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Short Communication

Primary Sites and Clinicopathological Features of Corneal Melanoma: A SEER Population-Based Study of 29 Cases

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ISSN : 2578-0360

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Submission: February 08, 2024
Published: February 27, 2024

Volume 3 - Issue 4

How to cite this article: Alexander W Suh*, Kenneth Tran, Isabelle Lian, Preston Tsang1, Minqi Huang, Elisa Ledet, Jian Li and Nguyen Duc Dinh Dang. Primary Sites and Clinicopathological Features of Corneal Melanoma: A SEER Population-Based Study of 29 Cases. Med Surg Ophthal Res. 3(4). MSOR. 000566. 2024.
DOI: 10.31031/MSOR.2024.03.000566

Abstract

Introduction: Corneal Melanoma (CM) is a rare malignancy that develops from melanocytes within the cornea, constituting a minority of all ocular tumors. In this study, we sought to investigate the clinicopathological characteristics correlated with the prognosis of CM patients.

Methods: We collected patients with CM between 1983 and 2018 from the Surveillance, Epidemiology, and End Results (SEER) database. Cox proportional hazards regression was used for univariate analysis to value Hazard Ratio (HR) of malignant CM versus spindle cell melanoma and nodular melanoma subgroups.

Results: A total of 29 eligible patients were collected in our study. Age at diagnosis, laterality, primary site, tumor size, the extent of disease, marital status, income, residential area, and treatment showed no significant prognostic factors for CM patients (P>0.05). However, when concerned with the primary site of malignant melanoma, spindle cell melanoma (P<0.05) and nodular melanoma (P<0.05) were found to show significantly poorer prognosis in CM patients.

Conclusion: Age at diagnosis, laterality, primary site, tumor size, the extent of disease, and treatment were not significant prognostic indicators for CM patients. Spindle cell melanoma and nodular melanoma were notable for showing worse survival outcomes than malignant melanoma. Although the sample size in the SEER database was limited, our findings may provide motivation for tailoring individualized treatments for patients with CM with different primary sites.

Introduction

Corneal Melanoma (CM), first reported in 1892, is an extremely rare variation of ocular melanoma [1]. As there is limited documentation describing the origin of the disease, there are multiple proposed theories to explain the possible etiologies. One theory is that CM arises from contiguous spread of an undetectable conjunctival melanoma into corneal tissue, which lacks melanocytes. Another theory, called primary acquired melanosis (PAM), suggests that melanocytes undergo malignant change and extend into the cornea. PAM tumors originate from conjunctival melanocytic migration arising at the limbus. Migrating melanocytes can then invade corneal stroma by way of penetrating traumas or complicated surgeries to infiltrate Bowman's membrane [2]. CM is incredibly rare and has yet to be summarized beyond a case study setting . A deeper understanding of the disease pathology and prognosis is necessary to better treat future patients.

The presentation of CM usually includes gradual loss of vision, pain, discomfort, and a dense pigmentation over the cornea, subsequently interfering with vision [3]. Two case reports have described extensive evasion of tumor tissue, resulting in dense pigmentation covering the cornea and difficulty with eyelid closure [3,4]. Risk factors are poorly defined for such an extremely rare cancer and any disposition or origins of primary CM has not been

fully characterized. While there is no consensus on a gold standard for diagnosis, slit-lamp examinations, ultrasound, and excisional biopsies have been used in case reports to detect and identify cases of CM [3]. Panagiotou et al. [1] noted the rules of atypia for corneal melanoma mimic the rules of melanoma of the skin:: "Irregular boundaries, change in shape, color, size, presence of epithelial defects or ulcers on the surface, dilated feeder blood vessels leading to the tumor, and displacement and/or infiltration of adjacent tissues" [1]. Therapeutical modalities have also not been well-defined due to the inherently rare incidence of CM. Surgical excision, cryotherapy, and topical chemotherapy followed by steroid and antibiotic medicine have been described to have a good prognosis [1,2]. However, there is a need for tailored treatment approaches for specific histologic subtypes. In this study, we conducted a SEER population-based study that included 29 cases to identify possible prognostic roles of several clinicopathogical factors of CM. Our aim was to investigate the patterns, risks for development, and socioeconomic factors that may contribute to the incidence of corneal melanoma. The rarity of this subject makes characterizing the disease difficult, but the data may provide support for future facilitation of clinical predictions, prognosis, and therapeutic guidance for patients diagnosed with CM.

