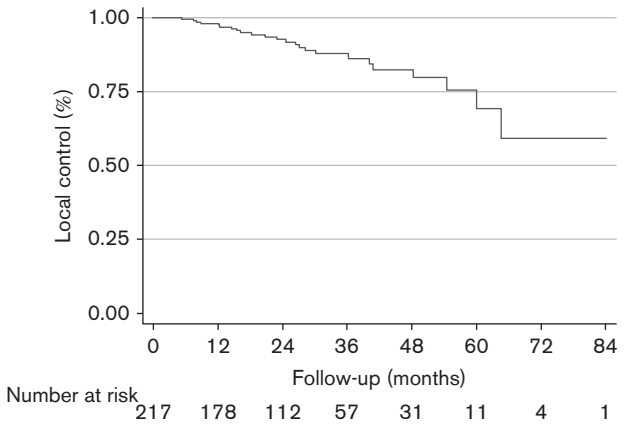
A total of 104 patients presented with functional vision (defined as visual acuity ≥0.3) before treatment. In this group, functional vision could be maintained in 30.9% of

Fig. 2



Bleeding complication.

Fig. 3



Local control: Kaplan–Meier-calculated local tumor control following radiosurgery for uveal melanoma.

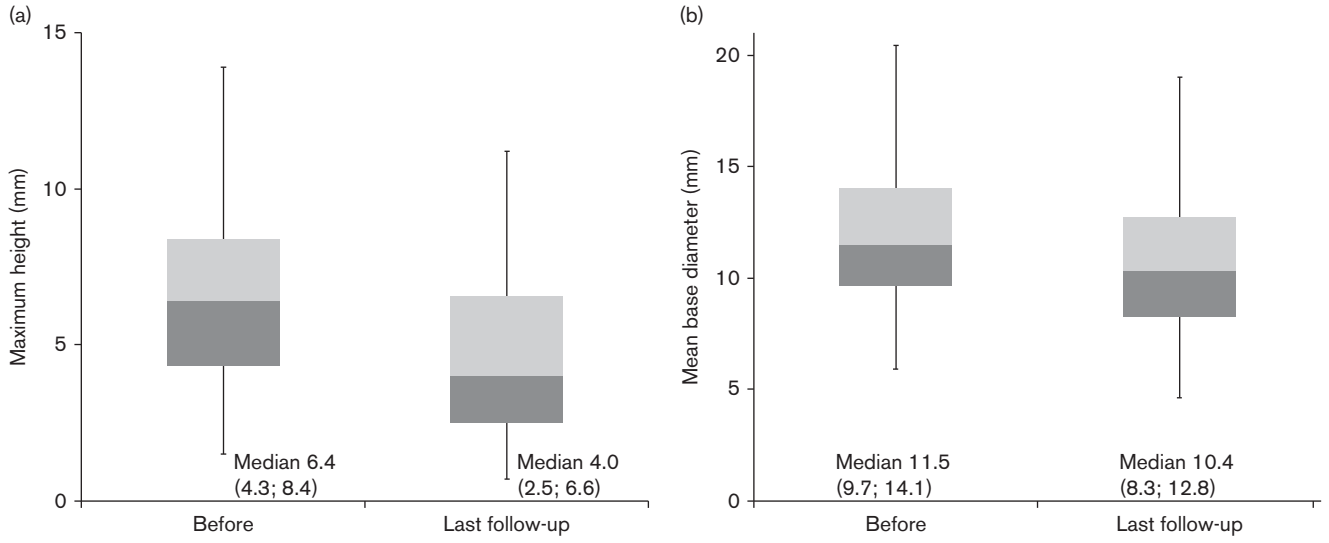
patients until the last available follow-up examination. Regarding treatment-induced toxicity rates, we saw 29 patients with radiation-induced retinopathy at the end of follow-up. We have collected the clinical data as best as possible in this study, given the obvious limitations of retrospective trials. More robust data for retinopathy rates after stereotactic radiosurgery need to be determined in future prospective clinical trials.

Treatment-induced glaucoma developed in 33 patients at a median time of 20.8 months (range, 5.8–54.0 months) after treatment. Other adverse effects were hemorrhage (26 patients) and macular edema (seven patients). Twenty-nine patients (13.4%) died from nonspecific causes during follow-up. Cause of death was metastatic progression in 11.5% (25 patients) and unrelated to the disease in 1.8% (four cases). Actuarial disease-specific survival was 84.8% (95% CI: 77.0–90.1%) at 3 years and 78.4% (95% CI: 67.1–86.2%) at 5 years (Fig. 7).

