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Metastatic Conjunctival Melanoma: A Multicenter International Study

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SYNOPSIS

This multicenter, international registry-based study on conjunctival melanoma validates multiple high-risk factors for metastatic conjunctival melanoma and discovered new information about post-metastatic survival.

ABSTRACT

Background: To reveal clinical findings related to metastatic conjunctival melanoma.

Methods: Ten ophthalmic oncology centers (9 countries and 4 continents) shared data to create a large clinical case series. The main outcome measures were the incidence and cumulative risk of systemic metastasis, study mortality rates, and Kaplan-Meier patient mortality after developing conjunctival melanoma metastasis.

Results: Of 288 patients, 29 developed metastasis. Five had metastasis at presentation, were AJCC cT3-category, and exhibited tumor-surface ulceration. Four of 5 (80%) had melanotic tumors with plical and or caruncular involvement, and died within one year. One survived 21 months. In contrast, 24 developed metastases during follow up (mean 4.6 $\pm$ 3.2 years). Their primary tumors were cT1 (n=13/24, 54.1%), cT2 (n=6/24, 25%), cT3 (n=2/24, 8.3%), and 3 cTx (12.5%) at presentation. Death had occurred in 17 patients (n=17/24, 71%) by the end of the study. The cumulative risk of systemic metastasis after treatment was 0.4% (95% CI, 0.6-2.9%) at 1 year, 8.6% (5.1-14.3%) at 5 years and 22.3% (14.5-33.5%) at 10-years. Each increase in AJCC cT-category was associated with an 89% higher risk for metastasis (HR = 1.89, $p<0.001$). Among all 29 patients who developed metastasis, those who presented with AJCC cT3 disease were at highest risk ($p<0.001$). Liver and lung (n=13 each) were the most reported metastatic sites.

Conclusion: Metastatic conjunctival melanoma was found in 10% of conjunctival melanoma patients. Tumor-specific characteristics including AJCC cT3-category, conjunctival location, and surface ulceration were associated with metastatic risk. Survival durations were shorter for those presenting with metastasis.

KEY MESSAGES

- **What is already known on this topic**

Conjunctival melanoma is a rare ocular malignancy with high mortality rates.

- **What this study adds**

This multicenter international data-sharing study revealed that patients who presented with metastasis had shorter survival. Further, that AJCC-cT3 category tumors were at highest risk for metastasis discovered both at presentation and during follow up. In addition, nodal disease may not be detectable in patients with metastatic conjunctival melanoma.

- **How this study might affect research, practice or policy**

This study helps identify significant predictors of metastatic disease and survival.

INTRODUCTION

Malignant melanoma of the conjunctiva is a sight and life-threatening cancer that comprises 5% of ocular and 0.25% of non-ocular melanoma. [1–4] The incidence of conjunctival melanoma is 0.2-0.8 cases per million which is 1/20th of cutaneous and 1/10th of uveal melanoma.[5–7] While the incidence of uveal melanoma is considered stable, cutaneous and conjunctival melanoma are on the rise.[6–14]

Though they share a melanocytic origin, the genetic defects associated with uveal melanoma differ from those found in conjunctival melanoma.[4,6,11,15–19] They also differ in metastatic routes, where they are venous and lymphatic respectively.[20] While early hepatic and cervical lymph node metastases have been reported respectively; with time both spread to multiple distant organ sites.[21–24] The location and extent of metastatic disease depends both on timing and methods of surveillance.[15,25]

Metastasis is a common cause of death for patients with conjunctival melanoma. The reported rate of metastatic mortality has been 30-40%, with no standard protocols for treatment.[6,19,26,27] Recently, several small case series have reported that systemic immunotherapy controlled diffuse, multifocal, unresectable, and systemic conjunctival melanoma.[16,28–32]

Herein, a multicenter, international, data-sharing registry was used to analyze patients with conjunctival melanoma. Though, data was collected prior to the advent of genetic analysis and immunotherapy; this collaborative work has revealed significant new medical evidence about the timing of presentation, specific tumor characteristics, and AJCC cT-categories predictive for metastatic death.

METHODS

Definitions

- Metastasis is defined as patients with distant metastasis, or “M1” (according to the 8th edition of the American Joint Committee on Cancer (AJCC) Staging System for Conjunctival Melanoma).[26]
- Metastases were further sub-grouped as those diagnosed at initial presentation or during follow-up.
- Time to death was defined as the interval between diagnosis of metastasis and death of the patient.

