Episcleral Brachytherapy In Portugal: Lessons Learned After 100 Patients

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ABSTRACT

Purpose: To evaluate the Portuguese Reference Center practice of Episcleral Brachytherapy (EBT) for uveal melanoma, with respect to local control, survival rates, metastatic rates and side effects; and compare those results with the international literature.

Material and methods: Prospective and consecutive study of patients referred to the Ocular Oncology Reference Center, Coimbra treated with EBT between November 2013 and September 2018. Follow-up data was collected regarding local control, survival, distant metastasis and side effects from treatment. Analysis was performed on factors influencing treatment outcomes and radiation side-effects.

Results: A total of 100 patients underwent EBT, but only 98 had a follow-up longer than 2 months. Ninety-six percent of patients achieved local control and the incidence rate of treatment failure was 2.2/100 person-years. The incidence rate of mortality was 6.0/100 person-years and for developing metastasis was 7.3/100 person-years. The most frequent radiation side-effect was cataract and the incidence rate for the development of radiation retinopathy was 31.5/100 person-years.

Conclusions: Our results demonstrate excellent clinical outcome for local control after treatment with ^{125}I EBT, with satisfactory overall survival and metastasis-free survival rates. The rate of ocular toxicity is acceptable, considering the high rates of local control and globe preservation. Therefore, EBT is a valid option for globe-sparing treatment in opposition to enucleation, with the advantage of better cosmetic results.

Keywords: Episcleral Brachytherapy; Uveal melanoma; Outcomes

RESUMO

Objectivos: Avaliar o desempenho do Centro de Referência Português de Onco-Oftalmologia no que diz respeito ao controlo local, taxas de sobrevida, taxas de metastização e efeitos secundários da Braquiterapia Episcleral (BTE), e comparar estes resultados com a literatura.

Material e métodos: Estudo prospectivo e consecutivo que incluiu os doentes referenciados ao Centro de Referência de Onco-Oftamologia por melanoma da úvea e tratados com BTE entre Novembro 2013 e Setembro 2018. Foram recolhidos dados de follow-up no que diz respeito ao controlo local, sobrevida, metastização e efeitos secundários. Foi igualmente realizada a análise de factores preditivos dos resultados e efeitos secundários.

Resultados: Um total de 100 doentes realizou BTE mas apenas 98 completaram *follow-up* de pelo menos 2 meses. Noventa e seis por cento dos doentes atingiram controlo local do tumor e a taxa de incidência de falência do tratamento foi de 2,2/100 pessoa-anos. A taxa de incidência da mortalidade foi de 6,0/100 pessoa-anos e a de desenvolvimento de metástases foi de 7,2/100 pessoa-anos. O efeito secundário mais frequente foi o desenvolvimento de catarata e a taxa de incidência de retinopatia da radiação foi de 31,5/100 pessoas-ano.

Conclusões: Os nossos resultados mostram um excelente desempenho no que diz respeito ao controlo local após tratamento com BTE, com taxas de sobrevida e metastização satisfatórias. A taxa de toxicidade ocular é aceitável considerando os altos níveis de controlo local da doença. Assim, a BTE é uma opção válida como tratamento conservador, em contraste com a enucleação, preservando a estética facial.

Palavras-chave: Braquiterapia Episcleral; Melanoma da úvea; Resultados

INTRODUCTION

Uveal melanoma is the most common primary intraocular tumor in adulthood and accounts for about 3-5% of all melanomas[1,2]. The incidence varies with sex, age, race and latitude[1]. In Europe, standardized incidence rates diverge from less than 2 cases per 1.000.000 in Southern countries as Spain and Italy, to 4-6/1.000.000 in Central Europe, up to more than 8/1.000.000 in Northern Countries like Sweden and Denmark[3]. Uveal melanomas include tumors arising from choroidal melanocytes in more than 90% of cases, but they can also develop from the ciliary body or the iris[4].