Discussion

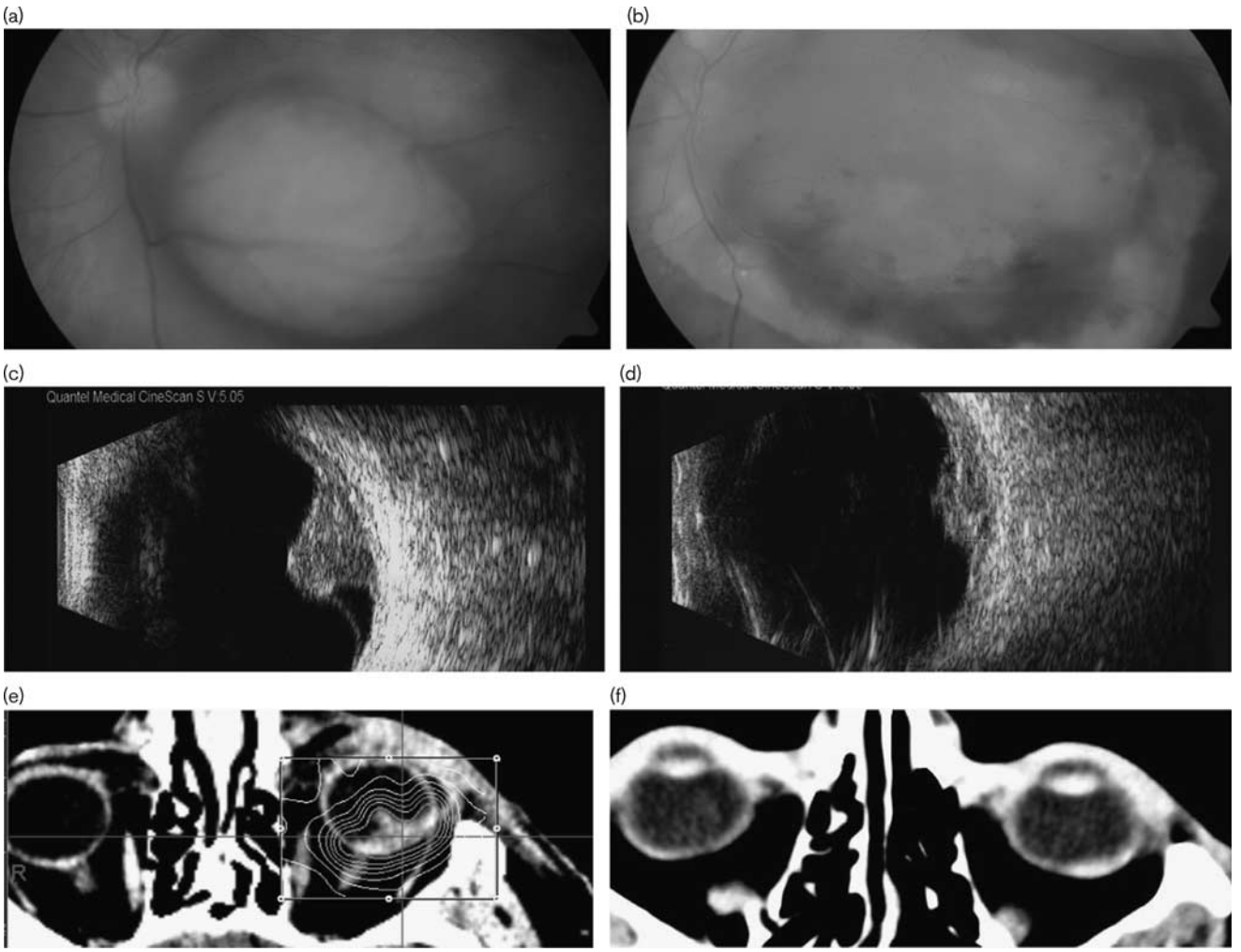
Eye conservation is achieved by several techniques today, with proton or other charged particle therapies, and episcleral radionuclide plaque therapy being among the most commonly used [16–19]. Adams *et al.* [16], for example, found no statistically significant survival difference in 223 patients treated with brachytherapy compared with 416 patients who underwent enucleation. Chang *et al.* [19] found in their review of 49 articles analyzing local treatment failure after globe-conserving therapy that rates of globe-conserving therapy of choroidal melanoma varied widely between modalities and between centers using similar modalities. Radiation therapy overall resulted in lower local treatment failures compared with surgical or transpupillary thermotherapy [20]. Semenova *et al.* [14] have published recently 10-year outcome data after Pd-103 plaque radiation therapy of 47 patients with T3 and T4 choroidal melanoma. Enucleation occurred in 11% and the local tumor control rate was 89%. Treatment complications included radiation retinopathy in 66% of patients, radiation optic neuropathy in 51%, secondary cataract in 36%, and secondary glaucoma in 17%. Macdonald *et al.* [8] have reported on 147 patients treated between 1993 and 2008 with proton beam radiotherapy for ciliary body and uveal melanoma not eligible for brachytherapy due to tumor size, location, or shape. In their report, they found an enucleation rate of 22.4% at a mean time of 23.8 months. Reasons for enucleation were suspected recurrence (48%) or

Fig. 4



(a) Tumor height: Boxplot of the mean height of the uveal melanomas before and after radiosurgery. (b) Tumor base: Boxplot of the mean tumor base of the uveal melanomas before and after radiosurgery.

