

Epidemiological profile of patients with conjunctival malignancy based on the data on patients presenting to SI “The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine”

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Purpose: To evaluate the incidence and assess the clinical features of conjunctival melanoma and carcinoma based on the data on patients presenting to the Ocular Oncology Department, SI “The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine”.

Material and Methods: Medical records of 125 patients with conjunctival malignancy (94 conjunctival melanoma (CM) patients (75.2%) and 31 conjunctival carcinoma (CC) patients (24.8%)) treated at the Filatov Institute in 2004-2024 were retrospectively reviewed. Of these CM patients, 49 (52.1%) were males (age range, 18 to 88 years; median, 51.1 years), and 45 (47.9%) were females (age range, 26 to 87 years; median, 56.6 years). Of these CC patients, 24 (77.4%) were males (age range, 28 to 82 years; median, 64.6 years), and 7 (22.6%) were females (age range, 36 to 77 years; median, 56.6 years).

Results: CM and CC were seen in 1.9%-3.4% and 0.5%-1.2%, respectively, of total annual patients presenting with ocular malignancy to the institute. The most common age group among CM patients was 40-59 years ($p = 0.02$), and among CC patients, 60-79 years ($p = 0.01$). Most CM patients (57 patients or 60.9%) lived in urban areas ($\chi^2 = 7.7$, $p = 0.01$), and most CC patients (17 patients or 56.3%) lived in rural areas. Primary tumors were seen in 84 CM patients (89.4%) and 22 CC patients (75.8%), and iatrogenic tumors, in 10 CM patients (10.6%) and 7 CC patients (22.5%). Most commonly, iatrogenic lesions were seen after surgical treatment (60% for CM and 83.3% for CC). The most common melanoma anatomic conjunctival location was inner inferior region (34 patients or 36.2%; $p = 0.03$). The two most common carcinoma anatomic conjunctival locations were outer inferior region (32.8%; $p = 0.004$) and inner inferior region (25.8%; $p = 0.01$). Disease duration at presentation was less than 12 months for most (60.7%) CM patients, and less than 3 months for most (72.4%) CC patients (median, 1.4 months).

Conclusion: CM and CC were seen in 1.9%-3.4% and 0.5%-1.2%, respectively, of total annual patients presenting with ocular malignancy to the institute. The majority of patients with conjunctival malignancy had CM (60.9%) and the majority (60.9%) of CM patients lived in urban areas. Primary tumors were seen in the majority of patients (89.4% of CM patients and 75.8% of CC patients). Most commonly, iatrogenic lesions were seen after surgical treatment (60% for CM and 83.3% for CC). The outer half of the eye was involved more frequently (50%) in CM patients, and the inner half was involved more frequently (43.8%) in CC patients. Disease duration at presentation was less than 12 months for most CM patients (60.7%), and less than 3 months for most CC patients.

Keywords:

ocular oncology, conjunctival melanoma, conjunctival carcinoma, epidemiology, clinical features of conjunctival malignancy

Introduction

Conjunctival melanoma accounts for approximately 9% of all ocular tumors. In Ukraine, a country with a hot and dry climate, the percentage is as high as 35%. Most (58-88%) patients are men of middle age (46 ± 18 years). The tumor is usually located within the interpalpebral fissure, and is malignant in around 20% of cases [1, 2]. Risk factors include ultraviolet light exposure, human immunodeficiency virus /acquired immunodeficiency syndrome infection, genetic susceptibility to conditions like xeroderma pigmentosum, and ocular surface injury.

Malignant conjunctival tumors are rare and include epithelial tumors (squamous cell carcinoma) and melanocyte lesions (melanoma) [1, 3, 4, 5].

Conjunctival melanoma (CM) accounts for about 2% of all ocular malignancies and 5% of all ocular melanomas, and has an incidence ranging 0.02 from to 0.08 individuals per 100,000. In recent years, there has been an increase in the incidence of skin melanoma, and CM incidence has also tended to increase. The age-adjusted incidence of CM doubled between 1973 and 1999 from 0.27 to 0.54 per million in the United States, and from 0.40 to 0.80 per million in Finland. This malignancy arises from a pre-existing nevus (7%), primary acquired melanosis (PAM) (74%), or de novo without pre-existing condition (19%). Others, how-

ever, have reported that CM originates de novo in about 5 percent of all cases [4, 5].

