Uveal Melanoma in Portugal: Incidence Trends and Geographical Analysis

Melanoma da Úvea em Portugal: Tendências de Incidência e Análise Geográfica

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ABSTRACT

INTRODUCTION: Uveal melanoma (UM) is the most common intraocular malignancy in adults. Despite successful local treatments, long-term survival is still a challenge, making early diagnosis of paramount importance. Comprehension of geographical disparities can influence disease surveillance and prognostic counseling. This study aimed to report UM incidence trends and to analyze their geographical variation in Portugal.

METHODS: A prospective, observational study was conducted at the Portuguese UM referral center between July 2013 and December 2022. Crude incidence rates and age-standardized incidence rates (ASIR) were calculated. Overall survival (OS) and disease-specific survival (DSS) were estimated and a multivariate Cox analysis was performed to evaluate the effect of tumor characteristics and patient demographics on survival.

RESULTS: A total of 316 patients were included. The mean age at diagnosis was 61.8±14.2 years. The Health Region (HR) of Lisbon and the Tejo River was responsible for most referrals to our center (n=119, 37.7%). Overall ASIR in Portugal was 2.4 cases per million people (95% CI: 2.1-2.8). Higher crude incidence rates were noted in the central coastal districts (5.4 per million people in Aveiro (95% CI: 3.3-7.5) compared with the southern districts (1.0 per million in Faro (95% CI: 0.2-1.7). Geographical analysis showed incidence variation across HR, with the Centro region presenting a higher incidence crude rate (4.0 per million). The 5-year OS rate was 84.6% (95% CI: 78.7-91.1). No significant differences were found in OS (p=0.74) or DSS (p=0.83) when the data was stratified by HR. Cox regression analysis revealed that only basal tumor dimension was significantly associated with lower OS and DSS (HR= 1.33, p<0.001).

CONCLUSION: This is the first study to report the incidence of UM and to analyze regional incidence rates in Portugal. Overall ASIR of UM indicates no sex predilection and lower incidence rates compared to the ones reported in Northern European countries. Geographical variation of crude incidence rates revealed the highest in central coastal districts of Portugal, but no significant

differences were found in OS or DSS by Health region or district. Basal tumor diameter was the only predictor of DSS in UM for the Portuguese population in this analysis.

KEYWORDS: Incidence; Melanoma/epidemiology; Portugal; Uveal Neoplasms/epidemiology.

RESUMO

INTRODUÇÃO: O melanoma da úvea (MU) é a malignidade intraocular mais comum nos adultos. Apesar do sucesso nos tratamentos locais, a sobrevida a longo prazo continua a ser um desafio e o diagnóstico precoce crucial. A compreensão das disparidades geográficas pode influenciar a vigilância da doença e o prognóstico. Este estudo tem como objetivo reportar as tendências nacionais e geográficas de incidência do MU em Portugal.

MÉTODOS: Estudo prospetivo, observacional, realizado no Centro de Referência Nacional de MU entre Julho 2013 e Dezembro 2022. Taxas brutas de incidência e padronizadas para a idade foram calculadas, bem como a sobrevivência global (OS) e a sobrevida livre de doença (DSS). A análise COX avaliou o impacto das características tumorais e demográficas na sobrevivência.

RESULTADOS: Um total de 316 doentes foram incluídos. A idade média ao diagnóstico foi de 61,8±14,2 anos. A Administração Regional de Saúde (ARS) de Lisboa e Vale do Tejo foi a maior responsável pela referenciação (n=119, 37,7%). A taxa de incidência ajustada para a idade em Portugal foi de 2.4 casos por milhão de pessoas (95% CI: 2,1-2,8). As taxas brutas de incidência foram mais elevadas nos distritos litorais do centro (5,4 por milhão em Aveiro (95% CI: 3,3-7,5)) comparativamente aos distritos do sul (1,0 por milhão em Faro (95% CI: 0,2-1,7)). A análise geográfica demonstrou incidência mais elevada na ARS do Centro (4,0 por milhão). A sobrevivência cumulativa aos 5 anos foi de 84,6% (95% CI: 78,7-91,1). Não houve diferença estatística na OS (p=0,74) ou DSS (p=0,83) entre ARS. A análise de Cox revelou que a dimensão basal do tumor está significativamente associada a menor sobrevida (HR=1,33, p<0,001).