Fig. 5

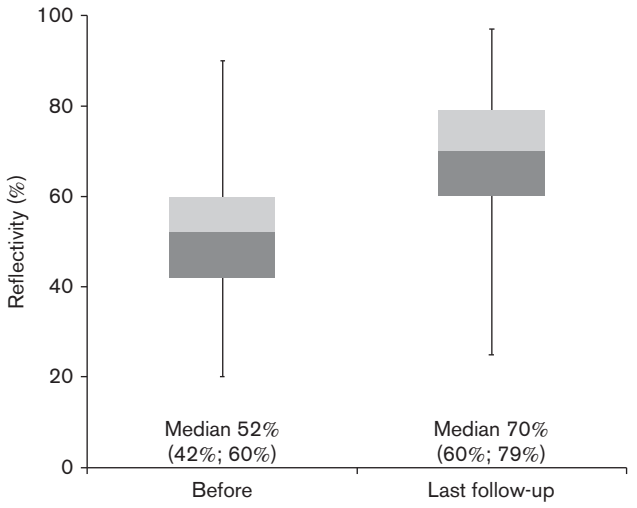


Fundoscopy, ultrasound, and computed tomography (CT) scans of the same patient before and 6 months after the radiosurgery procedure. (a) Fundoscopy of a peripapillary uveal melanoma. (b) Fundoscopy of a peripapillary uveal melanoma 6 months after radiosurgery. (c) Ultrasound scan before radiosurgery. (d) Ultrasound scan after radiosurgery. (e) CT planning scan with isodoses. The innermost line enclosing the tumor is the prescription isodose (70%). (f) CT control scan after 6 months.

neovascular glaucoma (42%). The overall survival rate was 87.7%, qualifying this treatment option as a first-line eye-preserving therapy for uveal melanoma of medium and large sizes (97.8% of patients). Interestingly, their patient cohort was similar to the patients analyzed in the current study with mostly challenging-to-treat medium to large uveal melanomas (medium to large size, 97%) with worse prognoses. Most other proton series involve a higher number of small tumors that are more amenable to treatment [21,22]. Our eye retention rate was 86.7% at a mean time of 36 months and the disease-specific survival rate was 84.8% at 3 years and, therefore, almost identical to the McDonald series. Even though comparison of outcome data from different centers are difficult to interpret as there is no uniform clearly defined indication for post-treatment enucleation, it is noteworthy that patient comfort (single-day treatment) and cost of treatment (proton versus SRS) are favorable using a single-day radiosurgery approach. This leads us to question the advantage of the widespread use of 1-week proton therapy for uveal melanoma. Robotic SRS also carries the advantage of not involving invasive surgery for plaque implantation and removal and hospitalization for several days.

The radiosurgery techniques described previously usually require immobilization of the eye to accurately plan and deliver the high-dose treatment. Typically, a stereotactic frame (frame-based stereotactic radiosurgery) is used along with retrobulbar anesthesia and suturing of two to four rectus muscles [9,13]. Others have described suction fixation devices for radiosurgical ocular treatments [23,24]. For 78 patients with uveal melanoma treated with Gamma Knife (Elekta AB, Stockholm,

Fig. 6



Reflectivity: Reflectivity measurements of the uveal melanomas before radiosurgery and at last follow-up.

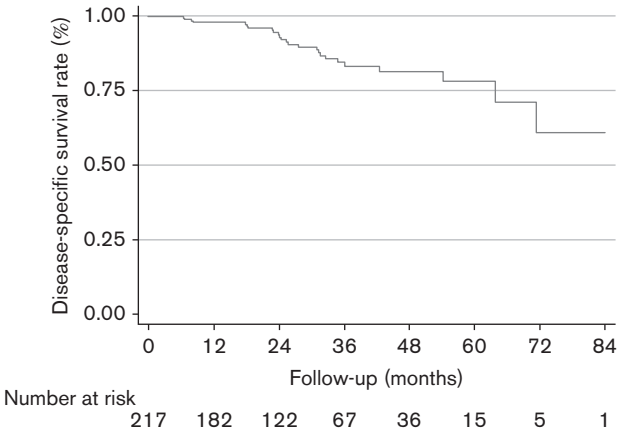
Table 3 Large uveal melanoma subgroup before CyberKnife and at last follow-up

