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The Incidence and Mortality of Ocular Melanomas

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Abstract: With the increasing incidence of ocular melanomas and gaps in existing literature, we hope to better understand the epidemiology, incidence, and mortality of ocular melanoma and its subtypes to inform clinical practice. The SEER (Surveillance, Epidemiology, and End Results) program, which focuses on compiling data on a multitude of cancers within the U.S. population, was utilized in data collection in a retrospective database analysis. We used this data to compare trends over a 10-year (2010-2020) period in adults aged 18 and older. A total of 1,944 patients were included in this study. Throughout the years of interest, there was a slightly positive R2 value of 0.17. The overall mean survival months was 54.7 with a standard deviation of 33.1. The ocular melanoma subtype with the lowest mean survival months was lacrimal gland (24.5 months) and the highest was corneal (109.3 months). Building upon conclusions of previous studies, the incidence of ocular melanomas is increasing slightly from 2010-2020 with an R2 value of 0.17. Each ocular melanoma subtype has differing epidemiological characteristics, incidence, and mortality, highlighting the importance of assessing and treating each patient in a personalized manner.

Keywords: ocular melanoma; ocular oncology; epidemiology

1. Introduction

Ocular melanomas (OMs) manifest through uncontrolled melanocyte proliferation within the eye [1]. They are classified into uveal and non-uveal types. Uveal melanoma, which accounts for the majority of OMs (85.0%), includes choroidal, ciliary body, and iris melanomas, while non-uveal melanoma consists of conjunctival, corneal, retinal, and orbital melanomas [2,3]. In the United States, the incidence of OM ranges from 5.1 to 6 cases per million people per year, with the highest rates occurring in the southern latitudes [4,5]. Uveal melanoma is the most frequently diagnosed primary malignant tumor within the eye in adults and is the second most common site for melanoma after the skin, accounting for 5% of all primary melanoma cases [6,7].

While there is no consistent sex-related difference in OM, epidemiological studies have shown that men exhibit a higher prevalence [4]. OM is more commonly found in older individuals, and it is less frequent in non-white populations, particularly among Black individuals, where the prevalence is the lowest [8]. The pathophysiology of Oms involves several mechanisms, including oxidative damage to pigmented ocular tissues, genetic mutations such as adenine-to-cytosine or adenine-to-thymine changes, and the development of OM from pre-existing pre-malignant lesions [9–11]. In terms of genetics, uveal melanomas are often associated with mutations in the GNAQ and GNA11 genes, while conjunctival melanomas typically involve mutations in BRAF, NRAS, and the TERT promoter gene [12]. Additionally, environmental factors such as light skin color, occupational sun exposure, atypical cutaneous nevi, and tanning can increase the risk of developing OMs alongside these genetic alterations [13].

Despite notable strides in understanding uveal melanomas, comprehensive epidemio- logical investigations into the diverse OM subtypes are conspicuously absent, creating agap in current scientific discourse. As the incidence of OMs demonstrates an observable increase, the scientific community stands at a juncture where a deeper comprehension of these malignancies becomes not only desirable but imperative. This study aims to guide the scientific community toward a more

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profound understanding of the complexities inher- ent in OMs, with the ultimate goal of translating such insights into enhanced diagnostic precision, prognostic accuracy, and therapeutic efficacy for improved patient outcomes.

2. Materials and Methods

The data for this retrospective study was sourced from the Surveillance, Epidemiology, and End Results (SEER) program, a comprehensive cancer registry with historical data based in the United States. The SEER database provided a robust platform for the examination of OMs, encompassing subtypes such as uveal, conjunctival, and iris melanomas. This study adhered to ethical guidelines outlined by the SEER program. As the data accessed was de-identified and publicly available, no specific ethical approval was required. The study design ensured confidentiality and privacy in compliance with ethical standards governing the use of patient-related information.

The study included adult patients aged 18 and older, diagnosed with OMs between 2010 and 2020. We collected both demographic variables, such as age, gender, ethnicity, and clinical variables, such as OM subtype, TNM staging, and survival outcomes. Data analysis was conducted using Microsoft® Excel® (Microsoft Office Corporation,

2021) to calculate descriptive statistics such as mean, median, standard deviation, and percentages. To explore trends over the 10-year period, a linear regression analysis was performed, and the coefficient of determination (R2 value) was calculated. It ranges from 0 to 1, where 0 indicates that the model does not explain any of the variability of the dependent variable, and 1 indicates that it explains all the variability. Additionally, representative tables were generated to visualize demographic characteristics, survival rates, and other relevant variables.