CM patients often follow an unpredictable course. Tumor size and location serve as reliable indicators of patient prognosis. Tumors not touching the limbus (extralimbal, especially those at the plica, caruncle and fornix) have a significantly poorer prognosis than limbal tumors. The literature reports that after treatment of invasive CM more than 50% of patients develop local tumor recurrence [3, 6, 7].

In a study by Werschnik and Lommatzsch [8], 5-year, 10-year and 15-year survival rates for CM were 84.4%, 77.7% and 75.0%, respectively. PAM-associated melanomas and limbal melanomas have a more favorable course. CM is a potentially lethal ocular malignancy with an overall 10 year mortality as high as 26%-30%. An increased mortality is seen in lesions thicker than 2 mm and those arising de novo. The tumor may metastasize to the regional lymph nodes and distantly to the brain, lung, and liver. There is still no effective treatment for metastatic CM [1, 3, 6, 7].

Squamous cell carcinoma of the conjunctiva (CC) represents the end-stage of epithelial tumors, with malignant cells breaking through the basement membrane. Two types of growth patterns can be distinguished clinically: exophytic growth and endophytic (alias, invasive) growth, with extensions into the corneal stroma, intraocular structures and orbit. The reported rates of intraocular and orbital involvement ranged from 2% to 15% [9] and 1% to 16% [10], respectively. The tumor may metastasize to preauricular, submandibular and anterior cervical lymph nodes. Systemic metastases are rare. Mortality rates are low even in the late stage of tumors.

Therefore, conjunctival malignancies are rare tumors of the eye. Late detection, inadequate treatment and the very nature of the disease may result in functional loss, loss of the globe and not uncommonly, in death [11-13]. Currently, conjunctival malignancies are not the subject of compulsory registration in foreign countries, and one has to assess their prevalence on the basis of statistical reports from different countries. Because there is lack of data on the prevalence of conjunctival malignancies (and the proportions attributed to individual conjunctival malignancies) in Ukraine, evaluating the incidence of these tumors and assessing their clinical features is believed to be important.

The purpose of this study was to evaluate the incidence and assess the clinical features of conjunctival melanoma and carcinoma based on the data on patients presenting to the Ocular Oncology Department, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine".

Material and Methods

Medical records of 125 patients with conjunctival malignancy treated at SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" during 2004 to 2024 were

retrospectively reviewed. Of these patients, 94 (76.4%) had CM, and 29 (23.6%) had CC.

Histomorphological studies of diagnostic biopsies and tumors removed during surgery were performed at the pathomorphology laboratory of the institute.

An MS Access database was developed to store, organize and retrieve the data associated with the results of examination and treatment of patients with CM or CC. This database was used for the retrospective review of medical records. Numerical parameters were entered as numerical data, and clinical characteristics as ordinal data. Mean and standard deviation (SD) were calculated for quantitative data. Pearson's chi-square test was used to compare nominal data, and Student's t-test was used to compare quantitative data. P values ≤ 0.05 were considered significant. The software program G*Power 3.1 was used to conduct a power analysis.

This paper is part of the research project "To Examine the Pathogenetic Mechanisms of the Clinical Effect of (Response to) Combination Treatment for Medium and Large Uveal Melanomas and Malignant Lesions of the Palpebral, Plical, and Caruncular Conjunctiva" (state registration number, 01224U00149). This study involved human subjects and followed ethical standards as outlined in the Declaration of Helsinki of the World Medical Association and the European Convention on Human Rights and Biomedicine, and relevant laws of Ukraine. The study was approved by the bioethics committee of the Filatov institute (committee minutes dated January 16, 2025). Informed consent was not obtained due to the retrospective nature of the study.

Results

The sample for this study included 125 patients with conjunctival malignancy. Of these, 94 (60.9%) had CM, and 31 (39.1%) had CC.

