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ONCOLOGY

Qualitiy of life in the follow-up of uveal melanoma patients after enucleation in comparison to CyberKnife treatment

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Abstract
Purpose To compare quality of life (QoL) in patients with uveal melanoma after enucleation and stereotactic radiosurgery to that in an age-matched patient collective.
Methods QoL was assessed in a cross-sectional survey and compared among 32 uveal melanoma patients after enucleation, 48 patients after stereotactic radiosurgery (CyberKnife®; Accuray® Incorporated, Sunnyvale, CA, USA), and an age-matched control group of 35 patients, using the SF-12 Health Survey. Statistical analysis was performed with Fisher's exact test, Student's *t* test, one-way ANOVA analysis, Wilcoxon rank-sum (Mann–Whitney test), and ordered logistic regression for multivariate analysis.
Results There was no significant difference in QoL between patients treated by stereotactic radiosurgery and the age-matched control group. After enucleation, patients presented significantly lower values in Physical Functioning (PF), Role Physical (RP), and Role Emotional (RE) compared to the radiosurgery and control group. To control for the overall QoL lowering effect of visual loss, the QoL of the patients who underwent enucleation was compared with the QoL of patients suffering severe functional loss after CyberKnife radiosurgery in a subgroup analysis, which showed no statistically significant difference. The number of comorbidities had a significant impact on QoL in multivariate analysis.
Conclusions Superior performance in PF, RP, and RE suggests that CyberKnife represents a suitable first-line therapy for uveal melanoma. In cases with painful amaurosis or vast tumor recurrence, enucleation can be performed with an acceptable QoL outcome.

Keywords Quality of life · SF-12 Health Survey · Enucleation · Stereotactic radiosurgery · CyberKnife · Uveal melanoma

Introduction

Uveal melanoma is the most frequent primary intraocular tumor in adults [1], with a reported incidence of 5-7 per million population [2]. Local tumor control can be achieved in the vast majority of cases [3]. Whilst eye-conserving plaque brachytherapy, proton therapy, and gamma knife therapy have long been established as treatment methods, stereotactic radiosurgery (CyberKnife®, Accuray® Incorporated, Sunnyvale, CA, USA) has emerged as a relatively new method with promising results [4, 5]. Enucleation is also an established therapy that has been employed for the past several decades, but according to the results of the COMS (Collaborative Ocular Melanoma Study), has proven no survival benefit [6, 7].

The effect of a specific treatment on a patient's quality of life (QoL) should be considered during treatment planning [8]. Whenever possible, the preservation of vision and prevention of recurrence and of side effects should be the primary goals in patient management, along with a cosmetically acceptable result. If enucleation cannot be avoided due to tumor characteristics or because of adverse events after irradiation (e.g. in cases of painful amaurosis or development of secondary

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glaucoma), patient acceptance after enucleation seems to be relatively high [9]. However, radical surgery in oncology may lead to functional and eventually cosmetic disturbances that may severely affect a patient's QoL.

Enucleation and radiation therapy have different reported physiological and psychological effects on patients that reflect on their QoL [10, 11]. The presence of a serious disease, in itself, can cause depression [12], and compared with other cancer diagnoses and normative data, higher proportions of uveal melanoma patients report reduced QoL and substantial emotional problems [13–15]. After radiotherapy, a decline in QoL of 5 % has been observed [16].

In a first analysis, we published QoL in the follow-up of 91 uveal melanoma patients during their first and second year after stereotactic CyberKnife radiosurgery [17]. To date, among the common medical databases, we have found no comparative studies on QoL in uveal melanoma patients treated with CyberKnife radiosurgery versus enucleation. To the best of our knowledge, there are no data available concerning QoL after proton beam therapy for uveal melanoma. QoL outcome after uveal melanoma treatment is important within the context of clinical practice. Therefore, in the current study, we evaluated differences in QoL between uveal melanoma patients treated by enucleation and CyberKnife radiosurgery, and compared both patient collectives with an age-matched melanoma-free patient collective within a cross-sectional study design.

