Demographic Characterization of Uveal Melanoma Population in Portugal

Caracterização Demográfica da População Diagnosticada com Melanoma da Úvea em Portugal

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Recebido/Received: 2022-10-15 | **Aceite/Accepted:** 2023-09-03 | **Published online/Publicado online:** 2023-11-03 | **Publicado/Published:** 2023-12-29

DOI: https://doi.org/10.48560/rspo.28274

ABSTRACT

INTRODUCTION: Uveal melanoma (UM) is the most common intraocular tumor and although rare, remains a clinical challenge for ocular oncologists. Therapeutic options have evolved throughout the years, focusing in eye-conserving modalities. However, long-term survival remains unchanged. Advances in early diagnosis and treatment represent a step forward in improving patients' outcomes and survival. The purpose of this study is to characterize demographically and clinically the Portuguese population with uveal melanoma evaluated at the National Reference Centre (NRC).

METHODS: Prospective, observational study of patients consecutively diagnosed with UM at the Portuguese NRC, between January 2016 and December 2021. Data was collected regarding tumor characteristics, staging (American Joint Committee on Cancer – AJCC), demographic assessment, treatment modality, local control, patient survival and distant metastasis.

RESULTS: A total of 215 patients (53% female) were included. The mean age at diagnosis was 61.5± 14.0 years, with symptoms at presentation reported by 75.6%. Choroidal location was the most frequent (83.3%), followed by ciliary body (10.2%), iridociliary (3.3%) and iris (1.4%). The AJCC stage IIA and IIB were the most common at presentation (33.0% and 32.6%, respectively); stage IIIC was the less observed (n=3). Mean baseline basal diameter and thickness were, respectively, 11.7± 3.7 and 6.9±3.4 mm. Primary treatment comprised brachytherapy (n=152, 70.7%), enucleation (n=50, 23.3%), proton beam radiation (n=8, 3.7%) and tumor resection (n=5, 2.3%; only for iris tumors). Mean disease-specific survival (DSS) was 45.8 months (95%CI: 44.5-47.1 months), with a cumulative survival of 89.4 months (95%CI: 83.1-95.7) at 4 years. Mean distant metastases-free survival (DMFS) was 53.4 months (95% CI: 50.8-56.0 months), with a cumulative survival of 83.9 months (95% CI: 76.7-91) at 4 years. Higher AJCC stages at presentation, enucleation and increased tumor thickness were associated with lower DSS and DMFS rates.

CONCLUSION: This is the first characterization of the Portuguese Population diagnosed with UM in the NRC. Our results highlight the importance of an early diagnosis given that almost 25% of patients were enucleated primarily and were not candidates for globe-sparing treatments. Lower AJCC stages and decreased tumor thickness at the time of diagnosis correlated with better DSS and DMFS, emphasizing the advantages of early treatment.

KEYWORDS: Melanoma/diagnosis; Melanoma/epidemiology; Melanoma/therapy¸Survival Analysis; Uveal Neoplasms/diagnosis; Uveal Neoplasms/epidemiology; Neoplasms/therapy.

RESUMO

INTRODUÇÃO: O melanoma da úvea (UM) é o tumor intraocular mais comum, constituindo um desafio clínico para os oncologistas oculares. Opções terapêuticas têm evoluído ao longo dos anos, centrando-se em modalidades conservadoras. Contudo, o prognóstico a longo prazo mantém-se reservado. No entanto, avanços no diagnóstico e terapêutica precoces podem vir a mudar este paradigma. Este estudo tem como objetivo caracterizar demográfica e clinicamente a população portuguesa com o diagnóstico de UM no Centro de Referência Nacional (NRC).

MÉTODOS: Conduziu-se um estudo prospetivo observacional de doentes consecutivamente diagnosticados com UM no NRC, entre janeiro de 2016 e dezembro de 2021. Foram colhidos dados respeitando as características tumorais, estadio (American Joint Committee on Cancer – AJCC), dados demográficos, modalidade de tratamento, controlo local, sobrevida e metástases à distância.