Fig. 1 shows annual numbers of patients presenting with CM to the institute for years 2004-2024. The two largest annual numbers of patients presenting with CM were recorded in 2012 and 2013. Thereafter, the annual numbers were similar, with a tendency to decrease compared to 2012-2013. CM was seen in 1.9%-3.4% of patients presenting with ocular malignancy to the institute during 2004-2024.

Fig. 2 shows annual numbers of patients presenting with CC to the institute for years 2004-2024. The largest annual numbers of patients presenting with CC were recorded in 2013, 2016-2018 and 2020. In 2021-2024, the annual numbers showed a tendency to decrease. During 2014-2012, patients presenting with CC were recorded only in 2005, 2009 and 2010. CC was seen in 0.5%-1.2% of patients presenting with ocular malignancy to the institute during 2004-2024.

Of the total sample of patients with CM, 49 (52.1%) were males (age range, 18 to 88 years; median age, 51.1 years), and 45 (47.9%) were females (age range, 26 to 87 years; median age, 56.6 years). No gender difference was observed ($p > 0.05$).

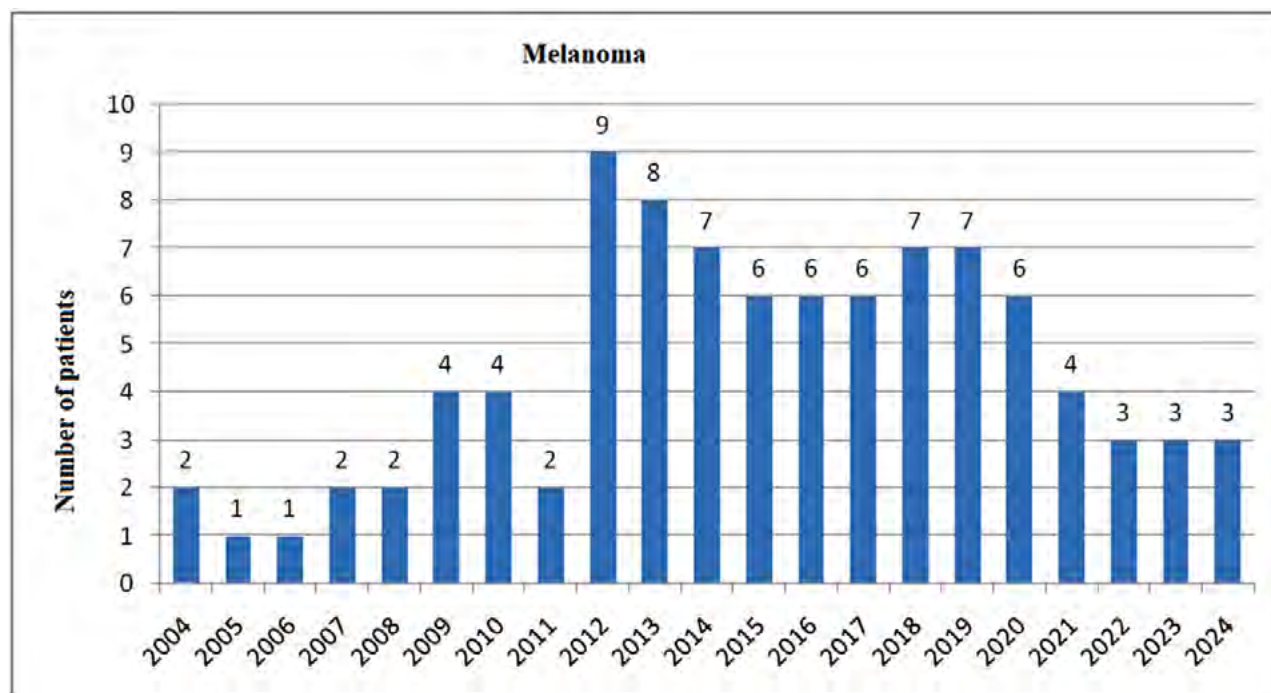


Fig. 1. Annual numbers of patients presenting with conjunctival melanoma to the institute in 2004-2024.