We again employed the 12-Item Short Form Health Survey (SF-12) questionnaire assessing both physical and mental health component summaries. The SF-12 is a measure of perceived health (health-related QoL) that describes the degree of general physical health status as well as mental health distress [18]. It covers 12 items, derived from the physical and mental domains of the 36-Item Short Form Health Survey (SF-36), and completion takes approximately 3 min. We published the exact content of the SF-12 employed in our previous study [17].

Methods

We evaluated the QoL of 32 uveal melanoma patients who had previously undergone enucleation, and compared QoL with an aged-matched control group of 48 uveal melanoma patients after CyberKnife radiosurgery and an age-matched control-group of 35 patients without uveal melanoma who presented in our outpatient department.

SF-12 Health Survey

With the multipurpose short-form SF-12 Health Survey, in only 12 questions, a summary of physical and mental health can be estimated [19]. One or more items represent the following eight health concepts: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH). The individual items assessed by the 4-week recall of the SF-12v2® Health Survey (©1992, 2000 Health Assessment Lab, Medical Outcomes Trust and QualityMetric Incorporated, German Version 2.0, 10/03) have been described elsewhere in detail [17]. Typically, all scores are transformed to a standardized (0–100) continuous scale, with 50 as the mean and a standard deviation of 10 [20], and with higher scores representing better health, function, and overall QoL.

Enucleation and primary dermis fat graft implantation (DFG)

From our melanoma database and surgery documentation files, we retrospectively collected the data for all patients with uveal melanoma who had undergone enucleation and primary DFG implantation at the Ludwig-Maximilians-University hospital. All enucleated eyes were histologically analysed, and uveal melanoma was confirmed in all cases. Enucleation and primary implantation of an autologous DFG was performed between April 2004 and March 2013. In total, we had access to the data of 87 patients, among whom 82 were reported to be living in Germany. Further work-up revealed the death of 17 patients. Of the remaining 65 patients, 32 [male-to-female ratio=24:8] responded to the SF-12v2 Health Survey sent to them by mail.

Surgery was performed under general anaesthesia, employing the technique described by Smith et al. [21]. In brief, the DFG with a standard size of 25 mm in diameter and thickness was harvested from the gluteal region of the patients by incising the epidermis superficially with a No. 15 scalpel, injecting saline intradermally at the donor site, and then dissecting and separating the epidermis from the dermis layer using a No. 20 blade. After deep transection of the fat layer, the DFG was explanted and the wound closed in two layers with 2.0 sutures. Implantation of the DFG followed enucleation and surgical trimming for best fitting to the recipient site, striving for the maximum volume of dermis and fat that easily fit into the ophthalmic socket, avoiding excessive pressure. The dermal side of the graft was implanted face-up, and the extraocular muscles were sutured to the dermal part of the graft. The conjunctiva was then sutured to the outer dermal part of the DFG, and a rigid conformer was inserted to support the fornices. A pressure dressing was applied for 2 days, and an inserted conformer was left in place for 4–6 weeks, at which point a first prosthesis was fitted. As the DFG is an autologous implant, rejection reactions are rare, and have not been reported within this patient collective.

Patients treated with CyberKnife radiosurgery

We previously published the QoL data of 91 uveal melanoma patients in their first and second year after having undergone local CyberKnife radiosurgery [17]. We continued follow-up of our patients treated by CyberKnife and have now analysed all available SF-12 Health Surveys completed by patients 3 years after CyberKnife therapy (n=48). Between September 2006 and November 2011, these patients underwent a standardized single-session procedure, the details of which were published previously [4]. Briefly, in this procedure, retrobulbar anaesthesia is applied to achieve complete akinesia of the affected eye for 2.5 to 3 hours. Within this time frame, the radiosurgery treatment is prepared and performed, including the following steps: magnetic resonance imaging (T2- and contrast-enhanced T1-weighted) and a computerized tomography scan of the head with 1.2-mm slice thickness are acquired and overlaid. The visible tumor is contoured as target volume. Inverse treatment planning is employed to create a dose distribution covering the target, with a steep fall-off towards adjacent risk structures (optic nerve, fovea, lens). A mean dose of 20.2 Gy (range 17–22 Gy) was prescribed to the isodose enclosing the tumor. After 30–40 minutes, this treatment plan is delivered with the CyberKnife: a compact 6-MV linear accelerator mounted on a robotic manipulator delivers 100–150 beams from different directions, which superimpose at the target volume. Periodically throughout the treatment, the target position is identified using a stereoscopic X-ray system to guide the treatment beam with sub-millimeter accuracy. This streamlined workflow is completed within 2.5 hours.

