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research article

Prognostic factors of choroidal melanoma in Slovenia, 1986–2008

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Introduction. Choroidal melanoma is the most common primary malignancy of the eye, which frequently metastasizes. The Cancer Registry of Slovenia reported the incidence of choroid melanoma from 1983 to 2009 as stable, at 7.8 cases/million for men and 7.4/million for women. The aim of the retrospective study was to determinate the prognostic factors of survival for choroidal melanoma patients in Slovenia.

Patients and methods. From January1986 to December 2008 we treated 288 patients with malignant choroidal melanoma; 127 patients were treated by brachytherapy with beta rays emitting ruthenium-106 applicators; 161 patients were treated by enucleation.

Results. Patients with tumours thickness < 7.2 mm and base diameter < 16 mm were treated by brachytherapy and had 5- and 10-year overall mortality 13% and 32%, respectively. In enucleated patients, 5- and 10-year mortality was higher, 46% and 69%, respectively, because their tumours were larger. Thirty patients treated by brachytherapy developed local recurrence. Twenty five of 127 patients treated by brachytherapy and 86 of 161 enucleated patients developed distant metastases. Patients of age ≥ 60 years had significantly lower survival in both treatment modalities. For patients treated by brachytherapy the diameter of the tumour base and treatment time were independent prognostic factors for overall survival, for patients treated by enucleation age and histological type of tumour were independent prognosticators. In first few years after either of treatments, the melanoma specific annual mortality rate increased, especially in older patients, and then slowly decreased.

Conclusions. It seems that particularly younger patients with early tumours can be cured, whereby preference should be given to eyesight preserving brachytherapy over enucleation.

Key words: choroid melanoma; therapy; brachytherapy; prognostic factors

Introduction

Uveal melanoma is the most common primary malignancy of the eye.[1] Approximately 90% of all uveal melanoma develop in the choroid, 7% in the ciliary body and 3% in the iris.[2] The disease is more common in older age, with the highest incidence at about 60 years of age.[1,2] For the period 1983–1994, the incidence of uveal melanoma in 16 European countries was analysed by the European Cancer Registry (EUROCARE).[3] The incidence in Europe was found ascend from South to North, being 2/million inhabitants in Spain and southern Italy and more than 8/million in Denmark and Norway. In Slovenia, the incidence of choroid melanoma between 1983-2009 was stable, at 7.8 cases/million for men and 7.4/million for women.[4]

In the majority of patients, the biopsy of tumour is not indicated because the accuracy of clinical diagnosis is reaching 99%.[5] However, there is no agreement

about the optimal therapy.[6-10] Until development of eye conserving therapies in 1960's, for more than 100 years, enucleation was the only mode of treatment. The first among eye conserving approaches was the plaque brachytherapy[9,11-14], followed by proton beam[15-17] and helium ion radiotherapy[18-20], stereotactic radiotherapy, transscleral or transretinal local resection[10,21,22], and phototherapy brachytherapy[23], several types of radioactive plaques with photon emitting isotopes were used, including cobalt-60, iodine-125, and iridium-192. Beta emitting plaques with ruthenium (106Ru/106Ro), however, were introduced in 1964 by Lommatzsch.[24-26]

In Slovenia, treatment of choroidal melanoma by brachytherapy with ruthenium plaques using the Lommatzsch method was introduced in 1985 by the Eye Clinic at the University Clinical Centre Ljubljana in collaboration with the Institute of Oncology Ljubljana.[27,28] Before that time, the only available treatment was enucleation of the diseased eye. The aim of this retrospective study was to evaluate these two modalities in the treatment of choroidal melanoma in Slovenia during the period from 1986 to 2008 and to determinate the prognostic factors of survival for choroidal melanoma patients in Slovenia.

Patients and methods

Patients

The database of the Cancer Registry of Slovenia was used for identification of patients with the diagnosis of choroidal melanoma in Slovenia in the years 1986–2008.[4] The medical records of identified patients from the Eye Hospital of the University Clinical Centre Ljubljana and from the Department of Ophthalmology of the University Medical Centre Maribor were reviewed for relevant information on clinical characteristics, treatment and outcome. The diagnosis of choroidal melanoma was based on clinical features and full ophthalmologic examination, indirect ophthalmoscopy, fundus photography, ultrasonography and fluorescein angiography. At the time of diagnosis, the patients were evaluated by chest radiography, lymph gland and liver ultrasonography[29] and routine blood tests. Genetic testing was not done because it was not available at the time of the study.

