Original Article

Incidence, clinical features, and survival outcomes of primary malignant conjunctival tumor: a US population-based retrospective cohort analysis based on the SEER database (1975–2018)

Lin-Feng He[1#], Shi-Yi Tang[2#], Yu-Jiao Wang[3#], Yun Zhang[1#], Sheng-Mei Huang[2], Xiao-Jing Huang[2]

[1]Department of Ophthalmology, Changzheng Hospital, Second Affiliated Hospital of Naval Medical University, Shanghai, China; [2]Department of Ophthalmology, Gongli Hospital of Shanghai Pudong New Area, Shanghai, China; [3]Department of Pediatrics, Changzheng Hospital, Second Affiliated Hospital of Naval Medical University, Shanghai, China

Contributions: (I) Conception and design: XJ Huang, SM Huang; (II) Administrative support: XJ Huang; (III) Provision of study materials or patients: SM Huang; (IV) Collection and assembly of data: Y Zhang, YJ Wang; (V) Data analysis and interpretation: LF He, Y Zhang, YJ Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Xiao-Jing Huang, MD; Sheng-Mei Huang, MD. Department of Ophthalmology, Gongli Hospital of Shanghai, Pudong New Area, 216 Miao-pu Rd., Shanghai 200135, China. Email: 13917000235@163.com; huangshengmei188@163.com.

Background: Primary malignant conjunctival tumors (PMCT) are rare. Their clinicopathological characteristics and survival outcomes are not well understood. The Surveillance, Epidemiology, and End Results (SEER) database includes approximately 30% of the total US. In this study, we aimed to investigate the epidemiology, clinical characteristics, and prognosis of PMCT via SEER.

Methods: Data on microscopically confirmed PMCT patients from 1975 to 2018 were retrieved. Patients who were lost to active follow-up, those for whom PMCT was not the primary malignant tumor, and those with unknown death information, laterality, race, or those who survived for less than 1 month after diagnosis were excluded. Disease-specific survival (DSS) and overall survival (OS) were the primary endpoints, calculated through the Kaplan-Meier analysis and log-rank tests. Univariate and multivariate Cox regression analyses were conducted to recognize independent predictive factors for DSS and OS.

Results: In total, we identified 2,853 eligible patients diagnosed with PMCT, with an average age of 61.25 years, among which 1,678 (58.82%) were males, 2,464 (86.37%) were whites, 1,567 (54.92%) were married, and 2,125 (74.48%) were in localized SEER stage. The three major types were lymphoma (39.64%), squamous cell carcinoma (SCC) (34.88%), and melanoma (21.98%). The overall incidence of PMCT was 0.136/100,000 between 1975 and 2020, with an annual incidence rate of 0.929 [95% confidence interval (CI): 0.289–1.573, P<0.05]. Multivariate Cox regression analysis discovered age, sex, marital status, histological type, SEER stage, and surgery as independent prognostic variables. Age ≥75 years [≥75 *vs.* <60 years, hazard ratio (HR) =3.211, 95% CI: 2.309–4.466, P<0.001], melanoma (melanoma *vs.* SCC, HR =4.637, 95% CI: 3.235–6.649, P<0.001), distant SEER stage (distant *vs.* localized, HR =4.318, 95% CI: 2.675–6.968, P<0.001), and no/unknown surgery status (performed *vs.* no/unknown, HR =1.565, 95% CI: 1.187–2.062, P=0.001) were related to worse DSS. Meanwhile, age ≥75 years (≥75 *vs.* <60 years, HR =9.399, 95% CI: 7.876–11.216, P<0.001), male (female *vs.* male, HR =0.701, 95% CI: 0.612–0.803, P<0.001), unmarried status (unmarried *vs.* married, HR =1.342, 95% CI: 1.17–1.538, P<0.001), distant SEER stage (distant *vs.* localized, HR =2.077, 95% CI: 1.498–2.881, P<0.001), and no/unknown surgery status (performed *vs.* no/unknown, HR =1.16, 95% CI: 1.018–1.322, P=0.03) were related to worse OS. Lymphoma (lymphoma *vs.* SCC, HR =0.628, 95% CI: 0.533–0.74, P<0.001) was associated with better OS.