RESULTADOS: Foram incluídos 215 doentes (53% do sexo feminino). A idade média de diagnóstico foi 61,5± 14,0 anos, e 75,6% apresentaram-se com sintomas. A localização coroideia foi a mais frequente (83,3%), seguida pelo corpo ciliar (10,2%), iridociliar (3,3%) e íris (1,4%). Os estadios AJCC IIA e IIB foram os mais comuns (33,0% and 32,6%, respetivamente); o estadio IIIC foi o mais raro (n=3). As médias do diâmetro basal e espessura iniciais foram, respetivamente, 11,7± 3,7 e 6,9±3,4 mm. O tratamento primário compreendeu braquiterapia (70,7%), enucleação (23,3%), feixe de protões (3,7%) e resseção tumoral (2,3%). A sobrevida específica de doença (DSS) média foi 45,8 meses (95% CI: 44,5-47,1 meses), com uma sobrevida cumulativa de 89,4% (95%CI: 83,1-95,7) aos 4 anos. A sobrevida livre de metástases à distância (DMFS) média foi 53.4 meses (95% IC: 50,8-56,0 meses), com uma sobrevida cumulativa de 83,9% (95% CI: 76,7-91) aos 4 anos. Estadios AJCC mais avançados, enucleação e maior espessura tumoral correlacionaram-se com piores taxas de DSS e DMFS.

CONCLUSÃO: Esta é a primeira caracterização da população portuguesa diagnosticada com UM no NRC. Os nossos resultados realçam a importância do diagnóstico precoce, atendendo que quase 25% dos doentes foram enucleados primariamente, não sendo candidatos a terapêuticas conservadoras. Estadios AJCC mais baixos e menor espessura tumoral à apresentação correlacionaram-se com melhores DSS e DMFS, sublinhando as vantagens do tratamento precoce.

PALAVRAS-CHAVE: Análise de Sobrevivência; Melanoma/diagnóstico; Melanoma/epidemiologia; Melanoma/tratamento; Neoplasias Uveais/diagnóstico; Neoplasias Uveais/epidemiologia; Neoplasias/tratamento.

INTRODUCTION

Although recognized as a rare condition, ocular melanoma is the most common ocular malignancy, representing 5% of the melanomas.[1,2] Among ocular melanomas, near 85% occur in the uveal tract,[1,2] of which 85%-90% arise from the choroid, followed by the ciliary body (5%-8%) and the iris (3%-5%).[2,3-6]

The incidence of uveal melanoma (UM) in Europe has been reported as ranging from 2 cases per million per year in Southern Europe to over 8 cases per million per year in Nordic countries, with this north-to-south decreasing gradient supporting the protective role of ocular pigmentation in the southern countries.[7] In the United States, the incidence has been estimated as 5.1 cases per million per year,[8,9] whereas in Asia and Africa the reports point a significantly lower incidence rate, of less than 1 case per million per year.[6,8]

Advanced age is related to higher incidence rates, with both mean and median ages at diagnosis of approximately 62 years old.[6,9-11] Regarding incidence by gender, there is not a true consensus, with variable results according to different studies.[6]

Along with location, tumor size, extrascleral extension and associated complications (vitreous bleeding, serous retinal detachment, inflammation) will determine the clinical presentation, with most patients complaining of decreased visual acuity and blurred vision; about 30% are asymptomatic at presentation.[6,12-15]

Regarding diagnosis and staging, in 2017, the American Joint Committee on Cancer (AJCC) released an updated 8th edition for the classification of UM, with two different systems for iris versus choroidal and ciliary body melanomas. For iris tumors, classification is based on tumor location, tumor size in clock hours, extension to the ciliary body and/or

the choroid, and associated features of secondary glaucoma and extrascleral extension. Ciliochoroidal melanoma is classified according to its basal diameter, thickness, ciliary body involvement and associated extraocular extension.[16]