The Registry

An internet-based retrospective registry was designed by participating eye cancer specialists including members of the American Joint Committee on Cancer Ophthalmic Oncology Task Force, AJCC-OOTF. It collected data on epidemiology, clinical and pathological features of patients with conjunctival melanoma.[26] Herein, this study focuses on patients found to have metastatic conjunctival melanoma, subdivided into those presenting at initial presentation and others where it developed during follow up.

Internet Database, Security and Patient Protection

This multicenter, international study adhered to the tenets of the Declaration of Helsinki and the United States Health Insurance Portability and Accountability Act (HIPAA) of 1996. Both central and local Internal Review Board (IRB) approvals were obtained to both perform retrospective chart reviews and contribute data to the registry.

Patient privacy was ensured by using unique identifications numbers for each patient and there being no personal identifiers. Data security was ensured by secure socket

layer encryption, record locking and trail auditing. The registry access was limited only to participating centers, each with its own unique login such that one center could not view other center's records.

Eligibility Criteria

Ten ophthalmic oncology centers in 9 countries (2 in the United States, and 1 in Canada, Colombia, Argentina, France, Netherlands, United Kingdom, Sweden, and Jordan), on 4 continents (North America, South America, Europe, and Asia) participated in the study. Each center entered consecutive patients with conjunctival melanoma diagnosed and treated between 2001 and 2013.

In consideration of the lack of consensus guidelines for nodal or systemic surveillance as well as treatment for metastatic disease; no restrictions were placed on participating ophthalmic oncology centers in terms of methods of diagnosis, treatment, or systemic screening for metastasis. As a result, our methods consisted of the best available methods of practice throughout the world. Each was performed according to the customs and practices of the local institutions. For example, metastatic surveys were reported to have included one or more of the following investigations: magnetic resonance imaging (MRI), chest X-ray, computed axial tomography (CT) (e.g., neck, chest, abdomen, and pelvis), abdominal or cervical lymph node ultrasound imaging (USG), and whole-body positron emission tomography/ computed tomography (PET/CT).

Statistical Analysis

Continuous variables were expressed as mean with standard deviation or median with interquartile range (IQR) and group-wise comparisons were made using the student's t-test or Wilcoxon rank sum test for nonparametric variables. Similarly,

categorical variables were expressed as proportions (n, %) and comparisons were made using the chi-square test or Fisher's exact test.

Survival analysis was performed using mortality as the censoring variable and Kaplan-Meier (K-M) curves were plotted to depict cumulative mortality rates at various time points. Time to death was defined as interval between time of diagnosis and death. Comparison between the mortality rates of those with metastatic tumor at presentation versus those who developed metastasis later was analyzed using the log-rank test. Cox's proportional hazards analysis was done to determine risk factors for systemic metastasis and outcomes were presented as hazards ratios (HR) with 95% confidence intervals (CI).

Data was entered online, into a custom database resident and protected by Princess Margaret Comprehensive Cancer Center in Toronto, Ontario, Canada. The data was exported into Microsoft Excel and was analyzed using STATA (version 12.1, I/C, Fort Worth, Texas, USA) statistical analysis software package. P-values <0.05 were considered statistically significant.

RESULTS

The total number of consecutive conjunctival melanoma patients entered into the registry was 288. Of these, there was a predominance of primary AJCC cT1-category tumors (n= 218/288, 75.7%) followed by cT2 (n=24/288, 11.8%), cT3 (n=15/288, 5.2%) and cTx (n=21/288, 7.3%). There were no cT4 tumors.

Of the total cohort of 288 patients, 29 patients (10%) developed metastatic disease and were included in subgroup analysis. Amongst those 29 patients, 5 (17%) were found at the time of initial presentation; while 24 (83%) were discovered during follow up to 12 years. The mean age of these 29 patients was 60.8 $\pm$ 15.8 years and 19

(66%) were male. The mean age in the non-metastatic group of patients (n=259/288) was 59.6 ± 17 years and 128 (49%) were males.