Conclusions: PMCT incidence increased after 1975 and decreased after 1997. Age, histological type, SEER stage, and surgery were all significantly associated with DSS and OS. Age ≥75 years, melanoma, and

distant SEER stage were associated with worse DSS, while age ≥75 years, male, unmarried status, distant SEER stage were related to worse OS and lymphoma was related to better OS. Surgery may improve the prognosis of patient with PMCT.

Keywords: Conjunctival tumors; Surveillance, Epidemiology, and End Results (SEER); incidence; prognosis

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Introduction

The conjunctiva is a continuous mucous membrane consisted of the epithelium and stroma (1). However, because of their special anatomical sites and greater exposure to sunlight, conjunctival tumors are slightly different from tumors of other mucous membranes (2). The spectrum of conjunctival tumors varies considerably from benign to aggressive and potentially life-threatening malignancies. In a clinical study of 4,625 patients with conjunctival tumors, Shields *et al.* demonstrated that 52% of the tumors were benign, 18% were premalignant, and 30% were malignant (3). Among the malignancies, the most common types were melanoma, squamous cell carcinoma (SCC), and lymphoma. Other uncommon malignant tumor types, including malignant fibrous histiocytoma, Kaposi's sarcoma, and metastatic tumors, have also been reported (3-6). Previous studies on conjunctival tumors classified tumors into histological types and specific diagnoses with relative frequencies and presented knowledge of the clinical characteristics of each tumor, which could help to establish a clinical diagnosis (3,7,8). However, epidemiological data on malignant conjunctival tumors, particularly primary malignant conjunctival tumors (PMCT), remain limited. Studying the epidemiology of PMCT can assist in assessing the public health burden associated with this disease. Additionally, it enables the identification of high-risk groups and facilitates the development of effective treatment strategies. Moreover, it enables clinicians to evaluate patient prognoses more accurately. The Surveillance, Epidemiology, and End Results (SEER) database involves about 30% of the total US population, and 48% of cancer patients in the US population (9,10). Based on the SEER program, Siegel *et al.* showed that the overall cancer incidence rate in the US has declined since the early 1990s, with a narrowing sex gap (11). Increasing regulation of smoking and advances in the early detection and comprehensive treatment of cancers have led to an overall lower mortality rate, decreasing from 215.1/100,000 in 1991 to 146.0/100,000 in 2019. In addition to incidence data, SEER also preserves annually uploaded data on patient demographics, date of diagnosis, tumor anatomic sites, tumor pathology, first course of therapeutic methods, stage at diagnosis, and follow-up vital status, acting as a tool for the study of cancers, especially uncommon ones (12,13). The SEER program conducts regular long-term follow-ups of patients to update information on patients' vital status and cause of death. Using these data, researchers can obtain the survival outcomes of patients and analyze the prognosis of specific cancers. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1629/rc).

Highlight box

Key findings

- The incidence rate of primary malignant conjunctival tumors (PMCT) increased after 1975 and decreased after 1997.
- Age ≥75 years, melanoma, and advanced stage were associated with worse Disease-specific survival (DSS).
- Age ≥75 years, male, unmarried status, and advanced stage were related to worse overall survival (OS). Lymphoma was related to better OS.
- Surgery may improve the prognosis of patient with PMCT.

What is known and what is new?

- PMCT is relatively uncommon and the epidemiological information is scare.
- This study described the epidemiological characteristics and successfully analyzed the risk factors for PMCT.

What is the implication, and what should change now?

- These findings are conducive to improving the management of patients with PMCT.

Methods

Data source and cohort selection

The data of patients with PMCT were extracted from the SEER database using SEER*Stat software (version 8.4.3) (14). More patients were enrolled, including those enrolled during 2000–2018 from SEER 18 Registries, patients diagnosed during 1992–1999 from SEER 13 Registries, and patients diagnosed during 1975–1991 from SEER 9 Registries (15-17). The inclusion criteria were as follows: (I) site-specific code C69.0 (conjunctiva) used to identify patients with first primary conjunctival malignancies, (II) active follow-up, and (III) microscopically confirmed diagnosis. The exclusion criteria were as follows: (I) diagnosis from autopsy or death certificate, (II) survival less than 1 month after diagnosis, and (III) unknown death information, laterality, or race. The following data were collected from the SEER database: age, year of diagnosis, sex, race, marital status, laterality, SEER stage, histological type, surgery, radiotherapy, chemotherapy, survival (months), cause of death, and vital status. Histological types were divided into four groups: SCC, melanoma, lymphoma, and others. The annual percentage changes (APCs) of PMCT from 1975 to 2020 were extracted from the SEER 8 Registries and the incidence rates were age-adjusted to the 2000 US standard population (18). The primary endpoints of this study were disease-specific survival (DSS) and overall survival (OS). DSS was calculated as the interval (months) between the diagnosis and death attributed to PMCT, and OS was calculated as the interval (months) between the diagnosis and death attributed to any cause. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