Enucleation was the treatment of choice for uveal melanomas until the mid-20th century. After the 70s, the controversy about the negative effects of enucleation described in the "*Zimmerman Hypothesis*" allowed the development of other therapeutic alternatives, especially globe-sparing approaches[5]. The two-multicenter randomized clinical trials from the Collaborative Ocular Melanoma Study (COMS) group contributed to establishing the pivotal role of episcleral brachytherapy (EBT) in the treatment of medium and some large melanomas, thus becoming the most common globe-preserving treatment for uveal melanoma in the world. The COMS study for patients with medium melanomas showed no significant differences in overall survival rates at 5 and 12 years between groups randomized to enucleation or EBT[6,7]. In the trial for large melanomas, the 5 and 10-year cumulative tumor-related mortality rates were similar, showing no advantage in pre-enucleation irradiation EBT[8,9].

Currently, EBT allows the local high-dose irradiation of the tumour with excellent 5-year local control rates around 89.5% and 5-year treatment failures of 10.3%[10].

The efficacy of EBT has been widely established throughout large institutions around the world, with great experience and expertise coming from hundreds of patients treated. However, it is important to investigate the results of this treatment modality in smaller institutions to understand if the same results can be translated into smaller practices and countries. Starting November 2013, Portugal implemented an EBT Program in the National Ocular Oncology Reference Centre (Centro Hospitalar e

Universitário de Coimbra) allowing Portuguese patients to be treated in their own country. The purpose of this study was to evaluate the Portuguese results of EBT for uveal melanoma, with respect to local control, survival rates, metastatic rates and side effects; and compare these results with those of international centres.

MATERIAL AND METHODS

Study Participants

This is a prospective case series of 100 patients treated with ^{125}I EBT for uveal melanoma at the Ocular Oncology Portuguese Reference Center, Centro Hospitalar e Universitário de Coimbra (Portugal) between November 2013 and September 2018. Based on the COMS classification system and the guidelines from the American Brachytherapy Society[11], EBT treatment was proposed to: (1) all patients with medium-sized melanomas; (2) patients with small melanomas with documented growth; and (3) some patients with large melanomas with potential for visual conservation, provided that plaques allowing for adequate safety margins were available. Cases of circumpapillary or peripapillary melanomas that could not be correctly irradiated with EBT were offered proton beam irradiation. Large-sized melanomas with no potential for visual conservation, extra-ocular extension greater than 2 mm and no possibility of adequate irradiation with EBT plaques were offered enucleation. Any evidence of metastatic uveal melanoma or any other cancer was an exclusion criterion for EBT. All patients were informed about the treatment and gave written consent. Data was registered for all patients including general demographic, past medical and family history and ophthalmological examination data.

Clinical evaluation

All patients underwent complete ophthalmological evaluation including best corrected visual acuity (BCVA), dilated fundus examination, retinography [Nikon Digital SLR Camera D7000 (Nikon Corporation, Japan) mounted on a TRC-NW7SF Mark II Retinal Camera (TopCon Corporation, Japan)] and measurements of tumor dimensions using B-mode ultrasound with vector A (*Ultra Scan Imaging SystemTM and UBM Plus-P40TM, Paradigm, Medical Industries, Inc., USA*). Systemic extension was ruled out by liver ultrasound, abdominal CT or hepatic MRI and general blood tests with complete blood count, liver and renal function markers.

Treatment failure was defined by any degree of enlargement of the residual tumor in base or height detected by ophthalmoscopy or ultrasonography[12]; or extrascleral extension greater than 2 mm. In all these cases, secondary enucleation was proposed to the patient.

Treatment Protocol

The tridimensional reconstruction of the tumor and adjacent ocular structures at risk was obtained based on ophthalmological observation and imaging exams. Treatment plannings were made using the Plaque Simulator® Software, (version 5.3.9, *Eye Physics LLL, EUA*), considering the dose prescription of 85Gy to the tumor apex or to 5mm tumour thickness, whichever the highest.. Accordingly, duration of the treatment, plaque size, number and distribution of ^{125}I seeds to provide the prescribed dose to the tumor surface and margins and radiation doses to the adjacent structures (sclera, optic nerve, macula, lens) were determined. Surgical planning, especially plaque relation to extra-ocular muscles was evaluated prior to the surgery, to prepare for the possible need of temporary disinsertion. Different sized COMS-type plaques (*IBT BEBIG, Inc*) and ROPES plaques (*Radiation Oncology Physics and Engineering Services Ltd, Australia*) were adequately prepared with ^{125}I seeds (*IBT BEBIG I25.S16, classes A04 to A14*) and used for the treatments.