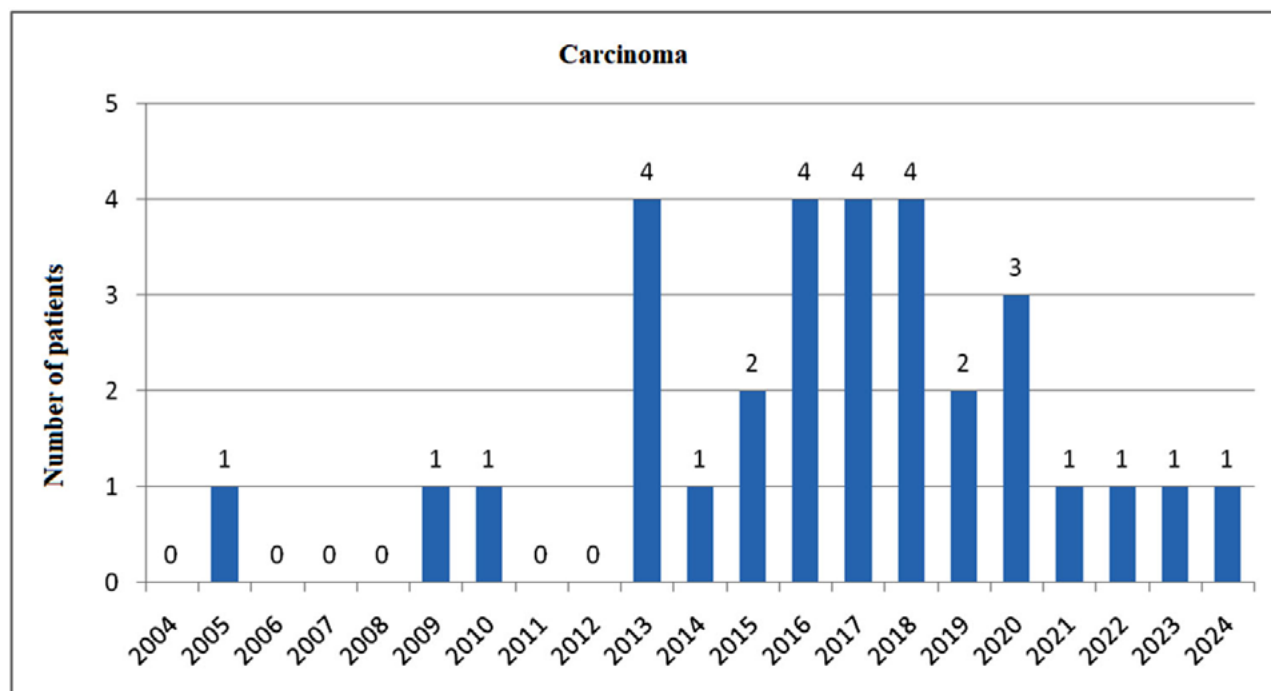


Fig. 2. Annual numbers of patients presenting with conjunctival carcinoma to the institute in 2004-2024.

Of the total sample of patients with CC, 24 (77.4%) were males (age range, 28 to 88 years; median age, 64.6 years), and 7 (22.6%) were females (age range, 36 to 74 years; median age, 59.2 years).

Gender and age distribution of patients with CM is presented at Fig. 3. Most patients with CM were in the age groups 40-59 years (42.6%; 21 men and 19 women) and 60-79 years (32.9%; 18 men and 13 women). These differ-

ences were statistically significant ($p = 0.02$ and $p = 0.04$, respectively). No gender difference was observed in these groups ($p > 0.05$). In the age groups 20-39 years and above 80 years, the number of females exceeded that of males ($p = 0.03$ and $p = 0.04$, respectively). Only two males and no females were younger than 20 years.