Materials and Methods

Cohort information for all patients was sourced from The National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) Program database across 18 registries, available at [www.seer.cancer.gov]. This database encompasses approximately 48% of the entire U.S. population and is widely utilized in reputable tumor epidemiology research [5]. The data, extracted from the database, underwent analysis through SEER*Stat software (version 8.4.2).

The following inclusion criteria was applied to the patient cohort for this study:

A. Patients distinguished with primary malignancy from 1983 to 2018 were reviewed;

B. The diagnoses for all cases in the cohort were established during the patients' lifetime, with exclusion criteria specifically omitting cases involving death certificates or autopsies;

C. Morphology codes defined by the international classification of diseases for oncology (ICD-O-3);

D. Primary Site Extent of Disease Data coded to the Cornea (C691);

E. Not otherwise specified Histology Terms and Codes for Melanoma in situ (8720/2).

After isolating cases matching the specified inclusion criteria, 24 malignant melanomas (Not Otherwise Specified (NOS)), 1 superficial spreading melanoma, 2 Spindle cell melanomas, 1 Nodular melanoma, and 1 epithelioid cell melanoma were identified.

Statistical Analysis

Relevant demographic or clinicopathological variables, including sex, age at diagnosis, laterality primary tumor site, tumor size, extent of disease, treatment, medical facility, marital status, income, and residential area were brought into the analysis. The age at diagnosis was sorted based on 10-year intervals. Overall Survival (OS), the time from diagnosis to death due to all possible causes, was our primary outcome measure. A Cox proportional hazards regression was used for univariate analysis of survivals. The Hazard Ratio (HR) and matched 95% Confidence Interval (CI) of OS were generated. Statistical significance was defined as $p<0.05$. Cox proportional hazards regression was performed using JMP Statistical Discovery, version JMP 17.2 (SAS Institute, Cary, North Carolina, USA).

Results

Patient baseline characteristics

Overall, 29 patients were included in the study. The clinicopathological characteristics of CM patients are shown in (Table 1). Among the patients included, 16(55%) were male. The median age for the CM patients at diagnosis was 69 years old. For histological subtype, 24(83%) were malignant melanoma (NOS), 1(3%) was superficial spreading melanoma, 2(7%) were spindle cell melanoma (NOS), 1(3%) was nodular melanoma, and 1(3%) was epithelioid cell melanoma. Among the overall patients, 23(79%) underwent surgery, 2(7%) underwent radiation, and the rest (14%) were unknown. The median survival time for all enrolled patients was 83 months.

Table 1: Baseline Demographics and Clinical Characteristics of Patients (n=29).

Characteristics	Variable	n	%
Sex	Female	13	45%
	Male	16	55%
Age at Dx	<50 years	6	21%
	50-59 years	3	10%
	60-69 years	7	24%
	70-79 years	5	17%
	80+ years	8	28%
Laterality	Left	13	45%
	Right	16	55%

Primary Site	Malignant melanoma, NOS	24	83%
	Superficial spreading melanoma	1	3%
	Spindle cell melanoma, NOS	2	7%
	Nodular melanoma	1	3%
	Epithelioid cell melanoma	1	3%
Tumor Size (in mm)	Unknown; size not stated; not stated in patient record.	21	72%
	Greater than 1cm	3	10%
	less than 1cm.	5	17%
Extent of Disease	Localized	19	66%
	Unstaged	10	34%
Treatment	None/Unknown	4	14%
	Surgery	23	79%
	Radiation	2	7%
Medical Facility	Hospital inpatient/outpatient or clinic	25	86%
	Physicians office/private medical practitioner (LMD)	2	7%
	Laboratory only (hospital or private)	1	3%
	Other hospital outpatient unit or surgery center (2006+)	1	3%
Marital Status	Unknown	5	17%
	Single (never married)	5	17%
	Married (including common law)	14	48%
	Widowed	3	10%
	Divorced	2	7%
Income	$35,000 - $49,999	5	17%
	$50,000 - $59,999	4	14%
	$60,000 - $69,999	8	28%
	$70,000+	12	41%
Residential Area	< 250,000 population metropolitan area	3	10%
	250,000-1,000,000 population metropolitan area	6	21%
	> 1,000,000 population metropolitan area	16	55%
	Near metropolitan area	3	10%
	Not near a metropolitan area	1	3%