All patients underwent surgery with general anesthesia and the radioactive plaque was sutured to the sclera underlying the tumor, accounting for a 2-mm margin to treat presumed microscopic disease extension. Pupillary transillumination was used to mark the base of the melanoma and radioactive implant correct position, which was further confirmed with intraoperative ultrasound. After the procedure, the patient remained in an isolated room with radioactive protection, during the pre-established period of treatment. Once completed, the patient went back to the operating room to extract the plaque under anesthesia.

Our patients underwent follow-up at the Ophthalmology Department two weeks after the treatment, at the first month, every 3 months during the first year and every 6-months during the following 5 years. This follow-up was personalized to each patient in case of ocular or systemic complications. Complete blood tests with liver function tests, chest X-ray and abdominal ultrasound were requested as complementary studies every 6-months. An ophthalmologist from the Ocular Oncology Unit examined the eye to monitor tumor progression, detect early recurrence and evaluate acute and late radiation toxicity.

Outcomes

The primary outcome of this study was treatment failure, as defined above. Mortality rate (overall survival), metastatic disease (metastasis-free survival) and side effects of EBT, in particular the risk of developing radiation retinopathy (RR), were all secondary outcomes. Radiation retinopathy included both radiation maculopathy and radiation neuropathy. Radiation maculopathy was defined as retinal capillary bed changes (non-perfusion, microaneurysms, retinal hemorrhages), retinal exudation, retinal edema, nerve fiber layer infarctions or vascular sheathing in macular area; radiation neuropathy was considered to be present if optic disc swelling, hemorrhages and peri-papillary exudation were observed.

The change from baseline to last follow-up in tumor dimensions was also defined as exploratory outcome.

Statistical Analysis

Consecutive patients were included and no sample size calculations were performed.

The study population demographics, clinical and imaging characteristics were summarized using traditional descriptive methods. Additionally, for the primary and secondary outcomes, the incident proportion and incident rates were calculated (the latter with 95% Confidence Intervals [95% CI]). The 2- and 4-year survival rates are also described with 95% CI.

In order to test which demographic and tumor characteristics or features of brachytherapy could predict the risk of treatment failure (the primary outcome), Cox Proportional-Hazard Models were built. First, each predictor was tested on separate univariate models; all variables with $p<0.10$ were subsequently included in a multivariate model, to test for confounding. Hazard Ratios (HR) with 95% CI are reported. The same modelling strategy was used to model the secondary outcomes (overall survival, metastasis-free survival and RR-free period). The changes from baseline to last follow-up of continuous exploratory outcomes were compared with paired t-tests.

All statistics were performed on STATA (version 14.2, StataCorp LCC, College Station, TX, USA). $P< 0.05$ were considered statistically significant.

RESULTS

A total of 101 patients with uveal melanoma underwent ^{125}I EBT planning between November 2013 and September 2018, but only 98 completed a minimum follow-up of 2 months. One patient refused treatment and was lost to follow-up and another patient underwent EBT but never attended the post-operative follow-up after discharge. The median duration of follow-up was 19.4 months (interquartile range [IQR] of 9.37 to 54.07 months) and the mean age was 62 years (standard deviation [SD] of 13.2 and a range of 26-87 years) with a slight predominance of females (56.4%). The baseline demographic and clinical characteristics are summarized in **Table 1.**

The mean treatment duration was 6.2 days (SD = 1.7; range 0-10), with a prescribed dose of 85Gy to the tumor apex. Dosimetric data to adjacent ocular structures are provided in **Table 2**. Eighty-one COMS plaques and 20 ROPES plaques were used, with sizes between 12 and 20 mm.

Regarding pre-treatment tumor dimensions, mean basal diameter was 11.7 mm (SD = 2.8; range 3.1-17.95) and mean thickness 6.6 mm (SD = 2.3; range 2-13). Uveal tumour classification according to COMS and the American Joint Committee on Cancer (AJCC)[13] systems are presented in **Table 3**. No tumors with extraocular extension were treated, except for one case in which the extension was small ($\leq$ 2mm) and found at the base of the tumor within the field of action of the radioactive plaque.