Subgroup large uveal melanoma (COMS)	Before CyberKnife	At last follow-up	*P*
Location (%)			
Posterior pole	10.9	–	
Periphery	78.2	–	
Periphery including ciliar body	10.9	–	
Height (mm)†			
Mean	10.4	7.5	< 0.0001*
Median (range)	10.0 (5.5–13.9)	7.3 (3.3–11.2)	
Base (mm)†			
Mean	14.3	13.3	0.04*
Median (range)	14.5 (8.3–20.5)	13.1 (8.0–19.0)	
Visual acuity ≥ 0.3 (%)	8.7	7.0	

COMS, Collaborative Ocular Melanoma Study.
*Paired Student's *t*-test, 95% confidence interval.
†Enucleated patients excluded.

Sweden) radiosurgery between 1994 and 2006, Modorati *et al.* [9] published a survival rate of 88.8% at 3 years and 81.9% at 5 years. Local tumor control rate was 91% and the eye retention rate was determined to be 89.7%. Treatment complications included 33% exudative retinopathy, 13.5% radiogenic retinopathy, 18.7% neovascular glaucoma, and 10.4% vitreous hemorrhage. A recent study by Sarici *et al.* [13] on single-session Gamma Knife stereotactic radiosurgery on 50 patients with medium to large-sized posterior uveal melanoma reported a tumor control rate of 90%, an eye retention rate of 82% (follow-up, 16–78 months; mean, 40 months), and an 18% incidence of metastasis [13]. Complications included 34% cataract, 30% radiation maculopathy, and 14% neovascular glaucoma [13] For hypofractionated stereotactic photon radiotherapy of 212 patients with uveal

Fig. 7



Disease-specific survival: Kaplan–Meier-calculated disease-specific survival following radiosurgery for uveal melanoma.

melanoma, Dunavoelgyi *et al.* [5] have shown a local tumor control rate of 92.6% at 10 years (treated between 1997 and 2007); 32 patients developed metastasis and 22 died because of metastasis. Larger basal diameter (>10 mm), ciliary body melanomas, and doses over 35 Gy appeared to be associated with increased complication rates [25]. Recently, there has been a trend toward dose de-escalation in this application. Several series showed equivalent local control but reduced toxicity rates with lower doses [25–27]. The dose level applied in the current study was lower than that in earlier series. The treatment regimen was developed based on our previous experience and the ability to deliver dose plans with steeper gradients and better tumor coverage compared with the earlier, frame-based techniques [27,28].

The probability of visual preservation and eye retention with the either technique is strongly dependent on tumor size and location. The dose to the lens and the optical disc is determined by the location of the tumor. However, for tumors of the lateral and posterior–lateral parts of the bulb, the dose to the lens and the optical disc could be kept to a minimum because of the steep dose gradient achieved using an inverse planning algorithm (Fig. 5). Hirasawa *et al.* [29] have identified the anterior segment of the eye and the optic disc as structures of great risk for neovascular glaucoma based on a multivariate analysis, and recommended irradiation techniques that would spare these structures as much as possible when treating uveal melanoma. The high flexibility of the robotic technology used in the current study is capable of achieving this goal [2,3,10]. Although these data cannot be directly correlated to visual outcome, it clearly documents the ability of the robotic system to adjust the dose to the tumor as much as possible by maximally sparing the sensitive structures of the eye from the dose.

The risk for metastasis and death increases with larger tumor size at initial presentation [15]. According to COMS, the predicted 5-year disease-specific mortality rate was 31–35% for large tumors, 10% for medium tumors, and 1% for small tumors [12,15]. Our 5-year disease-specific mortality was comparable to other studies [8,20,22]. Local effective therapy seems important as delay or refusal of treatment is associated with an increased incidence of metastatic disease and/or death compared with mortality rates of patients who received prompt treatment [30,31]. However, 5-year metastatic disease rates are probably not going to be favorably influenced by any treatment of the primary tumor as the interval can be long (up to 30 years) before micrometastases become clinically evident [32].

Local recurrence is associated with an increased risk for metastatic death [6,11]; therefore, effective local treatment concepts are crucial. However, overall mortality can only be reduced by effective systemic therapies, which have yet to be introduced.

Accurate treatment planning and delivery requires a stringent setup with an experienced interdisciplinary team comprising ophthalmologists, radiation oncologists, and imaging experts. Under optimal conditions, the described radiosurgical treatment paradigm is safe, effective, and comfortable for the patient.

Conclusion

The results demonstrate that robotic radiosurgery is an effective eye-preserving treatment option for medium-sized to large-sized uveal melanoma. Local tumor control and toxicity is comparable to more complex radiation techniques. Radiosurgery deserves more attention for treatment of uveal melanoma as it is also patient friendly and time saving.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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