The age-adjusted incidence rates of PMCT were calculated per 100,000 persons using SEER*Stat software (version 8.4.3). APCs with 95% confidence intervals (CI) were calculated as well. The turning points of the incidence rate were calculated using Joinpoint software. Incidence rates were compared based on age, race, sex, and histological type. All continuous variables were converted into categorical variables and performed statistical analysis through the Chi-squared test or Fisher's exact test. Survival curves were conducted through the Kaplan-Meier method and differences were analyzed by the log-rank test. The Cox proportional hazards regression model was used for the univariate and multivariate analyses. Significant variables ($P<0.05$) acquired in the univariate Cox regression model and treatment methods were analyzed using a multivariate Cox regression model to calculate the independent prognostic variables for DSS and OS. The results were demonstrated as hazard ratios (HR) with 95% CI. All statistical analyses were conducted utilizing SPSS 26.0 (IBM) and R software (version 4.3.2).

Results

Incidence of PMCT

The overall incidence of PMCT between 1975–2020 was 0.136 per 100,000 persons, with an APC of 0.929 (95% CI: 0.289–1.573, $P<0.05$). During the last 45 years, the incidence rate raised steadily before 1997 and declined slightly after peaking (*Figure 1A* and Figure S1). The incidence rate raised with age. The incidence rates in individuals aged <60, 60–74, and ≥75 years were 0.07, 0.39, and 0.605, respectively. The incidence rate was 0.176 in males and 0.105 in females, and the APC for females was 1.357 (95% CI: 0.536–2.185, $P<0.05$). Considering ethnicity, the incidence among whites (0.139) was higher than that among blacks (0.076). The incidence rates among American Indians, Alaskan natives, and Asian/Pacific islanders were 0.113. The overall incidence of SCC and melanoma was 0.043 and 0.033, respectively, with stable incidence trends (*Figure 1B,1C*). The overall incidence of lymphoma, the most frequent histological subtype, was 0.056, which increased steadily before 1998 and decreased slightly thereafter (*Figure 1D* and Figure S2). The detailed data can be seen in *Table 1*.

Demographics of patients with PMCT

Up to 2,853 eligible patients who underwent PMCT were enrolled in this study. The general information of this study cohort is presented in *Table 2*. The mean age of the 2,853 patients was 61.25±17.18 years with a median age of 63 years, among which 1,205 (42.24%) were aged <60 years, 968 (33.93%) were aged between 60–74 years, and 680 (23.83%) were aged ≥75 years. This study included 1,678 males (58.82%) and 1,175 females (41.18%). Most patients were whites (86.37%), married (54.92%), and unilateral (95.44%). Based on the SEER stage, most patients (74.48%) were in the localized stage. The proportion of patients in the regional and distant stages was 7.33% and 3.26%, respectively. Concerning treatment modalities, more than