CONCLUSÃO: Este é o primeiro estudo a reportar a incidência nacional e geográfica de MU em Portugal. A incidência padronizada para a idade não revelou predileção de sexo e foi inferior comparativamente aos países da Europa do Norte. As taxas brutas de incidência foram superiores na costa central de Portugal, mas não houve diferença significativa na OS ou DSS entre ARS ou distritos. O diâmetro basal tumoral foi o único preditor da sobrevivência de MU para a população desta análise.

PALAVRAS-CHAVE: Incidência; Melanoma/epidemiologia; Neoplasias da Úvea/epidemiologia; Portugal.

INTRODUCTION

Uveal melanoma (UM) is the most common intraocular malignancy in adults and arises from the choroidal melanocytes in the majority of cases but can also arise from the ciliary body and iris melanocytes.[1]

Incidence rates are heterogeneous across the globe, probably related to demographics and environmental risk factors; they vary with sex, age, race, and latitude. In Europe, the incidence of UM ranges from 1.3 to 8.6 cases per million per year. These differences in European countries account for higher incidences in Northern Europe when compared to Southern countries and follow a south-to-north increasing gradient. United States of America (USA) reported standardized incidence rates of 5.1 cases per million per year from 1973-2003.[1-3] In Canada, a recent population-based study reported an average annual incidence rate of 3.75 cases per million.[4] Correspondingly, UM is more common in the white population, compared to Black, Hispanic, or Asian races.[2]

Despite significant advancement in local treatments of this malignancy and increased overall survival, uveal melanoma still confers significant mortality and morbidity.[1,3,5] Clinical characteristics representing greater tumoral load, such as larger tumor basal diameter and increased tumor thickness, are definitively recognized as one of the most important clinical predictors of metastasis and death.[1,5] Hence, a better understanding of epidemiologic trends and geographical disparities in incidence and referrals of this malignancy may contribute to better disease surveillance and earlier diagnosis.

To the best of our knowledge, this is the first report of

incidence rates and geographical incidence variations of UM in Portugal, over the past decade.

METHODS

A prospective observational study of consecutive UM patients diagnosed and referred to the Portuguese National Referral Center for Intraocular Tumors (PNRCIT) between July 2013 and December 2022 was performed. The study was approved by the local Ethics Committees and followed the tenets of the Declaration of Helsinki for biomedical research.

Clinical and demographic information from all patients was collected, including age, gender, region of referral, symptoms, and tumoral characterization at presentation. All patients underwent complete ophthalmological evaluation including best corrected visual acuity (BCVA), dilated fundus examination, and multimodal imaging exams such as color fundus photographs, fundus autofluorescence, B-mode ultrasound, and optical coherence tomography. Tumor dimensions (thickness and largest basal diameter) were determined by ultrasonography and when this evaluation was not possible, measurements by orbital nuclear magnetic resonance were considered.

Population demographics, clinical, and imaging characteristics were summarized using descriptive statistics. Age-adjusted incidence rates (cases per million person-years, using the 1970 European Standard Population as reference population) and crude incidence rates, were calculated using the annual population living in Portugal for the period between 2014-2022, obtained from the Pordata databases (https://www.pordata.pt/). Patients' referral regions were analyzed according to territory division in Health regions (North, Centre, South, Lisbon and Tejo Valley, Alentejo, Algarve, Madeira, and Azores) and according to the division of the Portuguese territory division in Districts and Municipalities.

Overall survival (OS) and disease-specific survival (DSS) were defined as primary outcomes and Kaplan–Meier survival curves were generated. DSS was calculated from the date of primary treatment until the date of death from UM or the date of the last follow-up. Additionally, Cox regression was used to evaluate the impact of regions, districts, and tumor characteristics (basal diameter and basal thickness) on survival rates.

All statistical analysis was performed using IBM SPSS Statistics 25 for Windows. Statistical significance was defined as $p < 0.05$.