Table 1 - Baseline Demographics, Clinical Evaluation and Tumor Characteristics

Demographics	
Age (years)	61.26 ± 13.19
Sex (female)	57/101 (56.44%)
Side (right)	54/101 (53.47%)
Follow-Up (months) (median)	19.37 (9.37; 54.07)
Clinical Variables	
Visual Acuity (logMAR)	1.01 ± 0.96
Tumor Type	
Choroidal	93/101 (92.08%)
Ciliary Body	5/101 (4.95%)
Iris and ciliary body	2/101 (1.98%)
Conjunctiva	1/101 (0.99%)
Tumor Location	
Posterior to the equator	35/101 (34.65%)
Macular	33/101 (32.67%)
Anterior to the equator	17/101 (16.83%)
Peripapillary	10/101 (9.90%)
Ciliary body (± Iris)	5/101 (4.95%)
Conjunctiva	1/101 (0.99%)
Tumor Diameter (mm)	11.72 ± 2.77
Tumor Thickness (mm)	6.62 ± 2.29
AJCC Stage	
I	7/100 (7%)
IIA	48/100 (48%)
IIB	43/100 (43%)
IIIA	2/100 (2%)
COMS Classification	
I	2/100 (2%)
II	92/100 (92%)
III	6/100 (6%)

Table 2 - Details of Brachytherapy

Treatment Duration (days)	6.22 ± 1.74
Plaque Type	
COMS	(81/101) 80.2%
ROPES	(20/101) 19.8%
Plaque Size (median)	15mm (12-20)
Radiation Doses (Gy)	
Apex	92.95 ± 15.25
Sclera	401.98 ± 230.94
Optic nerve	11.74 ± 4.56
Lens	27.27 ± 15.94
Macula	98.35 ± 90.08

Treatment failure and Local control

In 95.9% of cases local control was achieved and only 4.1% underwent secondary enucleation, due to treatment failure and disease progression. In other words, only 4 patients underwent secondary enucleation due to treatment failure. Thus, the incidence rate of treatment failure was 2.2/100 person-years (2.2%/year risk) **(Table 3)**. The 2-year and 4-year local control rates were 98.8% and 88.4%, respectively **(Figure 1)**. In what concerns tumor dimensions, a significate reduction from baseline to last follow-up was detected both in basal diameter (t= -10.68; p< 0.001) and thickness (t= -8.86; p< 0.001).

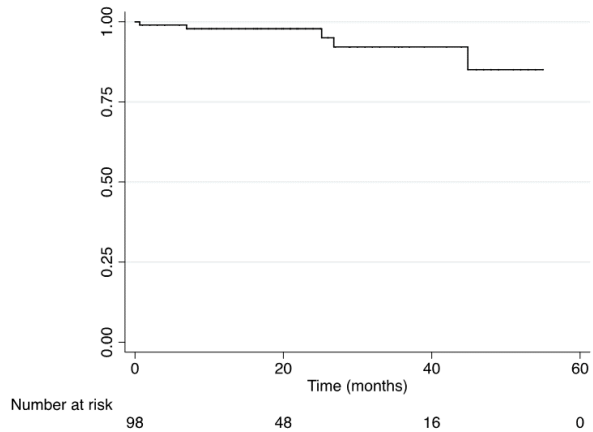

Figure 1 - Kaplan-Meier estimates of patients with local control after EBT

Survival and systemic disease

By the end of the September 2018, 11 patients had died of confirmed or suspected melanoma metastasis and 2 were still alive with systemic disease. Two-year and 4-year overall survival rates were 86.8% and 75.0%, respectively **(Figure 2a)**. The incidence rate of mortality from uveal melanoma was 6.0/100 person-years (6.0%/year risk) and the incidence rate for developing metastasis was 7.3/100 person-years (7.3%/year risk) **(Table 3)**. Regarding metastasis-free survival (MFS), the 2-year rate was 85.5% and the 4-year of 74.8% **(Figure 2b)**.