Patients Presenting with Metastatic Conjunctival Melanoma

Five patients were discovered with metastasis at presentation (n=5/29, 17.3%). Clinical characteristics, histopathological features, treatment modalities, and outcomes of those with metastasis at presentation are shown in **Table 1.** On clinical examination, most (n=4/5, 80%) were noted to have melanotic tumors with diffuse and indistinct margins. One was amelanotic. All tumors were described as multifocal and had a mean diameter of 12 ± 4.4 mm. Plica and caruncular involvement was noted in 4 (n=4/5, 80%). The eyelid skin was involved in 4 (n=4/5, 80%), orbital tumor invasion was noted in 3 or 60%, and no tumors had invaded the globe. There is considerable literature supporting risk related to caruncular involvement as well as excellent reasons why the recesses of the caruncle and proximity to the orbit could increase risk for mortality. [3,9,11,24] However, it is also reasonable to assume that the presence of skin extension might suggest that these tumors were either more aggressive or present for a longer duration, and thus more advanced disease. All patients presenting with metastasis had AJCC cT3-category tumors. Lung and liver were the most reported metastatic sites **(Table 1)**. All treatments involved excisional biopsy along with tumor-free margins **(Table 1)**. Histopathology showed invasive melanoma with conjunctival melanocytic intraepithelial neoplasia/ primary acquired melanosis (CMIN/PAM) and epithelioid cells (n=5/5). Histological tumor surface ulceration was noted in 4 patients (n=4/5, 80%). All but 1 of these patients died within 1 year and the last at 21 months despite treatment.

Table 1: Clinical Characteristics, Histological Features, Treatment, and Outcomes of Patients with Metastasis at Presentation.

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	81	64	63	28	40
Gender	Male	Female	Female	Female	Male
Clinical Characteristics					
Primary tumor location	Bulbar	Non-bulbar	Bulbar	Non-bulbar	Non-bulbar
Number of tumor foci	6	3	3	3	2
Tumor color	Pink	Melanotic	Melanotic	Melanotic	Melanotic
Tumor margins	Diffuse	Diffuse	Diffuse	Distinct	Diffuse
Biopsy performed	Tumor excision	Tumor incision	Tumor excision	Tumor incision	Tumor excision
Local and Systemic Spread					
Plica involvement	Present	Present	Present	Not present	Present
Caruncle involvement	Present	Present	Present	Not present	Present
Globe involvement	Not present	Not present	Not present	Not present	Not present
Eye lid involvement	Present	Present	Present	Not present	Present
Orbital involvement	Present	Not present	Not present	Present	Present

Nasolacrimal involvement	Not present	Present	Present	Not present	Not present
Sinus involvement	Not present	Not present	Not present	Not present	Not present
Ipsilateral lymph node involvement	Not present	Present	Present	Present	Present
Metastatic sites	Lung	Liver	Liver, lung	Lung	Lung, bone
Pathological Characteristics					
Histology	All were found to be invasive melanoma with CMIN/PAM and epithelioid cells				
Ulceration on tumor surface	Not present	Present	Present	Present	Present
Tumor diameter X thickness	16 X 2.7 mm[7]	10 X 7 mm[7]	11 X 9.5 mm[7]	8 X 8 mm[7]	14 X 9 mm[7]
TNM and pT staging[1]	T3, N0, M1, pT3	T3, N1, M1, pT3	T3, N1, M1, pT3	T3, N1, M1, pT3	T3, N1, M1, pT3
Treatment	Excision biopsy	Excision biopsy + Cryo[2] + IFN[3] + MMC[4]	Excision biopsy + Cryo[2] + EBRT	Excision biopsy + Cryo[2] + IFN[3]+ MMC[4]	Excision biopsy + Cryo[2] + IFN[3] + MMC[4] + 5FU[5]
Death	Yes	Yes	Yes	Yes	Yes
Time to death	6 months	4 months	5 months	21 months	8 months

[1]TMN staging according to the 8th edition of the American Joint Committee on Cancer (AJCC) Staging System for Conjunctival Melanoma, [2]Cryo= cryotherapy, [3]IFN= Interferon alfa-2B, [4]MMC= Mitomycin-C, [5]5FU= 5-fluorouracil, [6]EBRT= External Beam Radiotherapy, [7]mm = millimeters, p = pathologic, T= tumor, N= node, M=metastasis

Patients that Developed Metastasis during Follow-up

Most patients developed metastasis after presentation (n=24/29, 82.7%). These patients developed metastasis at a mean 4.6 ± 3.2 years after initial treatment (median= 4.2 years, IQR= 2.2 – 6.4 years, range= 7 months – 14 years). The AJCC clinical staging for this sub-group was- cT1 (n= 13/24, 54.1%) followed by cT2 (n=6/24, 25%), cT3 (n=2/24, 8.3%) and cTx (n=3/24, 12.5%). Out of the 24, 11 patients (n=11/24=46%) had local recurrence and 13 (n=13/24, 54%) developed metastasis without local recurrence. Liver was the most reported site of metastasis (n=11/24, 45.8%), followed by lungs (n=9/24, 37.5%), brain (n=3/24, 12.5%), bone (n=2/24, 8.3%), abdomen (n=2/24, 8.3%), as well as bladder, peritoneum, parotid gland, and skin. Multiorgan metastasis was seen in 10 patients (n=10/24, 41.7%) with the lung and liver being the most common combination. Metastatic sites were not documented in 3 patients (n=3/24, 12.5%). The nodal status of this subset of patients is summarized in **Table 2**. There were only 10 patients (n=10/24, 41.6%) reported to have regional lymph nodes positive.