RESULTS

POPULATION CHARACTERISTICS

From 2014 to 2022, a total of 316 cases were observed in the PNRCIT, among these 256 (81.1%), were located in the choroid. The mean and median ages at presentation were 61.8 ± 14.2 years and 64 years (range 20 to 90), respectively. There were slightly more females diagnosed with UM (n=170, 53.8%) than males (n=146, 46.2%). The number of UM diagnoses was highest in the most populous health region of Lisbon and Tejo Valley (LVT) (n=119, 37.7%), followed by North (n=102, 32.3%), Center (n=63, 19.9%), Alentejo (n=14, 4.4%), Islands (14, n=4.4) and Algarve (n=4, 1.3%). No statistical difference in age at diagnosis was noted between health regions (p=0.063, 95% CI:).

At presentation, the mean largest basal diameter of tumors was not significantly different between health regions (p=0.71) or districts (p=0.92), and neither was basal tumor thickness (p=0.91 and p=0.75, respectively).

Baseline general and clinical demographics are outlined in Table 1.

Table 1. Baseline clinical demographics of uveal melanoma in Portugal from 2014 to 2022.

Total cases			**316**
Age, years (mean ± SD)	61.8 ± 14.2	**Diagnosis per year, n (%)**	
Sex, n (%)		**2013**	3 (0.9)
Female	170 (53.8)	**2014**	26 (8.2)
Male	146 (46.2)	**2015**	22 (7.0)
Follow-up time, months (mean ± SD)	40.4 ± 27.6	**2016**	29 (9.2)
Diagnosis by Health region, n (%)		**2017**	42 (13.3)
North	102 (32.3)	**2018**	34 (10.8)
Center	63 (19.9)	**2019**	29 (9.2)
Lisbon and Tejo Valley	119 (37.7)	**2020**	49 (15.5)
Alentejo	14 (4.4)	**2021**	45 (14.2)
Algarve	4 (1.3)	**2022**	37 (11.7)
Madeira	7 (2.2)	**Location, n (%)**	
Azores	7 (2.2)	**Choroid**	256 (81.1)
Basal diameter, mm (mean ± SD)	12.4 ± 4.2	**Ciliochoroidal**	25 (7.91)
Basal thickness, mm (mean ± SD)	7.6 ± 3.8	**Ciliary body**	14 (4.4)
Eye, n (%)		**Iridociliary**	14 (4.4)
Right	169 (53.5)	**Iris**	3 (1.0)
Left	147 (46.5)	**Undetermined**	4 (1.3)

INCIDENCE RATES

The average age-standardized incidence rate (ASIR) of UM in Portugal was 2.4 per million people (95% confidence interval [CI]: 2.1 to 2.8) (Fig. 1A). The analysis of ASIR shows fluctuation over the years, reaching a peak in 2020 of 3.3 per million cases. Age-adjusted incidence rates of UM increased with older ages in both males and females but declined after the age of 70 in both sexes (Fig. 1B). There was no difference in ASIR between males and females.

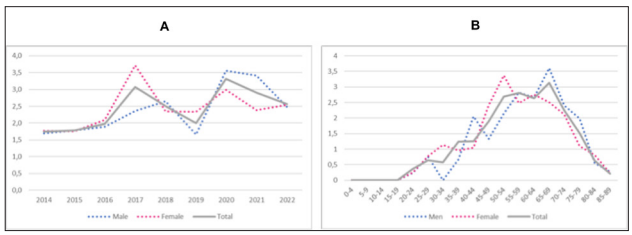

Figure 1. Incidence of uveal melanoma. (A) Crude incidence rates from 2014 to 2022 per million population; (B) Age-standardized incidence rates from 2014 to 2022 per million people across age groups.

Geographical analysis showed crude incidence variation across health regions, with the Centro region presenting with a higher incidence crude rate (4.0 per million people (95% CI: 3.5 to 4.6)), followed by LVT(3.6 per million people (95% CI: 2.3 to 4.4)), Alentejo (3.3 per million people (95% CI: 1.4 to 5.1)), North (3.2 per million people (95% CI: 1.8 to 4.5)), Madeira Island (3.1 per million people (95% CI: 0.6 to 5.6)), Azores (2.8 per million people (95% CI: -0.5 to 6.0)) and Algarve, with the lowest (1.0 per million people (95% CI: 0.1 to 1.8)) (Fig. 2A).