Gender and age distribution of patients with CC is presented at Fig. 4. Most patients with CC were in the age

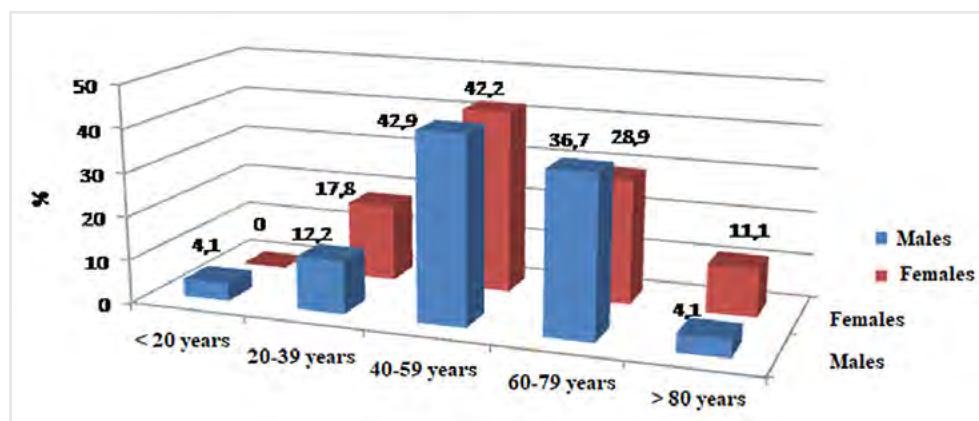


Fig. 3. Gender and age distribution of patients with conjunctival melanoma

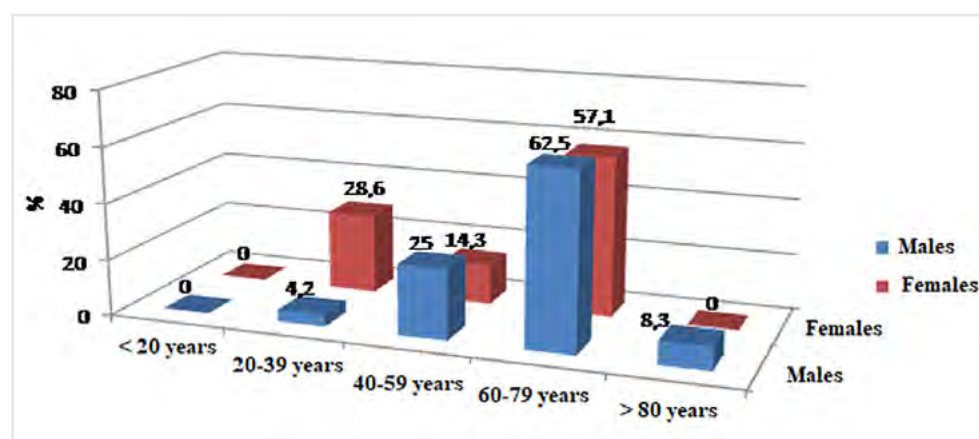


Fig. 4. Gender and age distribution of patients with conjunctival carcinoma

group 60-79 years (53.7%), and this difference was statistically significant ($p = 0.01$). No gender difference was noted in this age group ($p > 0.05$). In the age group 20-39 years, the number of females exceeded that of males ($p = 0.003$), whereas in the age group 40-59 years, the number of males exceeded that of females ($p = 0.04$). Two males and no females were older than 80 years and no patient with CC was younger than 20 years.

Most patients with CM lived in urban areas as opposed to rural areas (60.6% versus 39.4%, respectively; $\chi^2 = 7.7$, $p = 0.01$). That is, CM was found 1.5-times more frequently among individuals living in urban areas than among those living in rural areas. Most patients with CC lived in rural areas as opposed to urban areas (58.1% versus 41.9%, respectively).

In this study sample, the percentages of patients living in particular Ukrainian regions do not represent the entire picture of the prevalence of conjunctival malignant tumors in Ukraine. It should be, however, noted that, when asked to report what Ukrainian region they live in, the largest percentages of patients presenting with CM were from Kyiv, Donetsk and Kirovograd regions (10.86%, 8.69% and 8.89%, respectively), followed by Odesa, Dnipropetrovsk and Lugansk regions (6.52% each). Patients presenting with squamous cell carcinoma were more commonly from Odesa or Cherkasy region (12.5% each) than from any other region (6.25% each).

The number (and percentage) of patients with primary tumors were 84 (89.4%) for CM and 22 (75.8%) for CC.