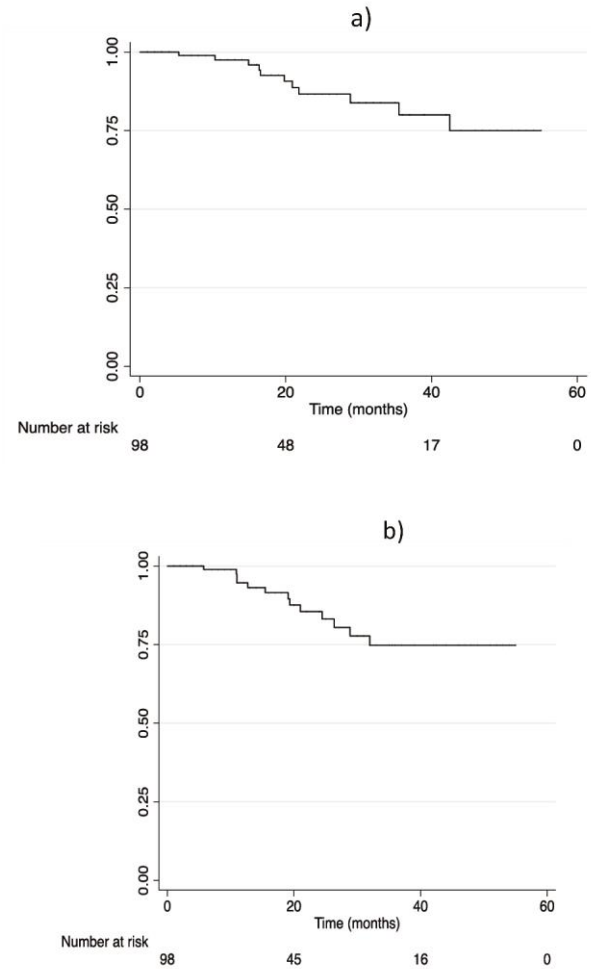

Figure 2 - Kaplan-Meier estimates of a) overall survival and b) metastasis-free survival after EBT

Treatment side-effects

Among the 98 patients followed, the most common radiation side-effect was cataract (51.5%), followed by the development of any form of radiation retinopathy (41,4%). *Rubeosis iridis* and neovascular glaucoma were also documented in 11.1% and 8.9% of the cases, respectively. For the treatment of radiation retinopathy, anti-VEGF intravitreal injections were administered, with a mean of 3.3 injections/patient. The incidence rate for the development of radiation retinopathy was 31.5/100 person-years (31.5%/year risk) **(Table 3)**. One patient underwent secondary enucleation due to uncontrolled neovascular glaucoma.

Table 3 - Descriptive Analysis of the Outcomes

Treatment Failure (primary outcome)	
Incidence Proportion	4/98 (4.1%)
Incidence Rate (95% CI)	0.022 (0.01-0.06)
Mortality (secondary outcome)	
Incidence Proportion	11/98
Incidence Rate (95% CI)	0,060 (0.03-0.11)
Metastasis (secondary outcome)	
Incidence Proportion	13/98
Incidence Rate (95% CI)	0.073 (0.04-0.13)
Radiation Retinopathy (secondary outcome)	
Incidence Proportion	38/98
Incidence Rate (95% CI)	0.315 (0.23-0.43)

CI. Confidence Interval

Exploratory Analysis of Predictors of the Outcomes

We used univariate Cox regression models to test for variables that may predict the primary outcome (treatment failure). Our analysis found no demographic, clinical or treatment variable predictive of treatment failure **(Table 4)**.