Figure 2. Crude incidence rates of uveal melanoma. (A) Crude incidence rates from 2014 to 2022 per million population per health region; (B) Crude incidence rates from 2014 to 2022 per million population per district; (C) Crude incidence rates from 2014 to 2022 per million population per municipality.

Further district evaluation documented higher crude incidence rates in central coast districts compared with the southern districts (Fig. 2B). Aveiro, a central district, showed the highest crude incidence rate (5.4 per million people) followed by Santarem (4.9 per million people) and Coimbra (4.8 per million people). Faro, a southern district (1.0 per million people), had the lowest incidence rate of UM in Portugal (Fig. 2B).

In terms of Portuguese municipalities, rural areas presented higher crude rates, such as Flores (70.5 per million people) in the Azores archipelago, Gavião (27.3 per million people), Sardoal (27.2 per million people), Vimioso (23.7 per million people), and Alfândega da Fé (22.2 per million people) (Fig. 2C). Additionally, crude incidence rate analysis revealed a slightly higher incidence in the littoral region (3.6 per million people) versus the interior of Portugal (3.3 per million people). When comparing Portugal's mainland with Portuguese's islands, we verified that the islands (Madeira and Azores) had a higher crude incidence rate (2.33 per million people vs 1.9 million people, respectively).

SURVIVAL ANALYSIS

During the period of this analysis, among the 316 patients diagnosed with UM, 31 patients (9.8%) deceased, 23 (74.2%) related to UM. The 5-year disease-specific survival (DSS) for patients with UM was 84.6% (95% CI: 78.7 to 91.1).

Fig. 3 illustrates the Kaplan–Meier for DSS of all patients with UM. There were no differences in OS (Log-R test: $\chi^2(1) = 0.4$, $p = 0.51$) or DSS (Log-R test: $\chi^2(1) = 0.2$, $p = 0.68$) among sex. Also, no significant differences were found in OS (Log-R test: $\chi^2(1) = 3.5$, $p = 0.74$) or DSS (Log-R test: $\chi^2(1) = 2.8$, $p = 0.83$) when the data was stratified by health regions or districts (OS: Log-R test: $\chi^2(1) = 14.9$, $p = 0.82$ and DSS: Log-R test: $\chi^2(1) = 13.8$, $p = 0.88$).

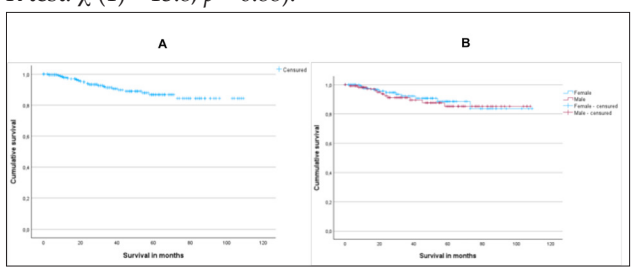

Figure 3. Kaplan–Meier survival curves of uveal melanoma in Portugal. (A) Disease-specific survival curve for uveal melanoma in Portugal; (B) Disease-specific survival curve by sex for uveal melanoma in Portugal.

In the Cox multivariate model, considering tumor size, patient origin, sex, and age, the only predictor of survival was basal UM diameter (Hazard Ratio: 1.33, 95% CI: 1.3 to 1.5, $p < 0.001$). Neither region, district, nor thickness at presentation had a statistically significant effect on survival.