3. Results

A total of 1,944 patients were included in this study, with both male (n = 1,037, 53.3%) and female (n = 907, 46.7%) participants. The median age range for OM patients was 60-64 years. The most common age group was 70-74 years (n = 317, 16.3%) and the lowest number of participants was observed in the 25-29 age group (n = 16, 0.82%). The most observed OM subtype was choroidal melanoma (n = 1,601, 82.4%), followed by ciliary body (n = 196, 10.1%) and conjunctival melanoma (n = 120, 6.2%). The majority of patients were white (n = 1,856, 95.5%), while American Indian/Alaskan natives constituted the smallest portion (n = 7, 0.36%) (Table 1).

Table 1. Demographics of Patients with Ocular Melanoma and Associated Subtypes.

	Ocular Melanoma Subtypes							
	Conjunctiva	Cornea	Retina	Choroid	Ciliary Body	Lacrimal Gland	Orbit	Total
Number	120	4	5	1601	196	2	16	1944
Age								
20-24	2	0	0	14	2	0	0	18
25-29	2	0	0	11	3	0	0	16
30-34	4	0	0	28	8	0	0	40
35-39	6	0	0	50	11	0	0	67
40-44	5	0	0	70	13	0	0	88
45-49	7	1	1	112	10	0	2	133
50-54	9	0	0	171	13	0	1	194
55-59	10	0	2	226	19	0	0	257
60-64	17	0	1	235	21	0	5	279
65-69	17	2	0	265	30	1	2	317
70-74	11	1	1	186	32	0	3	234
75-79	14	0	0	140	16	0	1	171

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80-84	16	0	0	93	18	1	2	130
Gender								
Male	70	1	2	863	88	1	12	1037
Female	50	3	3	738	108	1	4	907
Ethnicity								
White	106	4	4	1539	188	0	15	1856
Black	3	0	0	15	0	1	0	19
American Indian*	3	0	0	4	0	0	0	7
Asian**	5	0	1	33	4	1	1	45
Unknown	3	0	0	10	4	0	0	17
Year of Diagnosis								
2010	14	2	1	117	11	1	4	150
2011	10	1	1	121	14	0	3	150
2012	10	0	0	137	16	0	0	163
2013	17	0	0	174	26	0	0	217
2014	7	1	1	142	23	0	1	175
2015	9	0	1	159	18	0	0	187
2016	11	0	0	152	12	0	1	176
2017	8	0	0	145	18	0	0	171
2018	13	0	1	154	20	1	2	191
2019	7	0	0	159	25	0	3	194
2020	14	0	0	141	13	0	2	170

*American Indian or Alaska Native **Asian or Pacific Islander.

Throughout the years of interest, there was a slightly positive R2 value of 0.17 for incidence of OM between 2010 and 2020 (Table 1). The R^2 values, from largest to smallest, were 0.45 for corneal melanoma (n = 4), 0.24 for choroidal melanoma (n = 1,601), 0.16 for retinal melanoma (n = 5), 0.05 for ciliary body melanoma (n = 196), 0.025 for conjunctival melanoma (n = 120), 0.022 for lacrimal gland melanoma (n = 2), and 0.007 for orbital melanoma (n = 16).

The most common tumor size was T1 (n = 552, 43.2%), followed by T2 (n = 355, 27.8%), and T3 (n = 250, 19.6%) (Table 2). The most common nodal involvement stage was N0 (n = 1,453, 99.6%), followed by N1 (n = 6, 0.4%). There were no OMs with N2 or N3 classification. Regarding metastatic spread, the most common stage was M0 (n = 1,542, 98.2%), followed by M1 (n = 29, 1.8%). There were no OMs with M2 or M3 classification. The overall mean survival time for OM was 54.7±33.1 months. The OM subtype with the lowest mean survival months was lacrimal gland melanoma (n = 2, 24.5 months) and the highest was corneal melanoma (n =4, 109.3 months) (Table 2).

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Table 2. TNM Cancer Staging and Survival (Months) by Ocular Melanoma Subtype.