Control group

For a better comparison of QoL, we collected the data of the same health survey for 35 consecutive patients who presented in our general outpatient department with various ocular conditions.

Statistical testing

The SF-12 health surveys were evaluated via SF Health Outcomes™ scoring software (QualityMetric, Incorporated/Optum, Lincoln RI, USA). Statistical significance was tested using Fisher's exact test and Student's t test, as well as one-way ANOVA analysis, Wilcoxon rank-sum (Mann–Whitney) test, and ordered logistic regression (Stata/IC 10.1 for Windows; StataCorp LP, College Station TX, USA), with $p < 0.05$ considered to be statistically significant.

This study was approved by the institutional review board of Ludwig-Maximilians-University, Department of Ophthalmology, Munich, Germany, and was conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients prior to completion of the SF-12. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. All clinical data were gathered from the original medical files.

Results

Demographic data

Of the 32 patients who underwent enucleation, 16 right and 16 left globes were enucleated. Within the patient collective who underwent radiosurgery (n=48), uveal melanoma was situated in the right eye in 21 and in the left eye in 27 cases. Table 1 gives an overview of the following patient characteristics: gender, age, length of time after treatment when QoL was assessed, tumor T-category, metastatic progression, and relevant comorbidities. There was a significant difference in gender and T-category between the patient collectives: more women agreed to participate in the study in the control group, while more men answered the questionnaire in the enucleation group (p=0.02, Fisher's exact test). The difference in tumor T-category between the CyberKnife and enucleation group was highly significant (p<0.0005, Fisher's exact test).

Enucleation was performed as primary therapy in 14 cases, as second-line therapy due to tumor recurrence after brachytherapy or stereotactic radiosurgery in 12 cases, and due to painful amaurosis or secondary glaucoma after primary therapy in 6 cases. Only three patients had undergone local treatment before CyberKnife (one gamma knife, one brachytherapy, one transpupillary thermotherapy), and two patients had to undergo retreatment due to local recurrence after CyberKnife (initial tumor category T2=2).

Tumor localization included the ciliary body in 2, the peripapillary region in 6, the posterior pole in 11, the mid-periphery in 20, and the periphery in 9 of the 48 patients who underwent CyberKnife radiosurgery, and included the ciliary body in 1, the peripapillary region in 1, the posterior pole in 7, the mid-periphery in 13, and the periphery in 10 of the 32 patients who underwent enucleation. Subretinal fluid was present in 31 of the tumors treated by radiosurgery and in 23 of the tumors that were enucleated. Comorbidities possibly interfering with quality of life are summarized in Table 2.

The main coded ocular diagnoses of patients in our control group (n=35) were refractive conditions (n=5), retinal/vitreal conditions (n=20), glaucoma/optic nerve head alterations (n=3), trauma/ocular adnexa (n=2), and cataract (n=5).

Age at the time of completion of the questionnaire did not differ significantly among the different groups (mean age of patients in enucleation group 69.4±13.2 years, median 68.0 years; mean age of patients after CyberKnife radiosurgery

Table 1 Patient characteristics

	Control	CyberKnife	Enucleation	*p* value
Patients (no.)	35	48	32	
Gender (female/male)	22/13	24/24	9/23	0.02[a]
Age* (years)	66.0±12.2	66.3±10.6	69.4±13.2	NS[b]
QoL (months after treatment)	N/A	37.9±13.2	42.9±28.7	NS[c]
Tumor size (T1/2/3/4)	N/A	9/15/24/0	1/13/9/9	<0.0005[a]
Metastatic progression*	N/A	2	5	NS[a]
Comorbidities (n 0/1/≥2)[†]	25/8/2	32/13/3	16/12/4	NS[a]

Values are expressed as mean ± standard deviation

*At time of QoL assessment

[†] Number of comorbidities: all conditions listed in Table 2 are included, with the exception of arterial hypertension

[a] Fisher's exact test

[b] One-way ANOVA

[c] Student *t* test

NS not significant

66.3±10.6 years, median 67.4 years; mean age of control group 66.0±12.2 years, median 67.0 years; one-way ANOVA, not significant).