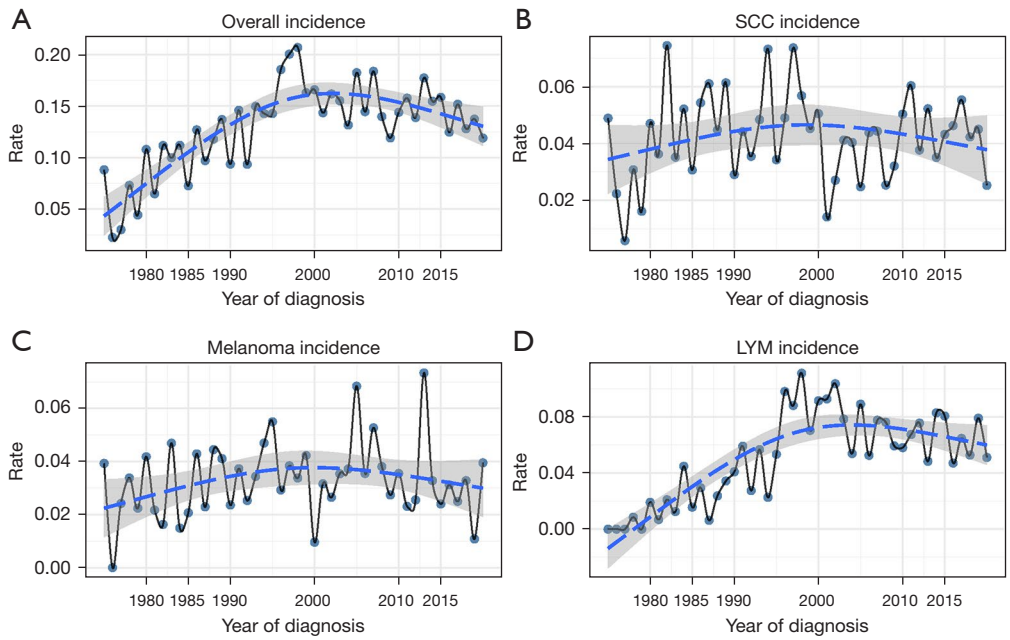

Figure 1 Incidence of PMCT from 1975 to 2020 adjusted to the 2000 standard US population: (A) overall; (B) SCC; (C) melanoma; (D) LYM. PMCT, primary malignant conjunctival tumor; SCC, squamous cell carcinoma; LYM, lymphoma.

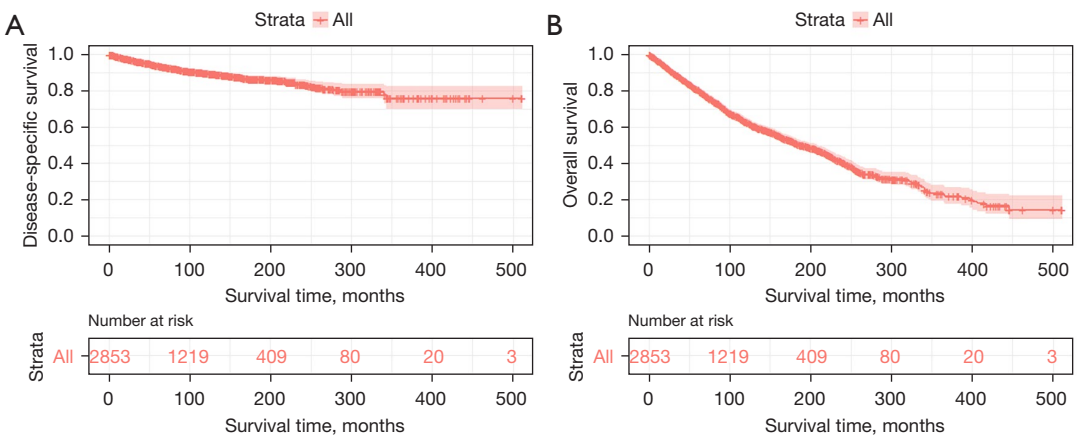

Figure 2 Survival analysis of PMCT for all patients: (A) disease-specific survival; (B) overall survival. PMCT, primary malignant conjunctival tumor.

half of patients with PMCT revived surgery (53.28%), the proportion were higher in patients with SCC (68.04%) and melanoma (69.7%). Only a fraction of patients received radiotherapy (28.11%) or chemotherapy (10.52%). The three major pathological types were lymphoma (39.64%), SCC (34.88%), and melanoma (21.98%). The mean age of patients with lymphoma was younger (57.79 years) than the overall mean age, whereas the mean age of patients with SCC was much older (64.87 years). More male patients (76.38%) had SCC. Compared with other pathological types, lymphomas were relatively prone to being bilateral (11.32%). The number of patients with lymphoma treated with radiotherapy (64.01%) was higher than the number of patients with other types. The proportion of patients with lymphoma who underwent surgery (30.24%) was lower than that of patients with other pathological types.