Table 2: Nodal Status of 24 Patients with Metastasis During Follow-up

S No.	Lymph node staging (N0 or N1)[1]	Lymph node group involved	Ipsilateral or contralateral group involved
1	N0	-	-
2	N0	-	-
3	N1	Cervical	Ipsilateral
4	N0	-	-
5	N0	-	-
6	N0	-	-
7	N1	Pre-auricular	Ipsilateral

8	N0	-	-
9	N1	Post-auricular	Ipsilateral
10	N1	Cervical	Ipsilateral
11	N0	-	-
12	N0	-	-
13	N0	-	-
14	N1	Cervical	Ipsilateral
15	N1	Cervical	Ipsilateral
16	N0	-	-
17	N1	Cervical	Ipsilateral
18	N0	-	-
19	N1	Cervical	Ipsilateral
20	N0	-	-
21	N0	-	-
22	N1	Cervical	Ipsilateral
23	N1	Cervical	Ipsilateral
24	N0	-	-

[1]TMN staging according to the 8th edition of the American Joint Committee on Cancer (AJCC) Staging, - leave blank

Amongst the 24 patients whose metastases were discovered during follow up, the cumulative rate of systemic metastasis after treatment was 0.4% (95% CI=0.6 to 2.9%) at the end of 1 year, and this increased to 8.6% (95% CI=5.1 to 14.3%) at 5 years and 22.3% (95% CI=14.5 to 33.5%) at 10 years (**Figure 1**). In this cohort,

13/24 eyes (54%) had cT1 disease at baseline, 6 (25%) had cT2, 2 (8%) had cT3 and 3 (13%) had cTx disease. There were no reported cT4-category tumors. AJCC cT3 disease was associated with the highest risk of systemic metastasis ($p<0.001$, log – rank) (**Figure 2**).

After excluding those with metastatic disease at presentation (n=24/29), there was an 89% higher risk (HR = 1.89, 95% CI= 1.29, 2.77, $p<0.001$) of metastasis for every +1 increment in cT-category. In addition, histologic evidence of invasive melanoma with CMIN/PAM increased risk of systemic metastasis 2.5 times (HR= 2.55, 95% CI = 1.1 – 5.9, p=0.03). Every 1.0 mm increment of increased tumor thickness (determined after excision) increased risk of systemic metastasis by 16% (HR=1.16, 95%CI=1.05 to 1.29, p=0.003). A total of 17 patients (n=17/24, 71%) died in this cohort. The cumulative mortality rate after developing systemic metastasis was 10.2% (95%CI=2.7 to 35.9%) at 2 years and increased to 42.1% (95%CI=23.7 to 66.7%) at 5 years.

Combined and Comparative Statistics

Including all 29 patients who develop metastasis, the liver and lung were the most common metastatic sites (44.8% for each). This was followed by CNS (n=3/29, 10.3 %), bone (n=3/29, 10.3%), abdomen (n=2/29, 6.9%), urinary bladder (n=1/29, 3.4%), peritoneum (n=1/29, 3.4%), and the skin (n=1/29, 3.4%).

A comparison between these two groups, that is, patients with metastasis at presentation compared to patients who developed metastasis during follow up is shown in **Table 3**. Those with metastasis at presentation were significantly more likely to be multifocal, plical and caruncle involvement, histopathologic findings of tumor surface ulceration, and deeper invasion on histopathology. Tumors in both groups had features of CMIN/PAM, it was found in only 50% of tumors that later

developed metastasis. The mortality rate was significantly higher for those with metastasis at presentation (**Figure 3**).

Table 3: Baseline Characteristics of Patients Presenting with Metastasis Versus those with Metastasis During Follow-up.