Quality of life comparison

For all eight QoL parameters summarized by the SF-12 Health Survey, we found no significant difference between patients treated by CyberKnife and our age-matched control group. Within the CyberKnife group, a small subset of 12 patients had experienced severe functional loss (resulting in light perception or no light perception) on the treated eye at the time of QoL assessment. For these patients, PF, RP, and RE were lower, with average values of 56.3±30.4, 58.3±31.7 and 63.5±33.5, respectively. However, there was no statistical difference in these values between the enucleation and CyberKnife groups for patients with severe functional loss.

The values for PF, RP, and RE were significantly lower among patients in the enucleation group than either the CyberKnife or control group. PF, RP, and RE were lower, although not significantly, in the group of patients treated with CyberKnife than in the control group (Wilcoxon rank-sum (Mann–Whitney) test; Table 3). To confirm the dependent relationships of the QoL values among the different treatment

Table 2 Comorbidities among the three patient collectives

Comorbidities	Uveal melanoma patients treated by enucleation (*n*=32)	Uveal melanoma patients treated by CyberKnife (*n*=48)	Comparative patient collective (*n*=35)
Cardiovascular diseases			
Arrhythmia	2	2	2
Coronary heart disease	3	2	0
Status post-myocardial infarction or cerebral stroke	2	2	2
Arterial hypertension	13	20	12
Cancer antecedents	2 (chronic lymphatic leukemia *n*=1, skin melanoma *n*=1)	5 (breast cancer *n*=4, rectal cancer *n*=1)	3 (chronic lymphatic leukemia *n*=1, breast cancer *n*=1, bladder cancer *n*=1)
Rheumatic diseases	1	1	2
Diabetes mellitus	6	2	0
Neurologic conditions	2	1	1
Hepatic cirrhosis	2	1	0
Asthma	0	0	1
None	10	22	19

Table 3 Overall Quality of Life

	PF	RP	BP	GH	VT	SF	RE	MH
Control	80.0±26.3	76.1±23.1	77.1±27.4	60.1±19.8	62.9±17.5	78.6±25.8	79.5±24.4	71.1±14.5
CyberKnife	71.7±28.0	69.1±27.3	82.3±26.3	61.6±20.5	62.8±23.2	79.2±26.0	72.1±27.9	70.5±21.4
Enucleation	50.0±33.7	48.4±31.6	70.3±30.1	51.6±24.9	53.4±29.7	64.8±35.3	55.6±29.2	68.1±22.8
p* (ctr vs. CK)	NS	NS	NS	NS	NS	NS	NS	NS
p* (ctr vs. enu)	**0.0003**	**0.0003**	NS	NS	NS	NS	**0.0006**	NS
p* (CK vs. enu)	**0.0063**	**0.0043**	0.037	NS	NS	NS	**0.012**	NS

PF Physical Functioning, *RP* Role Physical, *BP* Bodily Pain, *GH* General Health, *VT* Vitality, *SF*, Social Functioning, *RE* Role Emotional, *MH* Mental Health, *ctr* control, *CK* CyberKnife, *enu* enucleation, *NS* not significant

Values are expressed as mean ± standard deviation

*Wilcoxon rank-sum (Mann–Whitney) test

groups, we performed ordered logistic regression testing for multivariate analysis. Despite the difference in CyberKnife versus enucleation in the Mann–Whitney test (Table 3), we were unable to ascertain a significant difference in BP in ordered logistic regression.