Prognostic factors associated with the overall survival of corneal melanoma

Sex, age at diagnosis, laterality primary tumor site, tumor size, extent of disease, treatment, medical facility, marital status, income, and residential area were included in the analysis. Different outcomes were observed with different histologic subtypes compared to the malignant melanoma (NOS) subtype. Spindle cell melanoma (NOS) had poorer outcomes compared to malignant melanoma (OS, malignant melanoma, reference; HR 19.09, 95% CI 1.145-318.2, P<0.05). Nodular melanoma similarly had worse outcomes compared to malignant melanoma (OS, malignant melanoma, reference; HR 27.5, 95% CI 1.72-439.6, P<0.05). Survival outcomes were worse for patients treated at other hospital outpatient units or surgery centers compared to those who received care at inpatient/outpatient hospitals or private medical offices (OS, hospital inpatient/outpatient or clinic, reference; HR 27.5; 95% CI 1.72-439.6, P<0.05). Our results indicated that the sex, age at diagnosis, laterality, tumor size, extent of disease, treatment, marital status, income, and residential area had no significant impact on the OS (Table 2).

Table 2: Cox regression analysis of Overall Survival for Corneal Melanoma Patients (n=29)

Note: *P<0.05

Abbreviations: HR: Hazard Ratio; CI: Confidence Interval; NOS: Not Otherwise Specified

Characteristics	Variable	HR	Lower 95%	Upper 95%	p-value
Sex	Female	Reference			
	Male	0.91775	0.2034	4.141	0.911

Age at Dx	<50 years	Reference			
	50-59 years	<0.0001	0	Inf	0.999
	60-69 years	<0.0001	0.05352	3.732	0.457
	70-79 years	<0.0001	0	Inf	0.999
	80+ years	<0.0001	0	Inf	0.999
Laterality	Left	Reference			
	Right	0.4942	0.1092	2.237	0.36
Primary Site	Malignant melanoma, NOS	Reference			
	Superficial spreading melanoma	2.209	0.2644	18.46	0.464
	Spindle cell melanoma, NOS	19.09	1.145	318.2	0.0399*
	Nodular melanoma	27.5	1.72	439.6	0.0191*
	Epithelioid cell melanoma	<0.0001	0	Inf	0.999
Tumor Size (in mm)	Unknown; size not stated; not stated in patient record.	Reference			
	Greater than 1cm	1.494	0.1786	12.5	0.711
	less than 1 cm.	1.442	0.08312	5.788	0.735
Extent of Disease	Localized	Reference			
	Unstaged	0.3465	0.3467	24.03	0.327
Treatment	None/Unknown	Reference			
	Surgery	0.5415	0.1036	2.832	0.467
	Radiation	<0.0001	0	Inf	0.999
Medical Facility	Hospital inpatient/outpatient or clinic	Reference			
	Physician's office/private medical practitioner (LMD)	<0.0001	0	Inf	0.999
	Laboratory only (hospital or private)	<0.0001	0	Inf	0.999
	Other hospital outpatient unit or surgery center (2006+)	27.5	1.72	439.6	0.0191*
Marital Status	Unknown	Reference			
	Single (never married)	1.762	0.3399	9.136	0.5
	Married (including common law)	0.3489	0.06728	1.809	0.21
	Widowed	2.114	0.2509	17.82	0.491
	Divorced	7.963	0.7081	89.54	0.0929
Income	$35,000 - $49,999	Reference			
	$50,000 - $59,999	3.395	0.654	17.62	0.146
	$60,000 - $69,999	0.9015	0.1728	4.702	0.902
	$70,000+	0.2497	0.02993	2.084	0.2
Residential Area	< 250,000 population metropolitan area	Reference			
	250,000-1,000,000 population metropolitan area	4.344	0.9589	19.68	0.0567
	> 1,000,000 population metropolitan area	0.4521	0.08745	2.337	0.344
	Near metropolitan area	1.084	0.1299	9.047	0.94
	Not near a metropolitan area	<0.0001	0	Inf	0.999