Characteristics	**Metastasis at Baseline (n=5)**	**Metastasis at Follow-up (n=24)**	**p-value**
Age	55.2 ± 21.1	62.1 ± 14.5	**0.56**
Gender (% Men)	2 (40%)	17 (71%)	**0.18**
Primary tumor location (% bulbar)	2 (40%)	13 (57%)	**0.73**
Number of tumor nodules	3.4 ± 1.5	1.1 ± 0.3	**<0.001**
Ulceration on surface	4 (80%)	2 (18%)	**0.01**
Tumor color (% melanotic)	4 (80%)	20 (83%)	**0.77**
Plica involvement	4 (80%)	2 (8.3%)	**0.02**
Caruncle involvement	4 (80%)	2 (8.3%)	**0.02**
Tumor diameter (mm^1)	12.6 ± 4.2	9.1 ± 5.3	**0.22**
Tumor thickness (mm^1)	6.5 ± 3.4	2.2 ± 1.9	**0.03**
Histology (% Invasive melanoma with CMIN/PAM)	5 (100%)	13 (57%)	**0.04**
TNM staging: cT1 (%)	0	13 (54%)	**<0.001**
Stage cT2	0	6 (25%)	
Stage cT3	5	2 (8%)	
Stage cTx	0	3 (13%)	

Treatment: Excision biopsy (%)	5 (100%)	24 (100%)	**0.99**
Cryotherapy	5 (100%)	7 (29%)	**0.11**
Adjuvants (MMC/IF/5FU)	4 (80%)	16 (67%)	**0.52**
Cumulative mortality at 2 years (95% CI[2])	100%	10.2% (2.7 to 35.9%)	**<0.001**
Cumulative mortality at 5 years (95% CI[2])	---	42.1% (23.7 to 66.7%)	**---**

[1]mm= millimeters, [2]CI= confidence interval

DISCUSSION

Herein, a multicenter, international, internet-based study was used to examine characteristics of patients with metastatic conjunctival melanoma. The study describes the clinical course of a relatively large number of patients with metastatic conjunctival melanoma followed over median 4.2 years. Unique differences were revealed between primary tumor characteristics and patient mortality when metastasis were discovered at presentation compared to those found during follow-up. For example, patients discovered with metastases at presentation were more likely to present with larger (AJCC cT3), multifocal and histopathologically ulcerated primary tumors. In contrast, those patients with metastasis at follow-up presented with AJCC cT1 (54%), cT2 (25%), and cT3 (8%) tumors. Though there was a significantly higher risk associated with each increase in cT-category, the highest overall risk was found amongst cT3 tumors.

Our findings related to tumor size and characteristics are important despite advances in genetic sub-typing and multiple small case-series showing diffuse multifocal and metastatic conjunctival melanoma respond to immunotherapy. [4,6,16,29–33] This is because there exist barriers to the availability of immunotherapy drugs like PD-1. These include but are not limited to limited awareness, cost, regulatory hurdles, trained doctor availability, and if available then supportive care for side-effects. It is reasonable to assume that immunotherapy is largely unavailable to many, if not most of the world's patients. [34] Similarly, our data was collected during the pre-immunotherapy era and thus survival rates will be improved where immunotherapy is available.

Most patients who developed metastatic conjunctival melanoma in this study died from their disease. Despite the best locally available systemic treatments, not one of those patients presenting with metastasis survived more than 21 months.

The risk of developing metastasis subsequent to presentation was 9% within 5 years. Kaplan-Meier estimated mortality was 10% at 2 years and 42% at 5 years. In addition, with every 1.0 mm increment in local tumor thickness, there was a 16% increase in risk of metastasis. Lastly, of all 288 patients in the registry, the overall all rate of distant metastasis was 10% (mean follow-up of 4.6 years).

Detection of Metastatic Conjunctival Melanoma

Reporting metastatic conjunctival melanoma is complicated in that there exists no standard protocol for detection of nodal or systemic conjunctival melanoma metastasis. Perhaps this is why published literature often report nodal and distant metastasis together (category "N" and "M" together).[35]

Methods of detection of regional lymph node and distant metastasis also vary. Clinical regional lymph node examination (in order of both invasiveness and

increasing cost) varies from palpation to ultrasound then radiographic imaging (e.g., CT, MRI, PET/CT), followed by surgical sentinel lymph node biopsy.[21,36,37] Methods used systemic surveillance include regional CT, MRI, and whole-body PET/CT.[38,39]