For PF, QoL was significantly influenced by enucleation therapy, gender, age, and comorbidities (p=0.001, p=0.015, p=0.009, and p=0.004, respectively) (Table 4). The item RP was significantly influenced by enucleation and relevant comorbidities (p=0.023 and p=0.012) (Table 5). Enucleation, gender, patient age, and comorbidities had a significant influence on RE (p=0.003, p=0.046, p=0.004, and p=0.020, respectively) (Table 6). GH was significantly influenced by both metastatic progression and the presence of comorbidities (p=0.036 and p=0.002) (Table 7), which also had significant influence on VT in ordered logistic regression (p=0.003) (Table 8). In SF, there was a significant difference for the parameter metastatic progression in multivariate analysis (p=0.010) (Table 9). MH was significantly influenced by gender, metastatic progression, and comorbidities (p=0.021, p=0.049, and p=0.010) (Table 10).

Discussion

A cross-sectional QoL survey with statistical analysis among patients treated by enucleation versus stereotactic radiosurgery reflects the reality of a clinical outpatient setting, and is therefore of interest not only for the ophthalmic oncologist but also for the general ophthalmologist.

In our previous QoL study, we demonstrated a decline in PF and RP after stereotactic CyberKnife radiosurgery and an improvement in MH at 1- and 2-year follow-up, and discussed subgroup analysis of patients who developed secondary glaucoma and in whom visual acuity was able to be preserved

Table 4 Physical Functioning

	OR (95 % CI)	z	$p > \|z\|$
CyberKnife	0.62 (0.23–1.68)	−0.93	NS
Enucleation	0.15 (0.04–0.48)	−3.18	0.001
Gender (female/male)	0.37 (0.17–0.83)	−2.42	0.015
Age* (years)	0.96 (0.93–0.99)	−2.60	0.009
Large tumor size**	0.68 (0.28–1.63)	−0.87	NS
Metastatic progression*	0.78 (0.15–4.18)	−0.29	NS
Comorbidities (#)	0.45 (0.26–0.77)	−2.89	0.004

Ordered logistic regression: log likelihood=−134.05, number of observations=111,

LR chi2(7)=41.74, p>chi2=0.0000

*At time of QoL assessment

**St least T3 at time of treatment

NS not significant

Table 5 Role Physical

	OR (95 % CI)	z	$p > \|z\|$
CyberKnife	0.74 (0.30–1.80)	−0.67	NS
Enucleation	0.29 (0.10–0.84)	−2.28	0.023
Gender (female/mal)	1.00 (0.50–2.00)	−0.01	NS
Age* (years)	0.98 (0.95–1.01)	−1.22	NS
Large tumor size**	1.03 (0.45–2.35)	0.08	NS
Metastatic progression*	0.27 (0.06–1.14)	−1.78	NS
Comorbidities (#)	0.49 (0.28–0.85)	−2.52	0.012

Ordered logistic regression: log likelihood=−209.72, number of observations=112,

LR chi2(7)=27.83, p>chi2=0.0002

*At time of QoL assessment

**At least T3 at time of treatment

NS not significant

Table 6 Role Emotional

	OR (95 % CI)	*z*	$p > \|z\|$
CyberKnife	0.54 (0.22–1.39)	−1.26	NS
Enucleation	0.20 (0.07–0.57)	−3.00	0.003
Gender (female/male)	0.48 (0.23–0.99)	−2.00	0.046
Age (years)*	0.95 (0.92–0.99)	−2.87	0.004
Large tumor size**	1.00 (0.46–2.20)	0.00	NS
Metastatic progression*	0.31 (0.08–1.23)	−1.67	NS
Comorbidities (#)	0.52 (0.30–0.90)	−2.33	0.020

Ordered logistic regression: log likelihood=−192.64, number of observations=111,

LR chi2(7)=36.52, p>chi2=0.0000

*At time of QoL assessment

**At least T3 at time of treatment

NS not significant

Table 8 Vitality

	OR (95 % CI)	*z*	$p > \|z\|$
CyberKnife	1.09 (0.43–2.79)	0.18	NS
Enucleation	0.69 (0.24–2.04)	−0.66	NS
Gender (f/m)	0.86 (0.41–1.81)	−0.39	NS
Age* (years)	0.99 (0.96–1.03)	−0.44	NS
Large tumor size**	1.19 (0.49–2.88)	0.39	NS
Metastatic progression*	0.37 (0.07–1.83)	−1.22	NS
Comorbidities (*n*)	0.44 (0.25–0.76)	−2.93	0.003