The study was approved by the institutional review board and was carried out according the Helsinki Declaration.

Treatment

Applicators manufactured by Bebig (Eckert& Ziegler BEBIG Gmbh, Berlin; later Amersham, GB) were used. The applicators were concave, shell-shaped, with Ru-106/Ro-106 isotope covering the concave surface as a thin, insoluble film and emitting beta rays with the energy of 3.54 MeV and half-life of 373 days. The tumours were localized by transillumination and indirect ophthalmoscopy, and the applicators were sutured to the sclera. The dose at the tumour apex was aimed to be about 120 Gy. The applicator was removed after expiration of appropriate time.

Treatment was selected according to the tumour size: patients with tumours ≤ 16 mm in diameter and ≤ 7.2 mm thick, with useful vision preserved, were treated by brachytherapy, patients with larger tumours had enucleation. The enucleation was performed in general anaesthesia.

First follow-up visits took place one month after the procedure, in 3-month intervals during the first year and once a year thereafter. At each follow up visit, patients underwent ophthalmologic examinations with indirect ophthalmoscopy, fundus photography and ultrasonography.

Statistical methods

For comparative analyses, the Fisher exact test for two proportions as well as t-test and Mann-Whitney test for data of two independent groups were used. Survival estimates were carried out using the Kaplan-Meier method and reported at 5 and 10 years follow up. The difference between the survival curves was evaluated by means of a log-rank comparison. Multivariate survival analysis for study of an independent effect of various parameters that appeared statistically significant on univariate analysis to treatment outcome and survival was performed according to Cox's proportional hazard models with backward stepwise selection. The end points of survival analysis were locoregional control (LRC, persistent disease or locoregional recurrence considered as an event), disease-free survival (DFS, appearance of loco-regional recurrence or systemic metastases considered as event), disease-specific survival (DSS, melanoma related death considered as event) and overall survival (OS, death from any cause considered as event) which were measured from the first day of therapy. These statistical analyses were performed by using SPSS version 18.0 (SPSS Inc., Chicago, IL)

TABLE 1. The characteristics of patients and tumours by treatment modality

	Treatment		
	Brachytherapy	**Enucleation**	**Total**
All patients	130	161	291
Excluded	3 palliations	-	3
Treated	127	161	288
Gender			
Man	58	84	142
Women	69	77	146
Age (median)			
Men	58 (29-74)	58 (19-86)	
Women	60 (22-89)	61 (23-92)	
T-stage (AJCC)			
1	38		
2	69		
3	8		
No data	12		
Thickness			
< 3 mm	11		
3.1-5.0 mm	64		
5.1-7.2 mm	49		
> 7.8 mm	3		
No data	0		
Basal diameter			
≤ 10 mm	52		
10,1-12,0 mm	38		
> 12 mm	25		
No data	12		
Histology		161	
Spindle cell		33	
Epithelioid		38	
Mixed		23	
No data		37	

AJCC = American Joint Committee on Cancer

and nonlinear regression Gaussian curve fitting was performed by GraphPad Prism version 5. All tests were two-sided and a P-value of 0.05 was considered statistically significant.

Results

Clinical records of 288 patients with choroidal melanoma treated from January 1986 to December 2008 at the Eye Hospital of the University Clinical Centre Ljubljana and from the Department of Ophthalmology of the University Medical Centre Maribor were reviewed. The follow-up close-out date was December 31, 2013. Median follow-up of all patients was 15 years (range, 4–27 years). In December 2013, 130 patients were alive. The cause of death was melanoma in 107 patients and 51 patients died of melanoma unrelated disease; 20 among them died of other malignant diseases. The characteristics of patients and tumours are shown in Table 1.

Survival

In univariate analysis of all patients, the LRC and DFS were better in enucleation than in brachytherapy group and better in females than in males. Patients < 60 years had better DFS, DSS and OS than older patients. In brachytherapy group, females had statistically better LRC and DFS than males; younger patients had better DSS and OS than older patients. Tumour thickness < 6 mm was associated with better LRC and DFS than thicker tumours, while the base diameter < 11 mm was a good prognostic sign for LRC; DFS, DSS and OS. The treatment time influenced LRC and DFS, while the dose-rate had no influence of the outcome of the treatment. In the enucleation group, age and histology influenced DFS, DSS and OS, while sex had no effect on survival. The detailed data of survival are presented in Tables 2–4.