DISCUSSION

Our population data analysis provided detailed information on the UM incidence and mortality in Portugal over the last decade. During this period, the ASIR was 2.4

per million per year, which seems to be aligned with the largest UM epidemiology study in Europe. The European Cancer Registry-based study on survival and care of cancer patients (EUROCARE), included 6673 patients with UM diagnosed from 1983 to 1994 and found a standardized incidence rate of between 2 cases per million per year in Spain and southern Italy, to a maximum of 8 per million per year in Norway and Denmark.[1,7] Such results followed a north-to-south decreasing incidence pattern related to higher exposure to ultraviolet light at lower latitudes and the probability of the protective effect of ocular pigmentation in the southern populations.[1,3,4,7]

Concerning annual incidence trends, our study found a slight decline in UM incidence in the last three years in Portugal. Other countries such as Sweden and Germany have experienced a declining incidence of UM over the years, while Australia and the USA reported a stable ASIR over the past three and four decades, respectively.[8-10] Yet, Canada had a small annual increase in incidence over time.[4,7] Thus, we believe that further follow-up studies are vital for a better understanding of long-term trends.

The mean age at diagnosis in this study was approximately 62 years. Stratification of ASIR showed a progressive rise in incidence with age, which peaked at around 70 years old, and is in accordance with previous studies that report that UM is more commonly seen in older age groups.[1,4,9,11]

Our cohort showed no difference in age-adjusted incidence of UM between sexes, with a slightly higher number of female patients diagnosed with UM (53%). In this matter, literature is not consensual. Although the majority of population-based epidemiological studies support a higher incidence in males,[1,9,10] a large study of more than 8000 consecutive patients with UM in the USA described no sex difference (50% were males and 50% were females),[13] similar to our analysis.

Geographic analysis of UM in Portugal was heterogeneous, with the higher incidence values clustered on the littoral coast, particularly in Centro and LVT regions. The Algarve region showed the lowest incidence rate. This geographic variability related to latitude may be attributable to genetics, emigration, environmental factors, or ethnic variations.[1,7,9] Unfortunately, our data lacked race ancestrally analysis. In the remaining territory, we identified a few municipalities with high crude rates that corresponded with rural and low-populated areas. Such finding is consistent with previous Australian research, in which UM incidence was associated with rurality, latitude, and lifetime solar exposure.[10]

The overall 5-year disease-specific survival of UM in Portugal was 85%, slightly higher than recent reports from Australia and the USA, with an average of 81%.[5,10,14] This can be explained by the clinical demographics of our cohort, such as scarce cases of advanced local disease.

Previous studies concluded that higher incidence rates found in rural areas, coupled with health access disparities could potentially lead to delayed diagnosis, treatment, and poorer outcomes.[8,10] However, interestingly, no significant differences were found between the tumor basal characteristics, DSS and OS in each region of Portugal.

In terms of outcome predictors, Cox multivariate analysis showed that only basal tumor size was associated with reduced survival, which agrees with previous studies. Historically, UM diameter at diagnosis was believed to be the most important clinical prognostic factor.[1,12] Yet, in recent years, cytogenetics and molecular analysis have evolved into playing a decisive role in determining prognosis in UM.[1,15] Such prognostication techniques were not included in this analysis, which accounts for a limitation of this study.

Another limitation of the current study was the small number of patients with UM within some districts which may have resulted in inaccurate subgroup and trend analyses. Nevertheless, this study will provide a useful baseline for future analysis of long-term changes in incidence and mortality trends, which has implications for disease screening, therapeutic intervention, and prognostic counseling in Portugal.

To the best of our knowledge, this is the first report of incidence trends and geographic disparities regarding UM in Portugal, since the establishment of a dedicated national referral center in 2013 in Coimbra.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

TM and SG: Conceptualization, formal analysis, data collection, writing original draft.

PCS and TT: Data collection, writing – review.

BO: Statistical analysis, writing – review.

MLC, CH and RP: Conceptualization, formal analysis, writing - review & editing.

All authors have read and approved the manuscript.

TM e SG: Conceptualização, análise formal, recolha de dados, redação do rascunho original.

PCS e TT: Recolha de dados, redação - revisão.

BO: Análise estatística, redação - revisão.

MLC, CH e RP: Conceptualização, análise formal, escrita - revisão e edição.

Todos os autores leram e aprovaram o manuscrito.

RESPONSABILIDADES ÉTICAS

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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.

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ETHICAL DISCLOSURES

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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).

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