The number (and percentage) of patients with iatrogenic lesions were 10 (10.6%) for CM and 7 (24.2%) for CC. Most iatrogenic lesions were found after surgical treatment (63.6% for CM and 87.5% for CC).

Melanoma arose de novo in 47 patients (50%), from a pre-existing nevus in 37 patients (39.4%), and from PAM in 10 patients (10.6%). That is, de novo was the most prevalent origin of melanoma, and this difference was statistically significant ($\chi^2 = 4.1$, $p = 0.04$).

Among patients with CC, the right-eye involvement was almost as frequent as the left eye involvement (15 patients (48.4%) versus 16 (51.6%), respectively). Among patients with CM, the right-eye involvement was more frequent than the left eye involvement (54 patients (57.4%) versus 40 patients (42.6%), respectively), but the difference was not significant ($\chi^2 = 7.1$, $p = 0.4$).

The distribution of tumor locations for patients with CM is shown in Fig. 5. The most common melanoma anatomic conjunctival location was inner inferior region (34 patients of 36.2%; $p = 0.03$). Caruncular or plicial conjunctiva was affected in 6 patients with CM (6.4%). Tarsal conjunctival involvement was seen in 14 patients with CM (14.8%; tarsal conjunctiva of the upper eyelid and lower eyelid was involved in 4 patients and 10 patients, respectively).

The distribution of tumor locations for patients with CC is shown in Fig. 6. The two most common carcinoma anatomic conjunctival locations were outer inferior region (32.8%; $p = 0.004$) and inner inferior region (25.8%; $p =$

0.01). Caruncular or plica semilunaris conjunctiva was affected only in one patient with CC (3.2%). Tarsal conjunctival involvement was seen in 6 patients with CC (19.4%; tarsal conjunctiva of the upper eyelid and lower eyelid was involved in 3 patients and 3 patients, respectively).

Pigmented CM was significantly more common than non-pigmented CM (74 patients (78.7%) versus 20 patients (21.3%); $\chi^2 = 5.1$, $p = 0.02$). The lesion color was reddish pink in 15 patients (48.4%), yellow in 8 patients (25.8%) and grey in 8 patients with CC (25.8%).

Melanoma surface was smooth in 41 patients (43.6%), tuberos in 51 patients (54.3%), and squamous in 2 patients (2.1%). Carcinoma surface was smooth in 10 patients (33.3%), tuberos in 13 patients (41.9%), and squamous in 8 patients (25.8%).

Most (60.7%) patients with CM presented with disease duration of less than 12 months, with a median of 5.6 months for primary melanoma, 9.2 months for malignant nevus, and 10.9 months for PAM. Most (74%) patients with CC presented with disease duration of 1-2 months (median disease duration at presentation, 1.4 months). The lesion was multifocal in 25 patients (26.6%; PAM) with CM, and in only one patient (3.4%) with CC.

Therefore, based on the data on patients presenting to SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" with conjunctival malignancy in 2004 to 2024, the majority of the patients had CM (60.9%) and the majority (60.9%) of CM patients lived in urban areas. The most common age group among patients with CM was 40 to 59 years (42.6%). The majority of patients with CM (53.6%) were of 60-79 years. The lesion was primary in most patients with CM (89.4%) and most patients with CC (75.8%).

Most commonly, iatrogenic lesions were seen after surgical treatment (60% for CM and 83.3% for CC). Among patients with CM, the right eye was more commonly involved (65%) than the left eye, and the outer half of the eye was involved more frequently (50%), whereas among patients with CC, the inner half of the eye was involved more frequently (43.8%). In most patients with CM (60.7%), disease duration at presentation was less than 12 months, with a median value of 5.6 months for primary melanoma, 9.2 months for malignant nevus, and 10.9 months for PAM. Most (72.4%) patients with CC presented with disease duration of less than 3 months (median, 1.4 months).