In multivariate analysis for all patients, gender was independent prognostic factor for LRC, while first treatment and age were independent prognostic factors for DFS, DSS and OS. In the brachytherapy group, gender was independent prognostic factors for LRC; treatment time for LRC and DFS; base diameter for DFS and OS. The age was independent prognostic factor for DFS and OS. In enucleation group, age and histology were independent prognostic factors for DFS and DSS, while on OS influenced only age (Table 5).

Second treatment

In 30 patients treated by brachytherapy, a local recurrence of the tumour occurred. The second application of ruthenium plaque was performed in 13 of these patients, and in 17 patients had enucleation: 12 patients - because of extent of the recurrent tumour and 5 patients - because of the treatment-related side effects (glaucoma, cataract). The eyes were enucleated from 7 months to 18 years (median 24 months) after the first brachytherapy (Figure 1).

TABLE 2. Univariate analysis of survival: all patients (N = 288)

	n	LRC (%)			DFS (%)			DSS (%)			OS (%)		
		5 yrs	10 yrs	p	5 yrs	10 yrs	p	5 yrs	10 yrs	p	5 yrs	10 yrs	p
All	288	90	88	-	65	50	-	76	58		68	46	-
Ruthenium	127	78	75	0.000	71	60	0.014	92	79	0.000	87	68	0.000
Enucleation	161	100	100		60	42		64	42		54	31	
Men	142	85	82	0.026	61	51	0.673	74	61	0.647	66	47	0.952
Women	146	95	93		69	49		78	55		70	46	
< 60 years	150	89	86	0.648	74	58	0.002	86	68	0.000	84	64	0.000
≥ 60 years	138	90	90		56	40		65	47		52	28	

DFS = disease free survival; DSS = disease specific survival; LRC = loco-regional control; n = number of patients; OS = overall survival; yrs = years

TABLE 3. Univariate analysis of survival: patients treated by brachytherapy (N = 127)

		LRC (%)			DFS (%)			DSS (%)			OS (%)		
	n	5 yrs	10 yrs	p	5 yrs	10 yrs	p	5 yrs	10 yrs	p	5 yrs	10 yrs	p
Men	58	66	60	0.003	60	49	0.039	90	76	0.703	87	67	0.859
Women	69	89	87		81	69		93	81		88	70	
< 60 years	68	76	71	0.305	76	66	0.156	98	89	0.002	98	83	0.000
≥ 60 years	59	80	80		65	51		84	65		75	52	
T-stage													
1	38	79	79		73	67		97	84		94	71	
2	69	79	74	0.451	72	57	0.354	90	75	0.378	86	72	0.508
3	8	60	40		45	45		86	86		0	50	
Tumour thickness													
2-5.9 mm	97	83	82	0.003	74	66	0.021	92	79	0.489	86	68	0.724
6-.2 mm	29	64	54		64	39		96	80		96	70	
Base													
< 11 mm	61	83	83	0.043	80	72	0.002	96	84	0.024	96	77	0.002
≥ 11mm	54	70	64		60	45		87	72		78	64	
Dose rate Top (Gy/h)													
≥ 108 Gy	53	81	78	0.302	74	66	0.099	95	84	0.280	87	72	0.690
< 108 Gy	52	74	68		68	46		89	72		87	62	
Dose- rate base (Gy/h)													
≥ 532	53	82	74	0.708	74	57	0.804	95	81	0.665	87	69	0.862
< 532	52	74	71		68	55		89	75		87	65	
Treatment time													
≤ 96 hours	52	87	84	0.015	80	72	0.004	95	84	0.400	89	74	0.565
> 96 hours	53	68	62		62	40		89	71		85	60	

DFS = disease free survival; DSS = disease specific survival; LRC = loco-regional control; n = number of patients; OS = overall survival; yrs = years

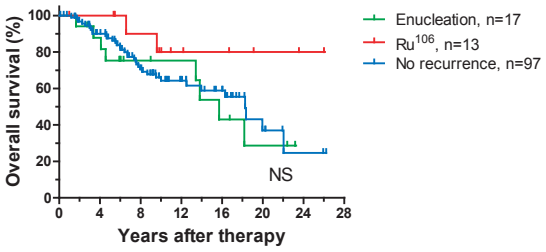

FIGURE 1. Overall survival of patients treated by brachytherapy after treatment of recurrence.