	Ocular Melanoma Subtypes							
	Conjunctiva	Cornea	Retina	Choroid	Ciliary Body	Lacrimal Gland	Orbit	Total
Staging*								
Tis**	4	0	0	0	0	0	0	4
T1	68	0	0	426	58	0	0	552
T2	7	0	0	322	26	0	0	355
T3	11	0	0	209	30	0	0	250
T4	0	0	0	103	13	0	0	116
TX	11	0	0	244	37	0	0	292
N/A	19	4	5	297	32	2	16	375
N0***	89	0	0	1210	154	0	0	1453
N1	3	0	0	3	0	0	0	6
N2	0	0	0	0	0	0	0	0
N3	0	0	0	0	0	0	0	0
NX	9	0	0	91	12	0	0	112
N/A	19	4	5	297	30	2	16	373
M0****	100	0	0	1284	158	0	0	1542
M1	1	0	0	20	8	0	0	29
M2	0	0	0	0	0	0	0	0
M3	0	0	0	0	0	0	0	0
MX	0	0	0	0	0	0	0	0
N/A	19	4	5	297		2	16	343
Survival	Conjunctiva	Cornea	Retina	Choroid	Ciliary Body	Lacrimal Gland	Orbit	Total
Months	56.5 ± 38.3	109.3 ± 26.7	46.4 ± 35	52.1 ± 35.6	47.7 ±34.7	24.5 ± 13.4	46.1 ± 47.8	54.6 ± 33

*Tumor size and extent (T): Assessment of tumor size and invasion into adjacent structures; Lymph node involvement (N): Evaluation of cancer spread to nearby lymph nodes around the ear or neck and within the eye; Distant metastasis (M): Determination of cancer spread to distant organs, with the liver being the most common metastatic site. **T categories for iris, ciliary Body, and choroidal melanomas based on American Joint Committee on Cancer (AJCC). For iris melanoma: TX: Primary tumor cannot be assessed. Tis: No growth in to deeper cell layers. T1: Tumor confined to the iris, further classified as T1a (1/4 of iris), T1b (> 1/4 of iris), or T1c (with glaucoma). T2: Tumor extends into the ciliary body or choroid, subcategorized into T2a (ciliary body), T2b (ciliary body and choroid), and T2c (with glaucoma). T3: Tumor invades the sclera. T4: Tumor extends outside the eyeball, classified by size (T4a 5 mm, T4b > 5 mm). For ciliary body and choroidal melanomas: TX: Primary tumor cannot be assessed. Tis: No growth in to deeper cell layers T1-T4 tumors further subdivided based on invasion into the ciliary body or spread outside the eyeball, with different classifications for tumors growing into or outside the eyeball and their respective size (5 mm or > 5 mm). *** N categories for lymph node involvement in ocular melanoma based on American Joint Committee on Cancer (AJCC). NX: Lymph nodes cannot be assessed. N0: No cancer spread to nearby lymph nodes. N1: Cancer has spread to nearby lymph nodes or to other parts of the eye as small deposits. N1a: Cancer has spread to nearby lymph nodes. N1b: No spread to lymph nodes, but small cancer deposits are present in other parts of the eye. **** M categories for distant metastasis in ocular melanoma based on American Joint Committee on Cancer (AJCC). M0: No cancer spread to distant parts of the body. M1: Cancer has spread to distant parts of the body. M1a: The largest area of cancer spread is no more

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than 3 centimeters (cm) — just over 1 inch — across. M1b: The largest area of cancer spread is between 3.1 and 8 cm (8 cm is just over 3 inches) across. M1c: The largest area of cancer spread is 8.1 cm or more across.

4. Discussion

OMs are complex in nature and result from an interplay of both genetic and environmental factors. Each subtype of OMs warrants specific considerations and are represented by unique epidemiological characteristics. In the current study, we analyzed OM cases registered in the SEER database from 2010 to 2020, concentrating on the epidemiological, demographic, staging, and survival characteristics of various subtypes of OM.

Our datasets indicated that choroidal melanoma was the most frequently diagnosed form of OM in the United States between 2010 and 2020. Over 92% of the cases in our dataset were choroidal, ciliary body and iris melanomas, consistent with previous reports highlighting the higher prevalence of uveal melanoma among the various types of OM [6]. Older individuals were more likely to be affected by OM, with the median age of diagnosis being 60-64 years. This pattern was consistent across different subtypes, as the median age groups for choroidal, ciliary body, and conjunctival melanomas were all within the 60-64 range. Previous reports have also highlighted an increasing incidence of OM with age, noting that the peak occurrence is typically between 55 and 70 years [5,14]. Age-adjusted incidence in previous epidemiological studies shows a higher prevalence of OM in men (5.8 per million) compared to women (4.4 per million) [4]. However, in our study, no significant gender differences were observed, with nearly equal representation of male (53.3%) and female (46.7%) patients.