Table 1 Incidence rate from 1975 to 2020

Characteristics	Incidence rate	APC
Overall	0.136	0.929 (0.289 to 1.573)*
Age, years		
<60	0.07	1.349 (0.448 to 2.258)*
60–74	0.39	NA
≥75	0.605	NA
Sex		
Male	0.176	0.287 (–0.465 to 1.044)
Female	0.105	1.357 (0.536 to 2.185)*
Race		
White	0.139	0.924 (0.274 to 1.578)*
Black	0.076	NA
Others#	0.113	NA
Histological type		
SCC	0.043	–0.21 (–0.962 to 0.548)
Melanoma	0.033	NA
Lymphoma	0.056	NA
Others	0.004	NA

*, the APC is significantly different from zero (P<0.05). Others#, American Indian/Alaska Native, and Asian/Pacific Islander. APC, annual percentage change; SCC, squamous cell carcinoma.

Survival analysis

Kaplan–Meier analysis was conducted to evaluate DSS (*Figure 2A*) and OS (*Figure 2B*). A total of 1,107 patients died in the cohort, 254 of whom died of PMCT. The DSS rates at 5, 10, and 20 years were 94%, 89.6%, and 83.6%, respectively. The median OS was 118 months, and the OS rates at 5, 10, and 20 years were 80.9%, 63%, and 40.4%, respectively. Survival plots for age, year of diagnosis, sex, race, marital status, laterality, histological type, SEER stage, and treatment modality were plotted using Kaplan–Meier analysis. Survival outcomes improved over the years; the DSS for patients diagnosed in 2008–2018 was enhanced significantly compared to that of patients diagnosed in other periods (*Figure 3A*), while OS for patients diagnosed in 1997–2007 and 2008–2018 was better than that for patients diagnosed in 1975–1985 and 1986–1996 (*Figure 3B*). Survival time decreased with age, and patients aged over 75 had lower DSS (*Figure 3C*) and OS (*Figure 3D*) than younger patients. Males and females shared the same DSS (*Figure 3E*), whereas females tended to have better OS than males (*Figure 3F*). White people had worse DSS (*Figure 3G*) and OS (*Figure 3H*) than individuals of other races. Marital status had no impact on DSS, while married patients had better OS (*Figure 4A*,*4B*). Laterality had no impact on DSS, but bilateral lesions impacted OS (*Figure 4C*,*4D*). According to histological type, patients with conjunctival SCC had better DSS (*Figure 4E*), and patients with lymphoma had better OS (*Figure 4F*). Patients with local-stage lesions tended to have prolonged DSS and OS (*Figure 4G*,*4H*). Regarding treatment strategies, surgery was significantly related to better DSS (*Figure 5A*) but not OS (*Figure 5B*). Patients who underwent radiotherapy showed better DSS (*Figure 5C*) and OS (*Figure 5D*). However, chemotherapy did not influence DSS or OS (*Figure 5E*,*5F*).

Cox regression analysis was performed to discover the independent prognostic factors for both DSS and OS. Age, histological type, SEER stage, and surgery were all significantly related to DSS (*Table 3*). Multivariate Cox regression analysis showed that DSS was independently related to age (60–74 *vs.* <60 years, HR =2.033, 95% CI: 1.499–2.758, P<0.001; ≥75 *vs.* <60 years, HR =3.211, 95% CI: 2.309–4.466, P<0.001), histological type (melanoma *vs.* SCC, HR =4.637, 95% CI: 3.235–6.649, P<0.001; lymphoma *vs.* SCC, HR =1.141, 95% CI: 0.761–1.711, P=0.52; others *vs.* SCC, HR =2.055, 95% CI: 0.994–4.249, P=0.052), SEER stage (regional *vs.* localized, HR =1.55, 95% CI: 1.04–2.309, P=0.03; distant *vs.* localized, HR =4.318, 95% CI: 2.675–6.968, P<0.001; unknown *vs.* localized, HR =1.495, 95% CI: 1.072–2.085, P=0.02), and surgery status (performed *vs.* no/unknown, HR =1.565, 95% CI: 1.187–2.062, P=0.001). At the same time, age, sex, marital status, histological type, SEER stage, and surgery were significantly related to OS (*Table 4*). OS was independently related to age (60–74 *vs.* <60 years, HR =3.725, 95% CI: 3.139–4.421, P<0.001; ≥75 *vs.* <60 years, HR =9.399, 95% CI: 7.876–11.216, P<0.001), sex (female *vs.* male, HR =0.701, 95% CI: 0.612–0.803, P<0.001), marital status (unmarried *vs.* married, HR =1.342, 95% CI: 1.17–1.538, P<0.001, unknown *vs.* married, HR =1.204, 95% CI: 1.008–1.439, P=0.04), histological type (melanoma *vs.* SCC, HR =1.022, 95% CI: 0.873–1.197, P=0.78; lymphoma *vs.* SCC, HR =0.628, 95% CI: 0.533–0.74, P<0.001; others *vs.* SCC, HR =0.866, 95% CI: 0.633–1.184, P=0.37), SEER stage (regional *vs.* localized, HR =1.26, 95% CI: 1.017–1.561, P=0.04; distant *vs.* localized, HR =2.077, 95% CI: 1.498–2.881, P<0.001; unknown *vs.* localized, HR =1.114, 95% CI: 0.944–1.314, P=0.2), and surgery status (performed