Clinical characteristics as older age at presentation, male gender, larger tumor basal diameter, increased tumor thickness, ciliary body tumor location, diffuse tumor configuration, association with ocular/oculodermal melanocytosis, extraocular tumor extension at presentation and advanced AJCC category and staging have been pointed has predictive clinical features of worse clinical outcomes.[17]

Currently, primary local treatment options for UM, depending on the tumor location and dimensions, include globe-sparing modalities as tumor resection and radiation therapy, which comprises plaque brachytherapy (iodine-125, ruthenium-106, palladium-103 or cobalt-60) and teletherapy (proton beam, helium ion, or stereotactic radiosurgery using cyber knife, gamma knife or linear accelerator). In contrast, primary enucleation remains a valuable treatment option in large tumors and blind painful eyes.[6] Although satisfactory local disease control is generally achieved with these modalities, long-term survival rate for patients with UM remains poor, with approximately half resulting in clinical metastases by 10 years, with liver being the first site involved in 90%.[17,18] For metastatic disease, the prognosis is very poor, with a median overall survival of 10-13 months.[18]

A dedicated UM Oncology Department was established in Coimbra in 2013. There are no previous studies reporting the clinical demographics and epidemiology of UM in Portugal. Therefore, the purpose of this study was to characterize demographically and clinically the Portuguese population with UM diagnosed at the National Reference Center in the period between January 2016 and December 2021.

METHODS

STUDY DESIGN AND PATIENTS SELECTION

We conducted a prospective, observational study including consecutive patients diagnosed with UM at the Portuguese National Referral Center of Intraocular Tumors (PNRCIT) between January 2016 and December 2021. All enrolled patients were Portuguese residents at the time of diagnosis. The study was approved by the local Ethics Committees and followed the tenets of the Declaration of Helsinki for biomedical research.

DEMOGRAPHIC FEATURES, CLINICAL EVALUATION AND STAGING

A detailed medical history was obtained for every patient at the time of diagnosis and included age, gender, naturality, symptoms and their characterization at presentation.

All patients underwent a complete ophthalmological examination including (1) best corrected visual acuity (VA) converted to logMAR; (2) slit-lamp anterior segment and dilated fundus examination and, whenever necessary, gonioscopy; (3) multimodal imaging comprising ocular ultrasound, color fundus photography (recently with widefield imaging) and optical coherence tomography (OCT). The diagnosis of UM was based on clinical and ultrasonographic findings by ocular oncology specialists. Tumor location was documented according to ophthalmological exam findings, as well as ultrasonographic evaluation, which was also used to measure tumor dimensions (thickness and largest basal diameter); when ultrasonographic evaluation was not able to obtain reliable measurements, an orbital nuclear magnetic resonance was performed to ascertain those parameters. All patients were also submitted to systemic evaluation with blood workup and abdominal imaging (ultrasound and/or computerized tomography) in order to exclude systemic metastases at diagnosis.

Staging was determined using the American Joint Committee on Cancer (AJCC) staging criteria, and all patients were referred for medical oncology follow-up.

TREATMENT PROTOCOLS

Treatment options available at the PNRCIT included plaque brachytherapy, enucleation and external resection in selected iris/iridociliary tumors. For treatment decision, COMS tumor size classification system and the guidelines from the American Brachytherapy Society[19] were considered. UM patients were offered episcleral plaque brachytherapy (EBT) treatments in: (1) all medium-sized melanomas; (2) melanocytic lesions with more than 3 risk factors for growth and documented growth; (3) some 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. Those patients were referred to Jules Gonin Hospital in Lausanne, Switzerland.

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 primary enucleation. Patients with circumscribed iris and iridociliary tumors, not larger than 4 clock-hours nor evidence of extrascleral extension were offered iridectomy/ iridociclectomy.