Previous studies highlighted differences in risk associated with race with non-Hispanic white populations being affected in a much greater proportion compared to others [1]. This conclusion is also supported by the results of the current study, as white patients made up 95.5% of all OM patients from 2010 to 2020. Asian/Pacific Islander, Black, and American Indian/Alaska Native patients were significantly lower in number (2.3%, 0.98%, and 0.36%, respectively). We observed a slight rise in incidence of OMs over the 10-year period. Although similar increasing incidence of OM over time has been previously reported [15], the low R^2 value suggests that other significant factors influencing OM incidence were not captured in our analysis, potentially including lifestyle factors, changes in diagnostic practices, or unmeasured environmental exposures. There were stark differences when evaluating the incidence trends of each OM subtype. It is difficult to make conclusions regarding the OM subtypes with lower numbers, such as those affecting the cornea, retina, lacrimal gland, and orbit. However, it is apparent that choroidal melanoma has increased from 2010 to 2020 (R2 = 0.24), while rates of ciliary body (R2 = 0.05) and conjunctival (R2 = 0.025) melanomas were remaining rather steady. Many studies combine information regarding melanomas affecting the uveal tract into a single metric, including choroidal, iris, and ciliary body. The findings of this study highlight the importance of evaluating the epidemiology of each individually, as they can differ significantly. Though data on TNM staging of OMs is limited, it is apparent that there are some differences present among each subtype. According to TNM staging information available in SEER for OMs, the most common size classification for choroidal, ciliary body, and conjunctival melanomas was T1 (40.2%, 45.7%, and 75.6%, respectively). While a strong majority of conjunctival melanomas presented as T1, choroidal and ciliary body melanomas had more diversity in T-staging. Nodal involvement was rare for OMs with nearly all being classified as N0 (99.6%) and only 6 total cases of N1 (0.4%). Metastatic spread was also rare, with M0 stage accounting for 98.2% of cases. When evaluating each subtype, 4.8% of ciliary body cases had M1 classification. Accordingly, it is possible that ciliary body may have higher rates of metastasis, in comparison with other OM subtypes.

When evaluating the subtypes of OM with higher representation, we find differences in survival in each subtype. The mean survival months for conjunctival, choroidal, and ciliary body melanomas were 56.5, 52.1, and 47.7 months, respectively. This again highlights the importance of evaluating each subtype of OM individually when evaluating mortality. Though lacrimal gland melanoma has the lowest mean survival months and cornea had the highest, the low number of patients make it difficult to accurately analyze the results.

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There were several limitations in this research study that make it difficult to draw generalizable conclusions. The first limitation was low numbers of certain OM subtypes, such as corneal, retinal, lacrimal gland, and orbital melanoma. It is difficult to draw mean- ingful conclusions regarding incidence and mortality due to these low patient numbers. Another limitation was in the availability of TNM staging information. In addition to the complete lack of information regarding OMs affecting the cornea, retina, lacrimal gland, and orbit, there were many unavailable data points for conjunctival, choroidal, and ciliary body melanomas. A final limitation that may affect external validity is the inclusion of only patients from the United States in the SEER database. This limitation makes it difficult to generalize the results to patients internationally. On the other hand, findings of this study, including an increasing incidence of OMs over the 10-year period, varying rates of increase among different subtypes, potential differences in mortality rates between sub- types, and diverse survival durations, highlight the importance of providing tailored care for each subtype. By understanding the incidence and mortality associated with various subtypes of OMs, clinicians can better understand the follow-up and surveillance necessary to appropriately address the melanoma and associated conditions.

5. Conclusions

The findings of this study provide novel insight into the epidemiology of various subtypes of OM. Each OM subtype has differing epidemiological characteristics, incidence, and mortality, highlighting the importance of assessing and treating each patient in a personalized manner. OMs can be fatal and the findings of this study highlights the importance of effective surveillance, diagnosis, and treatment.

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