Table 4 - Univariate of the Treatment Failure (Primary Outcome)

Univariate Analysis		
	HR (95% CI)	**p-value***
Demographic Variables		
Age	1.01 (0.93-1.09)	0.858
Female Sex	2.24 (0.23, 21.57)	0.485
Clinical Variables		
Baseline BCVA	1.20 (0.45-3.20)	0.717
Tumor Baseline Diameter	1.12 (0.79-1.58)	0.521
Tumor Baseline Thickness	0.79 (0.47-1.31)	0.365
COMS Classification	3.13 (0.35-27.80)	0.306
AJCC Stage	4.16 (0.90-19.30)	0.068
Treatment Variables		
Brachytherapy Duration	1.05 (0.56-1.94)	0.888
Plaque Type	0.82 (0.08-7.92)	0.860
Plaque Size	1.04 (0.66-1.64)	0.863
Apex Dose	0.76 (0.42-1.37)	0.361
Sclera Dose	1.00 (0.99-1.00)	0.754
Optic Nerve Dose	0.98 (0.94-1.02)	0.252
Retina Dose	0.81 (0.55-1.19)	0.278
Macula Dose	0.96 (0.92-1.01)	0.098

CI. Confidence Interval; BCVA. Best-Corrected Visual Acuity; *p< 0.05

When considering secondary outcomes, we aimed to explore whether any demographic, clinical or treatment variable(s) could predict mortality. The only predictor that marginally met the criteria of statistical significance for time to death was plaque size on a univariate Cox regression analysis (HR= 1.32 [95%CI- 1.00-1.72], p= 0.045). Although basal diameter and tumor thickness did not meet statistical criteria as predictors of tumor mortality, they showed a tendency towards significance on univariate analysis (HR = 1.23 [95%CI- 0.98-1.53], p= 0.074; and HR = 0.75 [95%CI- 0.54-1.03], p= 0,078, respectively) **(Table 5)**. Regarding time to metastasis, we found that maximum basal diameter was predictive of time to metastasis (HR= 1.42 [95%CI- 1.16-1.84], p = 0.015), after multivariate adjustment for potential confounders. Neither AJCC or COMS staging, sex or tumor thickness showed significance as predictors for time to metastatic disease **(Table 6)**.

Concerning EBT side effects, we aimed to evaluate possible predictors of the development of radiation retinopathy. Both COMS staging and dose to the macula were predictors of the development of radiation retinopathy on univariate analysis, but only COMS staging mustered at the significance level after adjusting for confounders on multivariate analysis (HR = 3,11 [95% CI- 1.24-7.83]; p = 0.016) (**Table 7**).

Table 5 - Univariate and Multivariate Analysis of the Time to Death (Secondary Outcome)

	Univariate Analysis	
	HR (95% CI)	**p-value**
Demographic Variables		
Age	0.99 (0.95-1.04)	0.815
Female Sex	2.13 (0.56-8.03)	0.265
Clinical Variables		
Baseline VA	0.97 (0.52-1.81)	0.935
Tumor Baseline Diameter	1.22 (0.98-1.63)	0.073
Tumor Baseline Thickness	0.75 (0.54-1.03)	0.078
COMS Classification	1.13 (0.22-5.84)	0.883
AJCC Stage	1.02 (0.39-2.72)	0.961
Treatment Variables		
Brachytherapy Duration	1.17 (0.81-1.67)	0.401
Plaque Type	1.07 (0.28-4.04)	0.923
Plaque Size	1.32 (1.01-1.72)	**0.045***

CI. Confidence Interval; BCVA. Best-Corrected Visual Acuity; *p< 0.05

Table 6 - Univariate and Multivariate Analysis of Time to Metastasis (Secondary Outcome)

	Univariate Analysis		**Multivariate Analysis**	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Demographic Variables				
Age	0.96 (0.92-1.00)	0.042*	0.96 (0.93-1.00)	0.073
Female Sex	2.75 (0.76-10.00)	0.124	-	-
Clinical Variables				
Baseline VA	0.97 (0.52-1.81)	0.935	-	-
Tumor Baseline Diameter	1.42 (1.16-1.84)	0.001*	1.42 (1.07-1.87)	0.015*
Tumor Baseline Thickness	0.95 (0.75-1.22)	0.705	-	-
COMS Classification	1.08 (0.21-5.62)	0.922	-	-
AJCC Stage	0.92 (0.37-2.29)	0.863	-	-
Treatment Variables				
Brachytherapy Duration	1.23 (0.88-1.71)	0.225	-	-
Plaque Type	1.25 (0.38-4.08)	0.714	-	-
Plaque Size	1.40 (1.10-1.79)	0.007*	1.08 (0.84-1.40)	0.547