All cases were evaluated and discussed by a multidisciplinary team comprising ocular oncologists and radio-oncologists.

SURVIVAL ANALYSIS

The population demographics, clinical and imaging characteristics were summarized using traditional descriptive methods. Kaplan–Meier (KM) survival analysis was performed for both disease-specific survival (DSS) and distant metastases-free survival (DMFS). DSS times were cal-

culated from the date of primary treatment until the date of death from UM or the date of the last follow-up. DMFS times were calculated from the date of primary treatment until the date of metastization, date of death or date of last follow-up. For both DSS and DMFS, study population was analyzed for overall survival and comparative survival between subgroups after segregation by AJCC stage at presentation (I, II or III), treatment modality (brachytherapy, proton beam radiation, enucleation or tumor resection) and age at diagnosis (<65 years old *vs* ≥ 65 years old).

Statistically significant differences were analyzed using Cox proportional-hazard models to calculate hazard ratios. Additionally, Cox regression was also used to evaluate the impact of UM diameter/thickness at presentation in both DSS and DMFS.

All statistical analysis and graphics were performed using IBM SPSS Statistics 25 for Windows. $P < 0.05$ was considered statistically significant.

RESULTS

DEMOGRAPHIC ANDC LINICAL CHARACTERIZATION

A total of 215 adult patients with a mean age of 61.5± 14.0 (range 20-90) years old were diagnosed with UM at the PNRCIT between January 2016 and December 2021, with 2020 and 2021 being the years with higher number of registered diagnosis (n=44 and n=43, respectively).

A slightly superior female prevalence was observed (n=114, 53%), and more than half of the patients were referred from Centre region of Portugal (n=118, 54.9%), followed by Northern region (n=66, 30.7%).

Regarding the clinical aspects of the population, three quarters referred visual symptoms (n=149, 75.6%) prior to diagnosis, with the remaining 24.4% being asymptomatic and diagnosed in a routine check-up. The most frequently symptom was progressive visual loss (62.4%), with a mean baseline VA

Table 1. Baseline demographic and clinical data of the study population.

Sex, n(%)		**AJCC Stage, n(%)**	
Female	114 (53.0)	IA	36 (16.7)
Male	101 (47.0)	IIA	71 (33.0)
Age, years (mean± sd)	61.5± 14.0	IIB	70 (32.6)
Region, n(%)		IIIA	20 (9.3)
North	66 (30.7)	IIIB	15 (7.0)
Centre	118 (54.9)	IIIC	3 (1.4)
South	20 (9.3)	**Basal diameter, mm (mean± sd)**	11.7±3.7
Madeira	7 (3.3)	Choroid	11.9 ±3.4
Azores	4 (1.9)	Ciliary body	11.2± 4.9
Diagnosis per year, n (%)		Iridociliary	8.2 ±3.6
2016	28 (13.0)	Iris	2.9 ±0.6
2017	41 (19.1)	**Thickness, mm (mean± sd)**	6.9±3.4
2018	32 (14.9)	Choroid	6.8 ±3.2
2019	27 (12.6)	Ciliary body	8.1 ±3.8
2020	44 (20.5)	Iridociliary	5.6 ±4.1
2021	43 (20)	Iris	2.0 ±0.0
Eye, n (%)		**Visual acuity, logMAR scale (mean± sd)**	0.96±0.92
Right	112 (52.1)	**Symptoms, n (%)**	149 (75.6)
Left	103 (47.9)	Progressive visual loss	93 (62.4)
Location, n(%)		Floaters/photopsias	17 (11.4)
Choroid	179 (83.3)	Visual field loss	16 (10.7)
Retro-equatorial	63 (35.1	Abrupt visual loss	15 (10.1)
Macular	41 (22.9)	Blurred vision	5 (3.4)
Antero-equatorial	35 (19.6)	Pain	2 (1.3)
Peripapilar	33 (18.4)	**Primary treatment**	
Unable to determine	7 (3.9)	Brachytherapy	152 (70.7)
Ciliary body	22 (10.2)	Proton beam radiation	8 (3.7)
Iridociliary	7 (3.3)	Tumor resection	5 (2.3)
Iris	3 (1.4)	Enucleation	50 (23.3)
Unable to determine	4 (1.9)		

of 0.96±0.92 logMAR. Other initial symptoms included floaters/photopsias (11.4%), visual field loss (10.7%), sudden visual loss (10.1%), blurred vision (3.4%) and ocular pain (1.3%).