Conventional teaching is that nodal metastasis both precedes and is more common than distant metastasis. [23,24,35,40,41] This was not true in our study, as 60% of patients with metastatic conjunctival melanoma discovered during follow-up were reported to be AJCC N0 (nodal metastasis absent). This shows that metastatic conjunctival melanoma can occur without detected or detectable nodal metastasis.[3,25,42] In consideration of the known lymphatic drainage from the conjunctiva, we hypothesize that in our AJCC N0 patients with systemic metastasis, there likely existed lymphatic, nodal micro-metastases which may have been too small to discover by clinical or radiographic examination (Table 2). We could find no study that quantifies the amount of melanoma required to make a regional lymph node palpable, nor a consensus guideline for regional lymph node imaging or biopsy (even in the setting of metastatic disease). [25,37] On one hand, there exists recent literature that demonstrates a significant association between sentinel lymph node biopsy and mortality, [43,44] In contrast, there also exists a multitude of studies that report metastasis without nodal involvement (including this study). These authors find it is reasonable to suggest that the significance of lymph node involvement warrants further study [3.25,42] Clearly, like any other AJCC-UICC tumor systems, ophthalmic oncology could better define the importance of the “N” portion of TNM-staging of conjunctival melanoma. Of interest, the National Comprehensive Cancer Network (NCCN) guidelines for cutaneous melanoma state that nodal basin ultrasound should be considered prior to a sentinel lymph node biopsy for patients

with equivocal regional lymph nodes on clinical examination and that suspicious lesions on a nodal basin ultrasound should then be biopsied. [45]

In our study, the most common sites of distant metastases were liver and lung, which are the same as found in other studies.[3,23,24,40] However, our findings were dissimilar to other literature where the lung and brain were most common.[24,35,40,46] In either case, all studies support the necessity of long-term follow up with periodic surveillance.[38,39] This conclusion is highlighted by our findings that the cumulative risk for metastasis (Kaplan-Meier curves) jumped from less than 1% at 1 year to 22% at 10 years.

The weaknesses of our study are that it is retrospective, and that there were relatively small numbers of AJCC cT3-category tumors and no cT4. Furthermore, the participating oncology centers used their own standard methods of systemic surveillance for metastasis. [38,39]

The advantages of this study include that our results were derived data from multicenter, international ocular oncology sub-specialty centers from both medium, and high-resource countries. Each used their best clinical practices for diagnosis and treatment. Thereby, this study provides new and widely applicable information about a rare ocular tumor that can be used for clinical practice and informed consent.

Conclusion

Herein is described the results of a multicenter, international, internet-based, data-pooling study of conjunctival melanoma. It was performed to gather statistically significant evidence and thereby answer questions about this rare ocular malignancy. Metastatic conjunctival melanoma occurred in 10% of study patients and was predicted to occur in 22% at 10 years follow-up. Specific AJCC cT-categories, clinical features, and timing of presentation were found to affect metastatic risk. Overall, AJCC-stage was higher and survival durations shorter for those patients who presented with metastatic conjunctival melanoma.

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REFERENCES

1. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer.* 1998;83(8):1664-1678.

2. Seregard S. Conjunctival melanoma. *Surv Ophthalmol.* 1998;42(4):321-350.

3. Wong JR, Nanji AA, Galor A, Karp CL. Management of conjunctival malignant melanoma: A review and update. *Expert Rev Ophthalmol*. 2014;9(3):185-204.

4. Gkiala A, Palioura S. Conjunctival melanoma: Update on genetics, epigenetics and targeted molecular and immune-based therapies. *Clinical Ophthalmology*. 2020;14:3137-3152.

5. Peil J, Bock F, Kiefer F, et al. New Therapeutic Approaches for Conjunctival MelanomaWhat We Know So Far and Where Therapy Is Potentially Heading: Focus on Lymphatic Vessels and Dendritic Cells. *Int J Mol Sci*. 2022;23(3):1478.

6. Brouwer NJ, Verdijk RM, Heegaard S, Marinkovic M, Esmaeli B, Jager MJ. Conjunctival melanoma: New insights in tumour genetics and immunology, leading to new therapeutic options. *Prog Retin Eye Res*. 2022; 86:100971.

7. Pandiani C, Béranger GE, Leclerc J, Ballotti R, Bertolotto C. Focus on cutaneous and uveal melanoma specificities. *Genes Dev*. 2017;31(8):724-743.

8. Yu GP, Hu DN, McCormick S, Finger PT. Conjunctival melanoma: Is it increasing in the United States? *Am J Ophthalmol*. 2003;135(6):800-806.

9. Tuomaala S, Eskelin S, Tarkkanen A, Kivelä T. Population-based assessment of clinical characteristics predicting outcome of conjunctival melanoma in whites. *Invest Ophthalmol Vis Sci.* 2002;43(11):3399-3408.