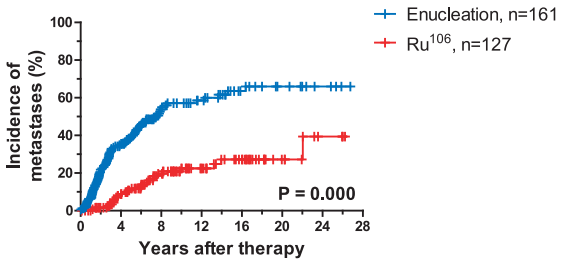

FIGURE 2. Incidence of distant metastases according to the type of treatment.

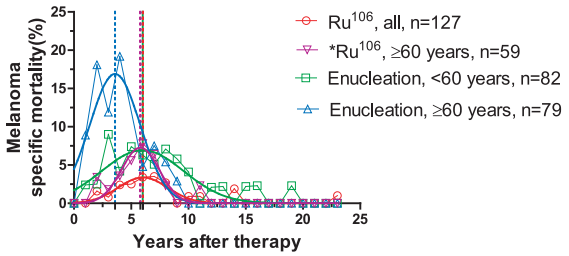

FIGURE 3. Percentage of annual post-treatment melanoma specific mortality according to the type of treatment. *There was no peak in ruthenium treated patients < 60 years.

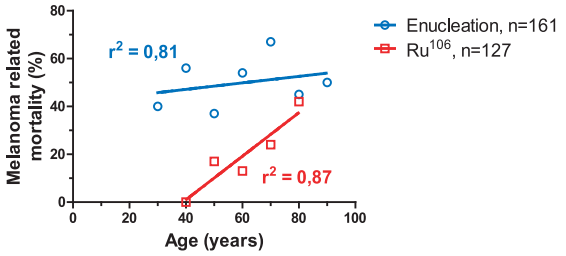

FIGURE 4. Linear regression analysis of melanoma related mortality per age decades, according to the type of treatment. Points represent percent mortality rate for the elapsed decade. No patient less than 40 years who was treated with Ru-106 died of melanoma.

Distant metastases

Twenty-five of 127 patients treated by brachytherapy and 86 of 161 those treated by enucleation developed systemic metastases. Seventy per cent of all metastases were localized in the liver. The actuarial rates of metastases by treatment modality are depicted in Figure 2. At 5 and 10 years, the incidences were 39% and 57%, respectively, for enucleated patients, and 11% and 21%, respectively, for irradiated patients ($P < 0.001$).

In patients treated by brachytherapy, half of the metastases developed in 5 years, and in those treated by enucleation in 2.6 years.

Annual melanoma specific mortality rate

The mortality of patients was increased in the first few years after treatment and then slowly returned to pre-treatment values. Melanoma specific mortality rate is displayed in Figure 3.

The peak percentage of annual melanoma specific mortality after treatment was achieved at 3.6 years for patients older than 60 years treated by enucleation and at approximately 6 years for younger enucleated patients and for all patients treated with brachytherapy. The irradiated patients below 60 years contributed little to the peak because of low mortality rate.

No patient from brachytherapy group aged below 40 years died of melanoma. In brachytherapy treated patients the mortality began to increase after the age of 40 and reached 40 % in 70–80 year's age group. In patients treated by enucleation, the mortality started to increase one decade earlier: the rise started with about 40% and reached about 70 % in patient's 80–90 years of age (Figure 4).

Complications

Because of retrospective character of the study, acute complications were not systematically recorded. For chronic complications patients were reviewed annually. Post-radiation retinopathy started to appear after two years and was documented in 18 patients (12 mild, 6 severe), neovascular glaucoma in 5 patients and cataract in 6 patients. None of the patients had optic neuropathy.

Vision after treatment

After brachytherapy, the eye was retained in all patients and the vision was assessed in 112 patients. Compared to pre-treatment status, 22 (19.6%) patients had better visual acuity; in 12 (10.7%) patients the vision was unchanged while in 78 (69.6%) patients the acuity of vision was worse. The majority of brachyradiotherapy patients retained vision which was better than counting fingers.