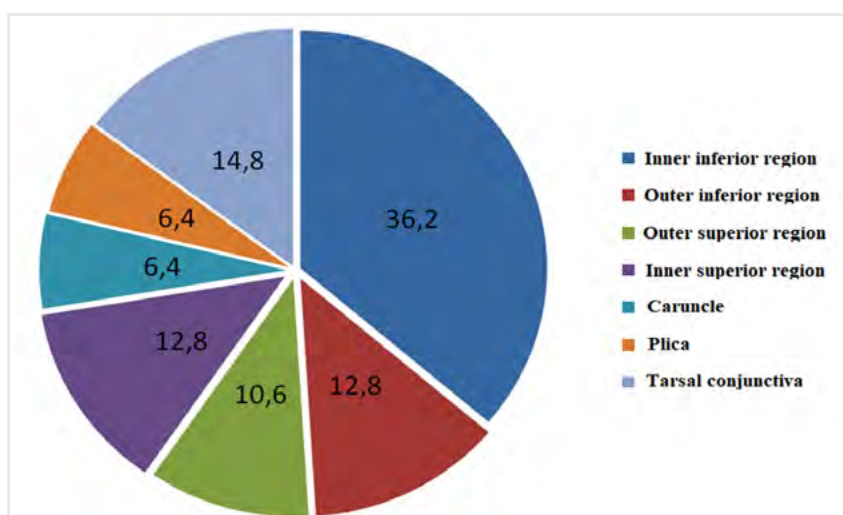


Fig. 5. Distribution of melanoma anatomic conjunctival locations for patients with conjunctival melanoma (portions of the total number of patients are indicated as percentages)

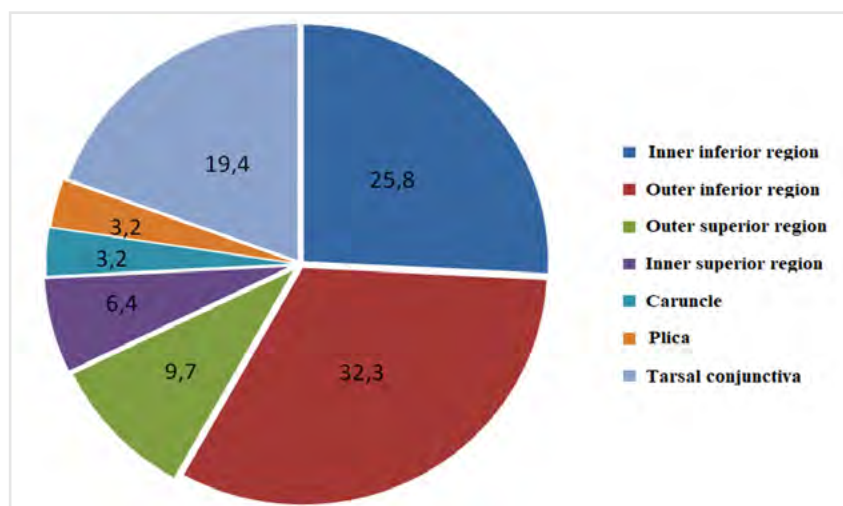


Fig. 6. Distribution of carcinoma anatomic conjunctival locations for patients with conjunctival carcinoma (portions of the total number of patients are indicated as percentages)

Discussion

CM and CC were seen in 1.9%-3.4% and 0.5%-1.2%, respectively, of total patients presenting with ocular malignancy to the institute. That is, among total ocular tumors, conjunctival malignancies were rarely seen, which is in agreement with other studies [1, 2, 4, 14].

We found that there was an increase in the annual number of patients presenting with CM to the institute from 2012 to 2020. This is in agreement with reports on a tendency for the incidence of CM to increase. Thus, data from Surveillance, Epidemiology and End Results (SEER) database registry indicated that the age-adjusted incidence of CM doubled over 26 years in the United States, Finland and Denmark [3-8].

Some researchers reported that males and females had similar prevalence of CM [12]. Others, however, reported that the prevalence for males was higher than that for females [12,15].

Among the Caucasian patients with CM, the most common age group affected is > 60 years, whereas American African patients with CM are most commonly younger than 60 years [12, 15, 16]. In the current study, most patients with CM were in the age groups 40-59 years (42.6%; 21 men and 19 women) and 60-79 years (32.9%; 18 men and 13 women), and there was no gender difference among patients in these groups. In addition, in the age groups 20-39 years and above 80 years, the number of females exceeded that of males.