CI. Confidence Interval; BCVA. Best-Corrected Visual Acuity; *p< 0.05

Table 7 - Univariate and Multivariate Analysis of Radiation Retinopathy (Secondary Outcome)

	Univariate Analysis		**Multivariate Analysis**	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Demographic Variables				
Age	0.98 (0.96-1.00)	0.123	-	-
Female Sex	2.75 (0.76-10.00)	0.124	-	-
Clinical Variables				
Baseline VA	1.20 (0.88-1.64)	0.245	-	-
Tumor Baseline Diameter	1.42 (1.16-1.84)	0.644	-	-
Tumor Baseline Thickness	1.09 (0.95-1.24)	0.206	-	-
COMS Classification	2.58 (1.09-6.11)	**0.032***	3.11 (1.24-7.83)	**0.016***
AJCC Stage	0.88 (0.53-1.45)	0.610	-	-
Treatment Variables				
Brachytherapy Duration	0.96 (0.79-1.17)	0.712	-	-
Plaque Type	1.90 (0.94-3.84)	0.075	-	-

(cont.)

Plaque Size	0.98 (0.85-1.12)	0.773	1.51 (0.68-3.34)	0.314
Apex Dose	0.98 (0.94-1.01)	0.228	-	-
Sclera Dose	1.00 (0.99-1.00)	0.795	-	-
Optic Nerve Dose	1.00 (0.99-1.00)	0.720	-	-
Retina Dose	1.02 (0.96-1.09)	0.479	-	-
Lens Dose	0.98 (0.95-1.00)	0.073	-	-
Macula Dose	1.00 (1.00-1.01)	0.037*	1.00 (0.99-1.00)	0.125

CI. Confidence Interval; BCVA. Best-Corrected Visual Acuity; *p< 0.05

DISCUSSION

The main purpose in conservative treatment of uveal melanoma is the destruction of the tumour and adequate local control. Secondly, EBT aims the preservation of the globe and, when possible, the maintenance of some visual function.

Local control and treatment failure

The primary outcome of interest of this work was treatment failure and local control (LC) after treatment with ^{125}I EBT. A recent Spanish study showed a 2-year local control of 95.3% and a 5-year control of 88.4%[14], values which are very close to our experience **(Table 3).** Similarly, another recent study from Spain reported secondary enucleation due to treatment failure in 4 patients and a local control rate of 92.6%[15]. Comparing results from another single institutional study, a work from the Huntsman Cancer Institute, University of Utah showed a 5-year control rate of 94%, with local failure documented in only 3 patients[16]. The COMS group reported a 5-year treatment failure rate of 10.3%, which is slightly higher than our estimate[10]. Our results demonstrate excellent outcomes for local control with EBT, alike other Institutions around the world and the COMS multicentric trial results.

No predictors of treatment failure were detected on univariate analysis in our study, which can be likely attributed to the fact that our sample was not specifically powered for this analysis. Correa *et* al found a statistically significant association between treatment failure and a higher COMS stage[14]. Gunduz *et al* reported that tumor recurrence was statistically associated with reduced tumor margin from the optic nerve and retinal invasion, after multivariate adjustment[12]. The 5-year COMS report for treatment failure and enucleation found that older age, greater tumor thickness and proximity to the foveal avascular zone were risk factors for treatment failure[10].

Survival and systemic disease

Other outcomes of interest were time-to-death and time to development of metastasis. Spanish authors Correa *et al* described a 2-year and 5-year OS rate of 94.4% and 84.1%, respectively[14] and the Valladolid group presented an even better OS rate of 97.1% at 13 years[15]. In contrast, Jensen *et al* at the Mayo Clinic showed a 5-year OS of 83%[17] and the COMS group reported a 5-year OS of 82% for EBT, similar to patients offered primary enucleation (81%)[6]. Our overall estimates are closer to Jensen and co-workers' series and the COMS group.

When studying possible predictors of mortality, we found that plaque size was a predictor of time-to-death, but there was also a weak association with basal tumor diameter and thickness. Since plaque size is calculated according to tumor basal diameter, these results are comparable to other published studies in which greater tumor basal diameters and apical heights were positively correlated with melanoma-related death[12].