Table 2 Demographic and clinical characteristics of patients

Variables	Total	SCC	Melanoma	Lymphoma	Others
Number of patients, n (%)	2,853	995 (34.88%)	627 (21.98%)	1,131 (39.64%)	100 (3.51%)
Age, years					
Mean (SD)	61.25 (17.18)	64.87 (15.33)	61.19 (17.9)	57.79 (17.43)	64.8 (18.86)
Median [IQR]	63 [50, 74]	66 [55, 76]	64 [50, 75.5]	59 [46, 71]	70 [50.75, 80.25]
<60	1,205 (42.24%)	343 (34.47%)	251 (40.03%)	579 (51.19%)	32 (32%)
60–74	968 (33.93%)	365 (36.68%)	210 (33.49%)	363 (32.1%)	30 (30%)
≥75	680 (23.83%)	287 (28.84%)	166 (26.48%)	189 (16.71%)	38 (38%)
Year of diagnosis					
1975–1985	135 (4.73%)	61 (6.13%)	47 (7.5%)	24 (2.12%)	3 (3%)
1986–1996	370 (12.97%)	140 (14.07%)	91 (14.51%)	125 (11.05%)	14 (14%)
1997–2007	1,048 (36.73%)	327 (32.86%)	214 (34.13%)	473 (41.82%)	34 (34%)
2008–2018	1,300 (45.57%)	467 (46.93%)	275 (43.86%)	509 (45%)	49 (49%)
Sex					
Male	1,678 (58.82%)	760 (76.38%)	325 (51.83%)	529 (46.77%)	64 (64%)
Female	1,175 (41.18%)	235 (23.62%)	302 (48.17%)	602 (53.23%)	36 (36%)
Race					
White	2,464 (86.37%)	918 (92.26%)	582 (92.82%)	877 (77.54%)	87 (87%)
Black	153 (5.36%)	32 (3.22%)	18 (2.87%)	98 (8.66%)	5 (5%)
Others[#]	236 (8.27%)	45 (4.52%)	27 (4.31%)	156 (13.79%)	8 (8%)
Marital status					
Married	1,567 (54.92%)	545 (54.77%)	333 (53.11%)	646 (57.12%)	43 (43%)
Unmarried	898 (31.48%)	269 (27.04%)	203 (32.38%)	384 (33.95%)	42 (42%)
Unknown	388 (13.6%)	181 (18.19%)	91 (14.51%)	101 (8.93%)	15 (15%)
Laterality					
Unilateral	2,723 (95.44%)	994 (99.9%)	626 (99.84%)	1003 (88.68%)	100 (100%)
Bilateral	130 (4.56%)	1 (0.1%)	1 (0.16%)	128 (11.32%)	0 (0%)
SEER stage					
Localized	2,125 (74.48%)	831 (83.52%)	452 (72.09%)	773 (68.35%)	69 (69%)
Regional	209 (7.33%)	64 (6.43%)	104 (16.59%)	32 (2.83%)	9 (9%)
Distant	93 (3.26%)	2 (0.2%)	12 (1.91%)	77 (6.81%)	2 (2%)
Unknown	426 (14.93%)	98 (9.85%)	59 (9.41%)	249 (22.02%)	20 (20%)
Surgery					
Performed	1,520 (53.28%)	677 (68.04%)	437 (69.7%)	342 (30.24%)	64 (64%)
No/unknown	1,333 (46.72%)	318 (31.96%)	190 (30.3%)	789 (69.76%)	36 (36%)