CC most commonly affects males older than 60 years [9, 10]. In the current study, most patients with CC (53.7%) were in the age group 60-79 years, and there was no gender difference among patients in this group. In the age group 20-39 years, the number of females exceeded that of males, whereas in the age group 40-59 years, the number of males exceeded that of females.

In the current study, CM was found 1.5-times more frequently among individuals living in urban areas than among those living in rural areas. To our knowledge, no study has reported on this subject.

The lesion was primary in most patients with CM (89.4%) and most patients with CC (75.8%). Most commonly, iatrogenic tumors were found in patients who had prior surgery elsewhere (60% for CM and 83.3% for CC). In a study by Shields and colleagues [6], most CM recurrences were also found in patients who had prior surgery elsewhere. Conjunctival malignant melanoma can sometimes be difficult to control locally, and enucleation or orbital exenteration may be necessary [6].

In the current study, CM arose most frequently de novo (50%), from a pre-existing nevus in 37 patients (39.4%), and from PAM in 10 patients (10.6%). It has been, however, reported, that CM most commonly arose from PAM [17,18]. Of note, we found pigmented CM to be more common (78.7%) than non-pigmented CM, which is in agreement with findings of others [14, 18, 19]. In the current study, among patients with CM, the right-eye involvement (65%) was more frequent than the left-eye involvement,

and the outer half of the eye was involved more frequently (50%), whereas among patients with CC, the inner half of the eye was involved more frequently (43.8%); this is in agreement with other studies [19]. Disease duration at presentation was less than 12 months for most patients (60.7%) with CM (with a median of 5.6 months for primary melanoma, 9.2 months for malignant nevus, and 10.9 months for PAM), and less than 3 months for the majority (72.4%) of patients with CC (median value, 1.4 months). As far as we know, no other study has reported on disease duration at presentation for large samples of patients with conjunctival malignancies.

In summary, it should be noted that conjunctival malignancies are rare tumors endangering the patient's eye and life. Because there is lack of data on the prevalence of conjunctival malignancies (and the proportions attributed to individual conjunctival malignancies) in Ukraine and abroad, evaluating the incidence of these tumors and assessing their clinical features is believed to be important.

Conclusion

Therefore, CM and CC were seen in 1.9%-3.4% and 0.5%-1.2%, respectively, of total patients presenting with ocular malignancy to "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" in 2004 to 2024. The majority of the patients had CM (60.9%) and the majority (60.9%) of patients with CM lived in urban areas. The percentage of patients with primary tumors was 89.4% for CM and 75.8% for CC. Most commonly, iatrogenic lesions were seen after surgical treatment (60% for CM and 83.3% for CC). The outer half of the eye was involved more frequently (50%) in CM patients, and the inner half was involved more frequently (43.8%) in CC patients. Disease duration at presentation was less than 12 months for most patients (60.7%) with CM, and less than 3 months for most patients with CC.

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Disclosures

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Author contributions: Conceptualization; Data curation and interpretation; Database development; Writing – draft, review & editing.

Ethical statement: The study involved human subjects, was approved by the local bioethics committee, followed ethical standards as outlined in the European Convention on Human Rights and Biomedicine and the Declaration of Helsinki of the World Medical Association, and complied with existing regulations of Ukraine.

Disclaimer: The views presented in this article are those of the author and do not necessarily represent those of SI “The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine”.

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Conflict of Interest: The author declares that she has no conflict of interest that could influence her opinion regarding the subject matter or material described and discussed in this manuscript.

Ethical Approval of Human Subject Research: The study was approved by the Bioethics committee of SI “The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine” (committee meeting minutes of January 16, 2025).

Informed Consent: Informed consent was not obtained due to the retrospective nature of the study.

Data Availability Declaration: All the data obtained or examined during this study has been incorporated into this published article.

Abbreviations: CC, conjunctival carcinoma; CM, conjunctival melanoma; PAM, primary acquired melanosis