Discussion

This study identified 29 patients with different characteristics and outcomes from the SEER database and systematically analyzed for potential prognostic factors of CM. From this nationwide sample, we found that spindle cell melanoma and nodular melanoma patients showed significantly worse survival outcomes ($p<0.05$). Most cases of CM arise from metastatic melanoma, but this primary site was not found to significantly correlate to survivability. Patients who received treatment from other hospital outpatient units or surgery centers had poorer survival outcomes in comparison to those who received care from either an inpatient/outpatient hospital or private medical office . Inpatient/outpatient hospitals and private medical offices may offer a more comprehensive range of services, including specialized treatments and a multidisciplinary

approach, which could contribute to better overall patient outcomes. Additionally, the continuity of care and follow-up provided by these settings may play a role in improving survival rates compared to more specialized or limited-care facilities. Beyond these factors, age at diagnosis, laterality, primary site, tumor size, the extent of disease, marital status, income, residential area, and treatment showed no significant prognostic factors for CM patients ($p>0.05$). This was likely due to the rarity of CM and the associated challenges of obtaining robust survival data for this disease. Survival rates are crucial in medical treatment planning as they inform the patient and care team about prognosis and potential outcomes for individuals diagnosed with life changing conditions. Based on the patient population recorded in the SEER database, we showed that those with spindle cell melanoma and nodular melanoma primary sites could benefit from treatments tailored to a specific primary site. While there was limited statistical significance, this study provides valuable insight into survival trends that are essential for clinicians and researchers to guide treatment decisions and tailor patient counseling. Patients and their families can make more informed decisions about their healthcare when they have access to survival rate and prognostic data to help weigh the potential risks and outcomes. Together, the healthcare team can assist in setting realistic expectations and facilitating shared decision making in the management of CM.

There are several limitations to note in this study. Due to the low prevalence of CM, our sample size was small, which limits the statistical power of the study. While the SEER Database provides ample individual factors to consider, some additional factors that would be beneficial to consider for CM include a more detailed characterization of radiotherapy (e.g., dosage and location), treatment plans (e.g., topical chemotherapy, cryotherapy), frequency of postoperative follow-up, and visual acuity. Therapeutic management in several case studies included surgical excision [1-4]. In a study describing corneal primary acquired melanosis, recommended treatment was to do a complete excision with alcohol debridement of Bowman's later. After excision, adjuvant double freeze- thaw cryotherapy was performed on adjacent conjunctiva free margins. This technique yielded favorable outcomes and a close nine-year follow-up period showed no recurrence in one recorded case of corneal melanoma [2]. In another case, feeder vessels were cauterized before the lesion was removed on free margins then the corneal epithelial was scraped. Post-procedural topical chemotherapy was administered (mitomycin 0.03%, 2x4 for 2 weeks and dexamethasone 0.1%, 2x4 for the following 2 weeks, followed by another cycle of mitomycin 0.03%, 2x4 for another 2 weeks). After two years, the eye was fully functional and there were no signs of local or distant recurrence [1]. Future studies should investigate diverse treatment modalities and prognosis associated with various cases of CM. Findings may provide comprehensive guidance for future cases, shedding light on the most effective treatment approaches and offering valuable insights into the expected outcomes for patients diagnosed with CM. Drawing from a multicenter database, we investigated numerous independent prognostic factors for CM survivability and uncovered several factors-primary site and alternative care facilities-for further research. These findings can help guide researchers in designing more targeted studies to explore these factors in greater detail. Being diagnosed with a rare and potentially serious cancer like CM can be incredibly demanding physically, mentally, and socially. We emphasize the importance of providing patients with as much information as possible to support their emotional well-being and empower them with knowledge of new avenues to explore with their care team.

Conclusion

Ultimately, age at diagnosis, laterality, primary site, tumor size, the extent of disease, and treatment were not significant prognostic indicators for CM patients. The incidence of corneal melanoma is rare and underrepresented in literature. In this study, we gathered and describe CM across the US from 1983-2018 year. We found that spindle cell and nodular melanoma were associated with significantly lower overall survival compared to other subtypes of malignant melanoma. Although the sample size in the SEER database was limited, our findings may provide support for future facilitation of clinical predictions, prognosis, and therapeutic guidance for CM patients.

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