Ordered logistic regression: log likelihood=−135.91, number of observations=111,

LR chi2(7)=14.50, p>chi2=0.043

*At time of QoL assessment

**At least T3 at time of treatment

NS not significant

[17]. In the present study, we have now performed a QoL analysis of uveal melanoma patients treated with radiosurgery after 3-year follow-up versus patients treated with enucleation and a melanoma-free age-matched patient collective. In our statistical analysis, we identified no significant differences in QoL between the stereotactic radiosurgery treatment group 3 years after therapy and the age-matched control group. This can be interpreted as an excellent result in tumors suitable for eye-conserving therapy. As QoL was determined 37.9 months after stereotactic radiosurgery versus 42.9 months after enucleation, we can now present a significant follow-up period relative to the overall life expectancy in this patient collective. As radiation retinopathy develops slowly yet progressively following radiation exposure [22], more long-term results after radiosurgery are warranted.

PF, RP, and RE were significantly lower in the enucleation group than either the stereotactic radiosurgery or control groups. Preservation of the globe is the goal whenever possible. Although half of the patients in the CyberKnife treatment group presented with T3 tumors, enucleated tumors were still significantly larger than tumors treated by radiosurgery. One must keep in mind that in uveal melanoma, tumor size according to AJCC staging predicts prognosis with the risk of metastasis and death increasing twofold with each increasing melanoma category [23], and metastatic disease remains the single leading cause of death over time [24]. However, while the metastatic status had a significant influence on GH, SF, and MH in multivariate analysis, the impact of tumor size was insignificant for all parameters, indicating that perceived risk for metastasis due to larger tumor size is a minor factor at best. Amaro et al. reported the greatest effect for the items PF, VT, SF, and MH after enucleation [20]. In the present study, patients who underwent enucleation reported their greatest deficits in PF, RP, and RE after a mean duration of 42.9 months,

Table 7 General Health

	OR (95 % CI)	*z*	$p > \|z\|$
CyberKnife	1.25 (0.48–3.27)	0.45	NS
Enucleation	0.59 (0.19–1.80)	−0.93	NS
Gender (female/male)	0.72 (0.34–1.54)	−0.85	NS
Age* (years)	0.98 (0.95–1.01)	−1.15	NS
Large tumor size**	1.34 (0.54–3.29)	0.63	NS
Metastatic progression*	0.15 (0.03–0.89)	−2.09	0.036
Comorbidities (*n*)	0.41 (0.23–0.72)	−3.11	0.002

Ordered logistic regression: log likelihood=−119.62, number of observations=115,

LR chi2(7)=24.36, p>chi2=0.0010

*At time of QoL assessment

**At least T3 at time of treatment

NS not significant

Table 9 Social Functioning

	OR (95 % CI)	**z**	$p > \|z\|$
CyberKnife	1.09 (0.43–2.75)	0.18	NS
Enucleation	0.61 (0.21–1.76)	−0.91	NS
Gender (female/male)	0.48 (0.23–1.01)	−1.92	NS
Age* (years)	0.97 (0.94–1.00)	−1.75	NS
Large tumor size**	0.87 (0.37–2.02)	−0.33	NS
Metastatic progression*	0.15 (0.04–0.64)	-2.57	0.010
Comorbidities (*n*)	0.62 (0.36–1.08)	−1.67	NS

Ordered logistic regression: log likelihood=−144.22, number of observations=115,

LR chi2(7)=20.54, p>chi2=0.0045

*At time of QoL assessment

**At least T3 at time of treatment

NS not significant

Table 10 Mental Health

	OR (95 % CI)	*z*	$p > \|z\|$
CyberKnife	1.25 (0.52–3.01)	0.50	NS
Enucleation	1.11 (0.41–3.04)	0.21	NS
Gender (female/male)	0.43 (0.21–1.02)	−2.31	0.021
Age* (years)	0.99 (0.97–1.02)	−0.44	NS
Large tumor size**	0.95 (0.41–2.18)	−0.12	NS
Metastatic progression*	0.18 (0.03–0.99)	−1.97	0.049
Comorbidities (*n*)	0.52 (0.31–0.86)	−2.57	0.010

Ordered logistic regression: log likelihood=−192.82, number of observations=111,

LR chi2(7)=17.57, p>chi2=0.014

*At time of QoL assessment

**At least T3 at time of treatment

NS not significant

which proves the importance of visual function and its impact on the patient's QoL.