Discussion

Our retrospective study reports results of the treatment of patients with choroidal melanoma in Slovenia from 1986 to 2008. In our study, the overall and specific mortality rate in patients treated by enucleation was higher mainly because larger tumours were selected for enucleation as compared to those treated by brachytherapy. Brachytherapy could be used only for selected tumours, depending on their size, location and shape of applicators, for which a satisfactory dose distribution of dose can be achieved. Because no data about the dimensions of the enucleated tumours was available, comparison of results between the two treatment modalities by tumour stage could not be made.

The randomized as well as nonrandomized studies reported no difference in survival rates in patients treated either by enucleation or brachytherapy when matched by the stage, age and other prognostic parameters.[6-8,11,12,30-33] The largest of these studies was the COMS, which included 1317 patients and prospectively compared on randomized fashion enucleation and brachytherapy. There was no statistical difference in 5- and 10-year OS between the two treatment groups.[30] In the matched pairs study of Guthoff *et al.* melanoma specific survival at 12 years of follow-up was 77.9% in irradiated patients and 78.6% in enucleated patients (P > 0.05).[31] When the OS at 10 years of our patients treated by brachytherapy was compared with that from COMS study, no difference could be observed: 32% vs. 35%; similarly, the DSS at 10 years in our series was 79% and was comparable with DSS reported by Guthoff.

There are several prognostic factors for outcome of the choroidal melanoma, including age[30-33], gender[33], basal tumour diameter[34], tumour thickness[33-37], T-stage[35], cell morphology[1,7,33,38] and various genetic changes of the tumour, especially monosomy of chromosome 3.[33,39-41] Some of them appeared statistically significant also in the present study, although the strength of our results should be interpreted with caution. Namely, we only had complete information on age and gender of the patients, histology of the enucleated tumours, and data of tumour diameter, thickness, irradiation dose on the base and top of the tumour and the treatment time for brachytherapy patients, but not also on some other highly relevant prognosticators (e.g. genetic alterations), which limits the strength of statistical analysis.

In both treatment groups, the post-treatment annual mortality related to melanoma at first increased, as expected due to systemic metastases, but few years later it decreased to a few or zero percent. In patients of 60 years or more who were treated by enucleation, mortality reached its peak of 18% at 3.7 years after treatment, while in patients younger than 60 years the peak was reached at six years after treatment and was 7%. Patients treated by brachytherapy fared better: regardless of age, six years after treatment completion the peak mortality was 3%. However, the mortality of irradiated patients aged ≥ 60 years reached the peak of 7% at 6 years post-treatment, while no increase in mortality was noticed among younger patients, probably due to the small number of deaths.

The increase in annual mortality following enucleation was first observed by Zimmermann.[42,43] He re-analysed the data of Paul *et al.*[38] who monitored 2652 patients for 40 years and found a steep increase in mortality following enucleation. In this study, the peak of 8% was reached at 2 years after enucleation, slowly diminishing during the next few years to the "normal" 1%.[43,44] Similarly, Seddon *et al.* reported the increase in mortality to 6.5 % in the first 2–3 years after treatment and slowly return to »normal« 1% during the next 7 years.[45]

The post-treatment increase in melanoma related mortality can be attributed to the loss of antiangiogenic activity of the primary tumour after its removal or destruction. Uveal melanoma cells produce angiostatin, growth inhibitor of metastatic foci[46,47], which was found to be present in the circulation only up to five days after the removal of the primary tumour.[48,49]

Damato *et al.*[33] found that the probability of metastases was greater in older patients as their

TABLE 4. Univariate analysis of survival: patients treated by enucleation (N = 161)*

		DFS (%)			DSS (%)			OS (%)		
	n	5 yrs	10 yrs	p	5y	10 yrs	p	5 yrs	10 yrs	p
Men	84	62	51	0.154	63	51		53	34	0.775
Women	77	59	33		65	34	0,275	56	27	
< 60 years	82	73	52	0.001	76	52		74	51	0.000
≥ 60 years	79	49	30		50	30	0.000	34	10	
Spindle cell	33	74	70		81	72		66	49	
epithelioid	38	56	36	0.050	61	33	0.029	55	24	0.026
Mixed cell	23	62	28		67	24		52	15	

*None of enucleated patients had local recurrence; DFS = disease free survival; DSS = disease specific survival; n = number of patients; OS = overall survival; yrs = years

TABLE 5. Multivariate analysis of survival of all patients (N = 288)