As for the incidence rate for developing metastasis, Correa *et al* presented a 2-year and 5-year MFS rates of 90.5% and 79.5%, respectively[14] and Jensen *et al* a 5-year rate of 91%[17]. The group from the Wills Eye Hospital reported a 12% risk of metastatic disease at 5 years[12]. Considering time to metastasis, we found that maximum basal diameter was a strong predictor of time to metastasis in either uni- and multivariate analysis. This can explain our higher incidence of systemic disease, since among patients who developed metastasis, the mean basal diameter was 14.9 mm. Gunduz *et al* previously described that a basal diameter greater than 10mm increases the risk of melanoma metastasis, which is true for all the patients in our sample that developed systemic disease[12].

Treatment side-effects

Radiation treatment is well-known to be associated with both early and late onset side-effects. Cataract is an early complication related to the high sensibility of the lens to radiation and appears mainly during the first year after EBT[15]. In our series, cataract was the most common

toxicity effect, documented in more than 50% of patients during follow-up. Garcia-Alvarez C. *et al* presented a 2-year and 5-year prevalence of 16.3% and 27.4%, respectively[15]. Gunduz K. from the Wills Eye Hospital group reported radiation cataracts in 30% of their patients and a 5-year probability of developing cataract of 32%[12].

Radiation retinopathy (RR) is a vision-threatening complication that tends to manifest later during follow-up, with an increasing incidence with time. Radiation induces a progressive vasculopathy with loss of endothelial cells and pericytes, leading to lipoprotein exudation and microvascular occlusion[18]. Radiation retinopathy developed in 41.4% of our patients and included both lesions of maculopathy or neuropathy. Gunduz *et al* reported radiation maculopathy to be the most common complication of EBT (38%), with 40% risk of developing it at 5 years[12]. In their work, radiation maculopathy was related to the use of ^{192}Ir isotopes and presence of subretinal fluid[12]. The Spanish group from Correa R. observed radiation retinopathy in 7.5% of their patients[14]. The rates of radiation retinopathy vary widely in the literature, depending on the dimensions of the tumor[12], apex dose rates[12], location[19] and isotope used[12]. The fact that we have such a high rate of RR may reflect the greater prevalence of tumours located in the macula and posterior to the equator, as in the study from Gunduz *et al*[12]. We found that only COMS staging was a predictor of the development of RR on multivariate analysis. Given that tumous with greater dimensions are prescribed higher radiation doses, and these higher prescriptions are related to the development of RR[16,17], we can hypothesize that eyes with higher COMS stages will have a greater risk for RR.

Several treatment modalities have been proposed for the treatment of RR, including intravitreal injections of anti-VEGF agents under the rational that VEGF and other inflammatory and vasculogenic factors have been implicated in the pathogenesis of radiation-induced macular edema and neovascularization. Intravitreal bevacizumab has been showed to stabilize visual acuity loss and progressively reduce RR lesions and macular edema[20]. Our patients were offered treatment with intravitreal bevacizumab injections on 3-injections loading dose followed by a PRN regimen, with a mean of 3.3 injections per patient. However, there is no approved treatment regimen for radiation retinopathy and large-scale randomized trials are lacking.

There are some limitations to our study. It is a single institution study with a moderate median follow-up time and, although our patients maintained a reasonably good follow-up, there are limitations inherent to missing data. Moreover, the absolute number of events was small, which limited the power of the exploratory analysis for potential predictors of the primary and secondary outcomes.

Nevertheless, our study constitutes the first report of EBT efficacy and safety in Portugal and highlights the adequacy of this modality for the treatment of uveal melanoma.

CONCLUSIONS

Our results demonstrate excellent clinical outcome for local control of uveal melanoma after treatment with ^{125}I EBT, with satisfactory overall survival and metastasis-free survival rates. The rate of ocular toxicity is acceptable, considering the high rates of local control and globe preservation. Therefore, it is a valid option for globe-sparing treatment in opposition to enucleation, with the advantage of better cosmetic results. In conclusion, this study shows that the Portuguese Reference Centre for uveal melanomas offers good results, comparable to those presented in large institutional studies and multicentric trials.

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