Tumors presented a choroidal location in the great majority (n=179, 83.3%), with more than one third of these being located at the retro-equatorial region of the eye (n=63; 35.1%). Ciliary body tumors were the second most frequent (n=22, 10.2%), and only 3 patients presented a lesion restricted to the iris. In six patients, the tumor origin was unable to determine due to its advanced stage and extension.

Mean largest basal diameter and mean thickness at presentation were respectively 11.7± 3.7 mm and 6.9±3.4 mm. Approximately one third of patients presented the AJCC stages IIA (n=71, 33%) or IIB (n=70, 32.6%). Stage IIIC was the less frequent (n=3, 1.4%) and no patients were classified as stage IV at diagnosis.

Brachytherapy was selected as the primary treatment for more than two thirds of the patients (n=152, 70.7%), whereas 23.3% were offered primary enucleation. Proton beam radiation was reserved for peripapillary tumors (n=8, 3.7%) and tumor resection (iridectomy/ iridociclectomy) was indicated in five patients, all of them with iris/iridociliary located lesions not larger than 4 clock-hours nor evidence of extrascleral extension.

All baseline demographic and clinical data are summarized in Table 1.

SURVIVAL ANALYSIS AND DISEASE CONTROL

During the course of follow-up (mean 27±21 months), 6 EBT patients were offered subsequent (secondary) enucleation: 5 due to local recurrence and extrascleral extension and one due to uncontrolled complications of radiation retinopathy. Regarding patients elected for tumor resection, one was offered secondary EBT due to local recurrence.

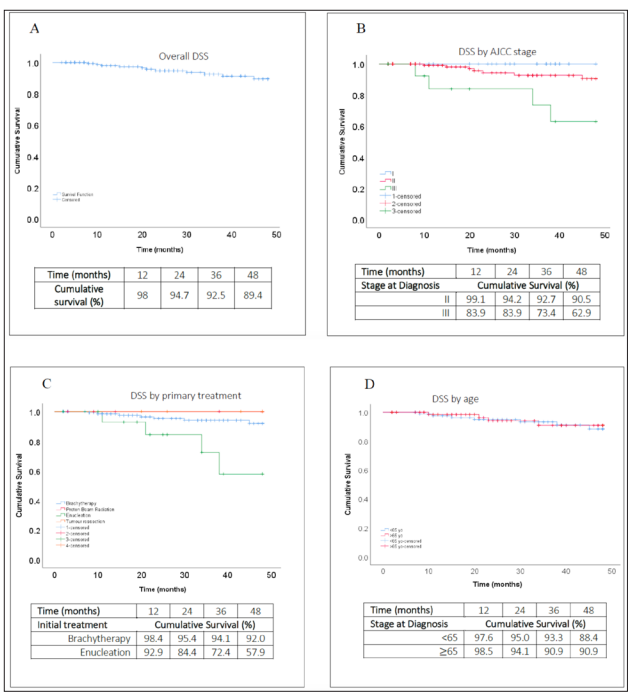

Figure 1. Kaplan-Meier curves for disease-specific survival. (A) Overall DSS; (B) DSS by AJCC stage at diagnosis; (C) DSS by primary treatment; (D) DSS by age (<65 vs ≥ 65 years old).