			HR	95% CI		p
				lower	upper	
All patients	LRC	First treatment	40.842	5.565	299.717	0.000
		Gender	2.658	1.245	5.678	0.012
	DFS	First treatment	1.628	1.144	2.316	0.007
		Age < 60 years vs. ≥ 60 years	1.800	1.275	2.540	0.001
	DSS	First treatment	3.937	2.509	6.178	0.000
		Age < 60 years vs. ≥ 60 years	2.534	1.714	3.747	0.000
	OS	First treatment	3.153	2.218	4.480	0.000
		Age < 60 years vs. ≥ 60 years	3.818	2.710	5.377	0.000
Ruthenium	LRC	Gender	2.306	1.013	5.251	0.047
		Treatment time (≤ 96 h *vs.* > 96 h)	2.841	1.220	6.623	0.015
		Treatment time (≤ 96 h vs. > 96 h)	2.674	1.276	5.587	0.009
	DFS	Base (< 11 mm *vs.* ≥ 11 mm)	2.519	1.015	6.250	0.046
		T-stage	2.320	1.002	5.376	0.050
	DSS	Age (< 60 years *vs.* ≥ 60 years)	4.762	1.709	13.333	0.003
	OS	Base (< 11 mm *vs* v11 mm)	3.610	1.391	9.434	0.008
		Age (< 60 years *vs.* ≥ 60 years)	5.650	2.538	12.658	0.000
Nucleation	LRC	-	-	-	-	-
	DFS	Age (< 60 years *vs.* ≥ 60 years)	2.132	1.149	3.968	0.016
		Histology S *VS* E VS M	1.467	1.000	2.151	0.050
	DSS	Age (< 60 years *vs.* ≥ 60 years)	2.326	1.229	4.403	0.009
		Histology S *vs.* E *vs.* M	1.555	1.052	2.298	0.027
	OS	Age (< 60 years vs. ≥ 60 years)	3.876	2.222	6.757	0.000
		Histology (S *vs.* E *vs.* M)	1.444	1.051	1.983	0.023

CI = confident interval; DFS = disease free survival; DSS = disease specific survival; E = epitheloid; HR = hazard ratio; LRC = loco-regional control; M = mixed cell; n = number of patients; OS = overall survival; S = spindle cell

tumours grew longer and had more time for accumulation of chromosome instabilities, making the tumour more malignant and more prone to metastasize. Accordingly, the younger patients should have smaller and perhaps less malignant tumours, and the appearance of metastases is less likely. It is assumed that following primary tumour removal, metastases in younger patients reach the lethal tumour mass at a later time. The peak in melanoma-related mortality in younger enucleated patients from our series appeared 2.5 years later than in older counterpart, confirming this assumption. However, not all patients from advanced age group have advanced primary tumour and metastases. In our series, 59 patients ≥ 60 years had primary tumours small enough to be treated by brachytherapy. The annual melanoma related mortality curve suggests that the burden of their metastases was also smaller, and reached the lethal mass at a later time. The synchronous peaks of enucleated patients < 60 years and of irradiated patients ≥ 60 years suggests that the burden of metastases in enucleated group, was similar in these two groups (Figure 3).

There is no good scientific evidence that treatment can prolong patients' life.[33] The increase in annual post-treatment mortality rate implies that the life of some patients might be shortened due to

the therapy, particularly of older ones. This observation and the fact that some tumours and their metastases grow very slowly raise the question when the treatment of uveal melanoma can be withheld. The COMS study showed that the estimated risk of death at 5 years of follow-up in 42 untreated patients was 50%, and risk of 1317 patients treated by a standard method, was 18%.[50] It seems that treatment in older patients without eyesight problems, in spite of evident metastases, could be postponed until the problems eventually ensue. On the other hand, it may be assumed that some of the younger patients are without micrometastases at the time of therapy and can be cured by the early treatment. Indeed, in our study, none of the patients younger than 40 years from brachytherapy group died of metastases, while death of metastases in older patients steeply increased with age (Figure 4).

To conclude, treatment-specific and age-dependent pattern of -related mortality was confirmed in our study, confirming observation of other authors. For quality of life reasons we believe that preference should be given to eyesight preserving brachytherapy or other eye preserving treatments of choroidal melanoma over enucleation, if the size and location are suitable even though the definite opinion on the best treatment differed in the literature.[51,52]

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