10. Triay E, Bergman L, Nilsson B, All-Ericsson C, Seregard S. Time trends in the incidence of conjunctival melanoma in Sweden. *British Journal of Ophthalmology*. 2009;93(11):1524-1528.

11. Larsen AC. Conjunctival malignant melanoma in Denmark: epidemiology, treatment and prognosis with special emphasis on tumorigenesis and genetic profile. *Acta Ophthalmol*. 2016;94 Thesis 1:1-27.

12. Kaštelan S, Gverović Antunica A, Beketić Orešković L, Salopek Rabatić J, Kasun B, Bakija I. Conjunctival Melanoma - Epidemiological Trends and Features. *Pathology and Oncology Research*. 2018;24(4):787-796.

13. Ghazawi FM, Darwich R, Le M, et al. Incidence trends of conjunctival malignant melanoma in Canada. *Br J Ophthalmol*. 2020;104(1):23-25.

14. Virgili G, Parravano M, Gatta G, et al. Incidence and Survival of Patients with Conjunctival Melanoma in Europe. *JAMA Ophthalmol*. 2020;138(6):601-608.

15. Jia S, Zhu T, Shi H, et al. American Joint Committee on Cancer Tumor Staging System Predicts the Outcome and Metastasis Pattern in Conjunctival Melanoma. *Ophthalmology*. 2022;129(7):771-780.

16. Hong BY, Ford JR, Glitza IC, et al. Immune Checkpoint Inhibitor Therapy as an Eye-Preserving Treatment for Locally Advanced Conjunctival Melanoma. Ophthalmic Plast Reconstr Surg. 2021;37(1):e9-e13.

17. van der Kooij MK, Speetjens FM, van der Burg SH, Kapiteijn E. Uveal versus cutaneous melanoma; same origin, very distinct tumor types. Cancers (Basel). 2019;11(6).

18. Chang E, Demirci H, Demirci FY. Genetic Aspects of Conjunctival Melanoma: A Review. Genes (Basel). 2023;14(9).

19. Vora GK, Demirci H, Marr B, Mruthyunjaya P. Advances in the management of conjunctival melanoma. *Surv Ophthalmol*. 2017;62(1):26-42.

20. Chen L. Ocular lymphatics: state-of-the-art review. Lymphology. 2009;42(2):66-76.

21. Esmaeli B, Eicher S, Popp J, Delpassand E, Prieto VG, Gershenwald JE. Sentinel lymph node biopsy for conjunctival melanoma. *Ophthalmic Plast Reconstr Surg*. 2001;17(6):436-442.

22. Seregard S, Kock E. Conjunctival malignant melanoma in Sweden 1969-91. *Acta Ophthalmol*. 1992;70(3):289-296.

23. Paridaens AD, Minassian DC, McCartney AC, Hungerford JL. Prognostic factors in primary malignant melanoma of the conjunctiva: a clinicopathological study of 256 cases. *Br J Ophthalmol*. 1994;78(4):252-259.

24. Shields CL. Conjunctival melanoma: risk factors for recurrence, exenteration, metastasis, and death in 150 consecutive patients. *Trans Am Ophthalmol Soc.* 2000;98:471-492.

25. Esmaeli B, Wang X, Youssef A, Gershenwald JE. Patterns of regional and distant metastasis in patients with conjunctival melanoma: experience at a cancer center over four decades. *Ophthalmology*. 2001;108(11):2101-2105..

26. Jain P, Finger PT, Damato B, et al. Multicenter, International Assessment of the Eighth Edition of the American Joint Committee on Cancer Staging Manual for Conjunctival Melanoma. *JAMA Ophthalmol*. 2019;137(8):905-911.

27. Jain P, Finger PT, Fili M, et al. Conjunctival melanoma treatment outcomes in 288 patients: A multicentre international data-sharing study. *British Journal of Ophthalmology*. 2021;105(10):1358-1364.

28. Dagi Glass LR, Lawrence DP, Jakobiec FA, Freitag SK. Conjunctival Melanoma Responsive to Combined Systemic BRAF/MEK Inhibitors. *Ophthalmic Plast Reconstr Surg*. 2017;33(5):e114-e116.

29. Finger PT, Pavlick AC. Checkpoint inhibition immunotherapy for advanced local and systemic conjunctival melanoma: a clinical case series. *J Immunother Cancer.* 2019;7(1):83.

30. Sagiv O, Thakar SD, Kandl TJ, et al. Immunotherapy with Programmed Cell Death 1 Inhibitors for 5 Patients with Conjunctival Melanoma. *JAMA Ophthalmol*. 2018;136(11):1236-1241.