DISEASE SPECIFIC SURVIVAL (DSS)

KM survival analysis revealed a mean overall DSS of 45.8 months (95% CI: 44.5-47.1 months), with cumulative survival rates of 98% at 1 year (95% CI 95.9-100), 94.7% at 2 years (95% CI 90.1-98.6), 92.5% at 3 years (95% CI 87.6-97.4) and 89.4% at 4 years (95% CI 83.1-95.7) (Fig. 1A). Regarding AJCC stage at presentation, we verified that no deaths were registered among patients presenting at stage I in this cohort, hence survival estimates were impossible (Fig. 1B). Cumulative survival rates among patients presenting at stages II and III at 1 year were, respectively, 99.1 (95% CI 97.3-100) *vs* 83.9% (95% CI 63.5-100); at 2-years 94.2% (95% CI 89.3-99.2) *vs* 83.9% (95% CI 63.5-100); at 3-years 92.7% (95% CI 87-98.4) *vs* 73.4% (95% CI 47.1-99.7); and at 4-years 90.5 (95% CI 83.4-97.6) *vs* 62.9% (95% CI 33.5-86.4). These results translated into a significantly lower mean survival time in patients presenting on stage III when compared to stage II (39.3 *vs* 45.9 months, Log-R test: $\chi^2(2) = 12.7$, p=0.002), corresponding to an increased risk of death for more advanced stage (HR: 4.85, 95% CI 1.42-16.60, p=0.010). Additionally, when accounting for initial treatment (Fig. 1C), enucleation was associated with lower survival rate when compared to brachytherapy as primary treatment of choice (46.2 *vs* 36.9 months, Log-R test: $\chi^2(1) = 9.2$, p=0.002), resulting in a higher risk of DSS (HR: 5.50, 95% CI 1.59-18.71, p=0.007). No deaths were registered among patients elected for proton beam radiation or tumor resection. There were no differences in survival when comparing diagnosis after and before 65 years of age (45.8 *vs* 45.7 months, Log-R test: $\chi^2(1) = 0.08$, p=0.780) (Fig. 1D). A Cox regression model using UM largest basal diameter and thickness at presentation was built; only tumor thickness showed significance as predictor of DSS with increased thickness contributing to decreased survival rates (HR: 1.3, 95% CI: 1.1-1.6, p=0.001).

DISTANT METASTATIC-FREE SURVIVAL (DMFS)

KM survival curves for DMFS (Fig. 2) revealed a mean of 53.4 months (95% CI 50.8-56.0 months), with a cumulative survival rate of 94.8% at 1 year (95% CI 91.3-98.3), 88.7% at 2 years (95% CI 83.2-94.2), 85.5% at 3 years (95% CI 79.0-92) and 83.9% at 4 years (95% CI 76.7-91). When analyzing AJCC stage at presentation, no patient presenting at stage I developed metastatic disease during the follow-up, hence survival estimates were not possible. Amongst the remaining patients, subgroup presenting at stage III showed a lower mean time to metastatic disease when compared to stage II (30.7 *vs* 44.0 months; HR: 5.87, 95% CI 2.31-14.93; p<0.001). Cumulative survival probability among patients presenting at stage II and III at 1, 2,3 and 4 years were, respectively, 95.3% (95% CI 91.2-99.4) *vs*