There was no significant difference in the number of comorbidities reported among the three groups, although the presence of comorbidities had a significant influence on the majority of QoL items (PF, RP, GH, VT, RE, and MH), and therefore must not be underestimated. The number of patients included in the study did not allow for assessment of specific comorbidities, which may differ in their potential to reduce QoL of individual patients.

There is a manageable amount of literature on QoL in the follow-up of uveal melanoma, and levels of anxiety, depression, and emotional problems after radiation therapy or enucleation remain controversial [13, 25, 26], with little overall difference demonstrated at later follow-up [26, 27]. Preservation of the treated eye with at least some remaining function has been reported to be of significant benefit to the QoL for many patients [28], which is in agreement with our findings. Early differences between treatments in visual function were found to be diminished by 3 to 5 years post-treatment, in parallel with the decline in visual acuity in eyes treated with brachytherapy [26].

Possible short-term advantages with respect to MH after radiation therapy have been published previously [26], but within the COMS-QOL group, patients treated with brachytherapy were more likely to experience symptoms of anxiety during follow-up than patients treated with enucleation [26]. We can now provide medium-term follow-up results, showing no significant difference in GH, VT, SF, or MH among the stereotactic radiosurgery, enucleation, and control groups.

A variety of tests have been introduced through the years to measure QoL and other patient-based outcomes in healthcare [8]. Treatment success should be based not only on medical therapy, but also on how well the interdisciplinary team can restore the patient's peace of mind [16]. The SF-12 is widely used, practical, efficient, and rapid to complete. Again, we employed the 4-week recall period of the questionnaire because it was thought that the previous 4 weeks would capture a more representative and reproducible sample of recent health, not unduly affected by daily or momentary fluctuations [29]. Our reasons for choosing this test were discussed previously [17]. In brief, we wanted to focus on uveal melanoma as not only an ophthalmologic but also a serious systemic condition, and we did not want to exceed the recommended maximum of 30 items [30], which might reduce compliance and concentration. We are planning to include the EORTC QLQ-C30 questionnaire in our clinical practice and future analyses, as it was specifically developed for cancer patients. These tests have been proven to be a reasonable combination [31].

As the study design is cross-sectional, the different patient collectives are not entirely comparable. We do acknowledge that only 49 % of patients who underwent enucleation responded to our survey. As these patients were asked to actively complete the survey at home and return it via mail, this could have led to a higher response rate in fitter patients, compared with our CyberKnife collective, where every patient was asked to complete the survey at follow-up visits. On the other hand, following eye-preserving therapy, tumor recurrence or painful amaurosis requiring enucleation might become necessary throughout further follow-up. In the literature, we found a local tumor control rate of 95 % after 3 years and 85 % after 5 years of single-dose stereotactic radiosurgery [32]. Within our stereotactic radiosurgery (CyberKnife) group, only 3 (6 %) patients had undergone previous therapy, while 18 (76 %) patients underwent enucleation due to either tumor recurrence (n=12) or secondary adverse effects (n=6). A negative effect on QoL among these patients can be assumed, caused by emotional distress and loss of function.

Given the significantly lower values in PF, RP, and RE in the enucleation group, eye-preserving stereotactic radiosurgery should be considered as first-line therapy. However, enucleation also yielded acceptable QoL results and can be recommended for patients with painful amaurosis, large tumors with extrascleral extension, or vast recurrence after primary therapy. Emotional stability was maintained in both groups throughout the follow-up period, and contributes positively to overall QoL. Treatment decisions should be individually based on tumor characteristics and patient preference with respect to visual function, mental distress, and appearance.

Compliance with ethical standards

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Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing

arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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