31. Fan K, Waninger JJ, Yentz S, McLean S, Demirci H. Neoadjuvant Immune Checkpoint Inhibition in Metastatic Conjunctival Melanoma. *Ophthalmic Plast Reconstr Surg*. 39(5):e152-e155.

32. Alhammad FA, Alburayk KB, Albadri KS, Butt SA, Azam F. Treatment response and recurrence of conjunctival melanoma with orbital invasion treated with immune checkpoint inhibitors: case report and literature review. *Orbit*. 2023:1-9.

33. Griewank KG, Westekemper H, Murali R, et al. Conjunctival melanomas harbor BRAF and NRAS mutations and copy number changes similar to cutaneous and mucosal melanomas. *Clinical Cancer Research*. 2013;19(12):3143-3152.

34. Bou Akl I, Berro J, Tfayli A, et al. Current Status and Future Perspectives of Immunotherapy in Middle-Income Countries: A Single-Center Early Experience. World J Oncol. 2020;11(4):150-157.

35. Kaliki S, Vasanthapuram VH, Mishra DK. Conjunctival Melanoma in Asian Indians: A Study of 42 Patients. *Semin Ophthalmol*. 2019;34(3):182-187.

36. Cohen VML, Tsimpida M, Hungerford JL, Jan H, Cerio R, Moir G. Prospective study of sentinel lymph node biopsy for conjunctival melanoma. British Journal of Ophthalmology. 2013;97(12):1525-1529.

37. Esmaeli B. Regional lymph node assessment for conjunctival melanoma: Sentinel lymph node biopsy and positron emission tomography. *British Journal of Ophthalmology*. 2008;92(4):443-445.

38. Alonso O, Damian A, Engler H, Gaudiano J. 18 F-FDG PET-CT for Staging of Conjunctival Melanoma . *World J Nucl Med*. 2013;12(1):45.

39. Kurli M, Chin K, Finger PT. Whole-body 18 FDG PET/CT imaging for lymph node and metastatic staging of conjunctival melanoma. *British Journal of Ophthalmology*. 2008;92(4):479-482.

40. Shields CL, Yaghy A, Dalvin LA, et al. Conjunctival Melanoma: Outcomes based on the American Joint Committee on Cancer Clinical Classification (8th Edition) of 425 Patients at a Single Ocular Oncology Center. *Asia-Pacific Journal of Ophthalmology*. 2021;10(2):146-151.

41. Grimes JM, Shah N V., Samie FH, Carvajal RD, Marr BP. Conjunctival Melanoma: Current Treatments and Future Options. *Am J Clin Dermatol*. 2020;21(3):371-381.

42. Brouwer NJ, Marinkovic M, Van Duinen SG, Bleeker JC, Jager MJ, Luyten GPM. Treatment of conjunctival melanoma in a Dutch referral centre. *British Journal of Ophthalmology*. 2018;102(9):1277-1282.

43. Esmaeli B, Roberts D, Ross M, Fellman M, Cruz H, Kim SK, Prieto VG. Histologic features of conjunctival melanoma predictive of metastasis and death (an American Ophthalmological thesis). Trans Am Ophthalmol Soc. 2012 Dec;110:64-73.

44. Esmaeli B, Rubin ML, Xu S, Goepfert RP, Curry JL, Prieto VG, Ning J, Tetzlaff MT. Greater Tumor Thickness, Ulceration, and Positive Sentinel Lymph Node Are Associated With Worse Prognosis in Patients With Conjunctival Melanoma: Implications for Future AJCC Classifications. Am J Surg Pathol. 2019 Dec;43(12):1701-1710.

45. National Comprehensive Cancer Network. Melanoma: Cutaneous. (Version 2.2024). https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492 (Last Accessed 07/28/2024)

46. Pinto Torres S, André T, Gouveia E, Costa L, Passos MJ. Systemic Treatment of Metastatic Conjunctival Melanoma. *Case Rep Oncol Med*. 2017;2017:1-3.

FIGURE LEGENDS

Figure 1: Kaplan-Meier curves showing cumulative metastasis rates over time for patients with conjunctival melanoma (including local recurrence).

Figure 2: Kaplan-Meier curves showing cumulative metastasis rates for patients with different clinical T-staging (including local recurrence).

Figure 3: Kaplan-Meier curves showing comparison between cumulative mortality rates for patients with metastasis at presentation versus patient developing metastasis on follow-up (including local recurrence).