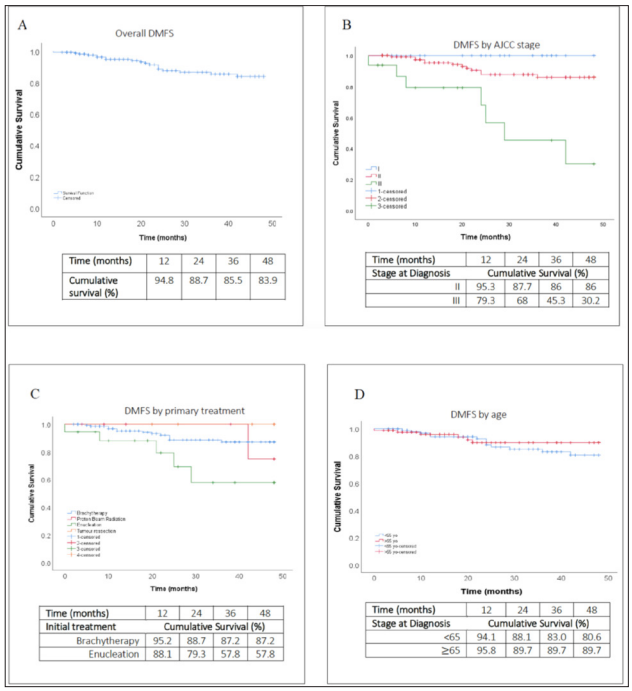

Figure 2. Kaplan-Meier curves for distant metastases-free survival. (A) Overall DMFS; (B) DMFS by AJCC stage at diagnosis; (C) DMFS by primary treatment of choice; (D) DMFS by age (<65 vs ≥ 65 years old).

79.3% (95% CI 58.3-100); 87.7% (95% CI 80.8-94.6) *vs* 68% (95% CI 40.8-95.2); 86% (95% CI 78.3-93.6) *vs* 45.3% (95% CI 13.9-76.9); and 86% (95% CI 78.3-93.6) *vs* 30.2% (95% CI 0-62.1). Comparison between primary treatment subgroups was remarkable for lower time to metastatic disease in enucleated patients compared to brachytherapy and proton beam radiation (35.9 *vs* 44.3 *vs* 46.5 months, Log-R test: $\chi^2(3) = 8.01$, p=0.050), translating into a higher risk for metastatic disease in the enucleated patients (HR 3.59, 95% CI: 1.28 – 10.09, p=0.015). No metastatic disease was registered among patients elected for tumor resection. There were no differences in DMFS when comparing diagnosis after and before 65 years of age (44.5 *vs* 43.2 months, Log-R test: $\chi^2(1) = 0.6$, p=0.430). Cox regression model using UM largest basal diameter and thickness at presentation showed that increase in thickness significantly predicted a decrease in DMFS (HR: 1.3, 95% CI: 1.1-1.6, p=0.001).

DISCUSSION

This is the first study to describe the epidemiology of UM in Portugal, offering important information regarding demographic and clinical aspects of this population, as well as considerable insight into this disease-related survival and prognostic factors.

The mean age of this cohort at diagnosis was 61.5 years, which is in accordance to previous reports that refer a mean age approximately of 62 years, with an increase in incidence with the advance in age.[6,9-11] Regarding sex, we registered a slightly higher number of female patients diagnosed with UM in our cohort (53%), and despite numerous works have reported an higher incidence in men,[11,20-22] there is no consensus about these data, with a large study of 8033 patients showing no differences between sexes.[12] It is important to note that in our study it was not performed an incidence analysis, hence not allowing to conclude about sex disparities in this field. Also, although more than half of our patients come from Centre Region of Portugal, the lack of an incidence analysis does not allow to extrapolate regional differences in incidence.

The findings respecting clinical presentation in our cohort are in accordance with previous works that report the majority of patients as symptomatic. In one study conducted at the United Kingdom[15] including 2384 patients diagnosed with UM, 30.2% were asymptomatic on referral, which approximates the percentage of asymptomatic patients observed in our cohort (24.4%).

In accordance to other reports,[2-5] the most common location for UM in our patients was the choroid (83.3%) followed by ciliary body (10.2%) and finally iris/iridociliary (4.7%), once again supporting the concept that more than 80% of these tumors have a choroidal origin.[6]

The majority of our cases were diagnosed at an initial AJCC stage, with more than 80% being classified as stage I or II, and no cases within stage IV were observed. These results align with several reports of higher prevalences of initial stages at diagnosis.[23] In fact, in one study conducted in Ireland enrolling 253 UM patients, the percentage of cases within stages I and II was 81%.[12] These results explain the fact that the most frequently offered treatment modalities are the conservative approaches,[24] which was also verified in our study, where enucleation was applied as primary treatment in 23.3% of the cases. The remaining patients underwent brachytherapy (70.7%), proton beam radiation (3.7%) or resection (2.3%; only for small iris/iridociliary tumors). Still, the fact that almost 25% of patients were not candidates for globe-sparing treatments emphasizes the need for early detection.

Regarding survival analysis, it has been reported a 5-year cumulative disease specific survival and a metastatic free-survival of 77%-84%[11,22] and 68-%,[25] respectively. In our cohort, the 4-year cumulative DSS and DMFS were, respectively, 89.4% and 83.9%, values that are slightly superior to those observed in the study conducted in Ireland that also evaluated the 4-year cumulative survival of UM, showing a DSS of 81.3% and a DMFS of 79.0%.[11] This could be explained by the fact that they presented a cohort with higher number of predictive factors for worse outcomes,[17,26] showing a higher number of patients with more advanced AJCC stages (namely stage IV, which was absent in our cohort) and more cases undergoing enucleation, thus representing more advanced local disease.

Additionally, these predictive factors were also relevant in our population, with advanced AJCC categories and enucleation being associated to lower DSS and DMFS; however, it has to be mentioned that the survival difference registered regarding primary treatment, as above mentioned, could be an effect of patient selection according to tumor

size rather than a result in different efficacies of treatment modalities. Nevertheless, other studies that have compared enucleation versus brachyteraphy for primary treatment in adjusted tumor size and stage cohorts also reported higher DSS and DMFS for radiation therapy,[25,27] but these results should be analyzed very carefully. Although Zimmerman and McLean have hypothesized that these findings could be explained by a dissemination of tumor cells through the vortex veins during enucleation due to an intraocular pressure spike while cutting the optic nerve,[28] the evidence that micrometastases occur months before therapy[29] has discarded this hypothesis long ago.

We also found a significant difference in DSS and DMFS regarding initial tumor thickness, with larger tumors representing worse outcomes. In fact, tumor size (largest basal diameter and thickness) has been appointed as one of the most important factors predictive of metastases and death.[6,17] In a cohort of 8033 patients consecutively diagnosed with UM, an increase in thickness by 1 mm was associated to a 5% increased risk for metastases at 10 years.[12] Unlike other works that also correlated largest basal diameter with survival,[25] in our study only increased in thickness demonstrated correlation with lower survival rates.

Similarly, advanced age at diagnosis has also been reported as an important factor for poorer prognosis[5,17]; however, comparing DSS and DMFS for patients with age <65 *vs* ≥ 65 years old, we did not find any statistical differences. This could be explained by the segregation in only this two groups, since the differences seem to be more relevant when comparing more extreme age groups.[5]

It is important to note that in this work, histopathologic and cytogenetic features were not integrated in the multivariate survival analysis, which constitutes a limitation, since these variables have also demonstrated to have relevant role in survival.[6,17] Other important study limitation include the limited follow-up in our group, hence not allowing to analyze the 5-year survival and consequently not permitting the comparison with the majority of works that analyzed this data.

CONCLUSION

To the best of our knowledge, this is the first study to characterize the Portuguese Population diagnosed with UM. Our results highlight the importance of an early diagnosis and treatment, since lower AJCC stages and tumor thickness at the time of diagnosis correlated with better DSS and DMFS. Additionally, considering the significant proportion of asymptomatic cases, it is important to raise health care workers and patients' awareness regarding this rare but deadly condition,

Further studies with larger samples are needed to support our results, evaluate the impact of other prognostic variables, estimate longer survival rates and analyze incidence trends of UM in the Portuguese population.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

All authors contributed to the study design and data acquisition and interpretation.

SG: Writing and approval of final version.

EN, TT, PCS, CF, RP: Critical review of the manuscript and approval of the final version.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

Provenance and Peer Review: Not commissioned; externally peer reviewed.

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