Table 2 *(continued)*

Table 2 *(continued)*

Variables	Total	SCC	Melanoma	Lymphoma	Others
Radiotherapy					
Performed	802 (28.11%)	31 (3.12%)	33 (5.26%)	724 (64.01%)	14 (14%)
No/unknown	2,051 (71.89%)	964 (96.88%)	594 (94.74%)	407 (35.99%)	86 (86%)
Chemotherapy					
Performed	300 (10.52%)	67 (6.73%)	66 (10.53%)	154 (13.62%)	13 (13%)
No/unknown	2,553 (89.48%)	928 (93.27%)	561 (89.47%)	977 (86.38%)	87 (87%)

Others[#], American Indian/Alaska Native, and Asian/Pacific Islander. SCC, squamous cell carcinoma; SD, standard deviation; IQR, interquartile range; SEER, Surveillance, Epidemiology, and End Results.

vs. no/unknown, HR =1.16, 95% CI: 1.018–1.322, P=0.03).

Discussion

Due to its low incidence rate, few studies have estimated the epidemiology of PMCT and its impact on patient prognoses. This study provides a population-based cohort analysis to investigate the epidemiological characteristics and survival outcomes of patients with PMCT using the SEER program. Using the data, the incidence of PMCT was calculated and its clinicopathological characteristics, treatment outcomes, and prognostic factors were evaluated.

The results revealed that PMCT is an uncommon lesion with an overall incidence of 0.136 per 100,000 persons over the past 45 years. The incidence rate tended to increase relatively steadily before 1997, decreasing thereafter. Across different histological subtypes, the incidence trends of SCC and melanoma were steady over the four decades. Lymphoma, which had the highest incidence rate, increased before 1998, and slightly decreased thereafter. In a study of ocular and orbital lymphomas, Alfaar *et al.* reported an increasing trend in the incidence of ocular lymphomas from 1995 to 1997, followed by a steady decrease (19). The increasing trend in the incidence rate could be partly attributed to the development of diagnostic methods, modifications in the classification systems of non-Hodgkin's lymphoma, and the increasing trend of acquired immunodeficiency syndrome (20,21). However, this decline could potentially be attributed to an inherent decrease in risk factors or a reduction in the ratio of solitary conjunctival lymphoma cases that are not related to other systemic lymphomas. The specific mechanisms underlying this pattern will require further investigation. Previous studies have shown that the incidence rate of conjunctival melanoma has been stable over time (22,23). Conjunctival SCC is the most common ocular surface malignancy in countries near the equator, with an increasing incidence rate, which may be due to human immunodeficiency virus infections and ultraviolet light exposure (24,25). In a study by Metekoua *et al.*, the incidence of conjunctival SCC in South Africa was found to decrease between 2004 and 2014 (26). The different incidence trend patterns of conjunctival SCC in the present study may be partly explained by the latitude of the American and the relative low prevalence of human immunodeficiency virus. In this study, the incidence of PMCT was found to be higher in males than in females. In general, conjunctival lymphoma and conjunctival melanoma do not seem to have sex predilections (27-30). Conjunctival SCC predominantly affects the males in temperate countries, as the male gender may be more exposed to ultraviolet B radiation because of their preponderance in outdoor occupations (25,31). The incidence rate of PMCT increases with age, and the median diagnostic age in this study cohort was 63 years, which is in line with previous studies that reported that conjunctival SCC, melanoma, and lymphoma are the primary conjunctival tumors in the elderly population (2,27,30,32).

In contrast to other studies, the most common histological subtype of PMCT in this study was lymphoma, followed by SCC and melanoma. Conjunctival SCC was the most common conjunctival malignancy in a study conducted by Grossniklaus *et al.*, whereas conjunctival melanoma accounted for the majority of the studies conducted by Shields *et al.* (3,8,33). Possible reasons for this difference include the identification of conjunctival SCC and corneal SCC and the increasing incidence of conjunctival lymphoma. Moreover, in the present study, different histological types of PMCT were demonstrated

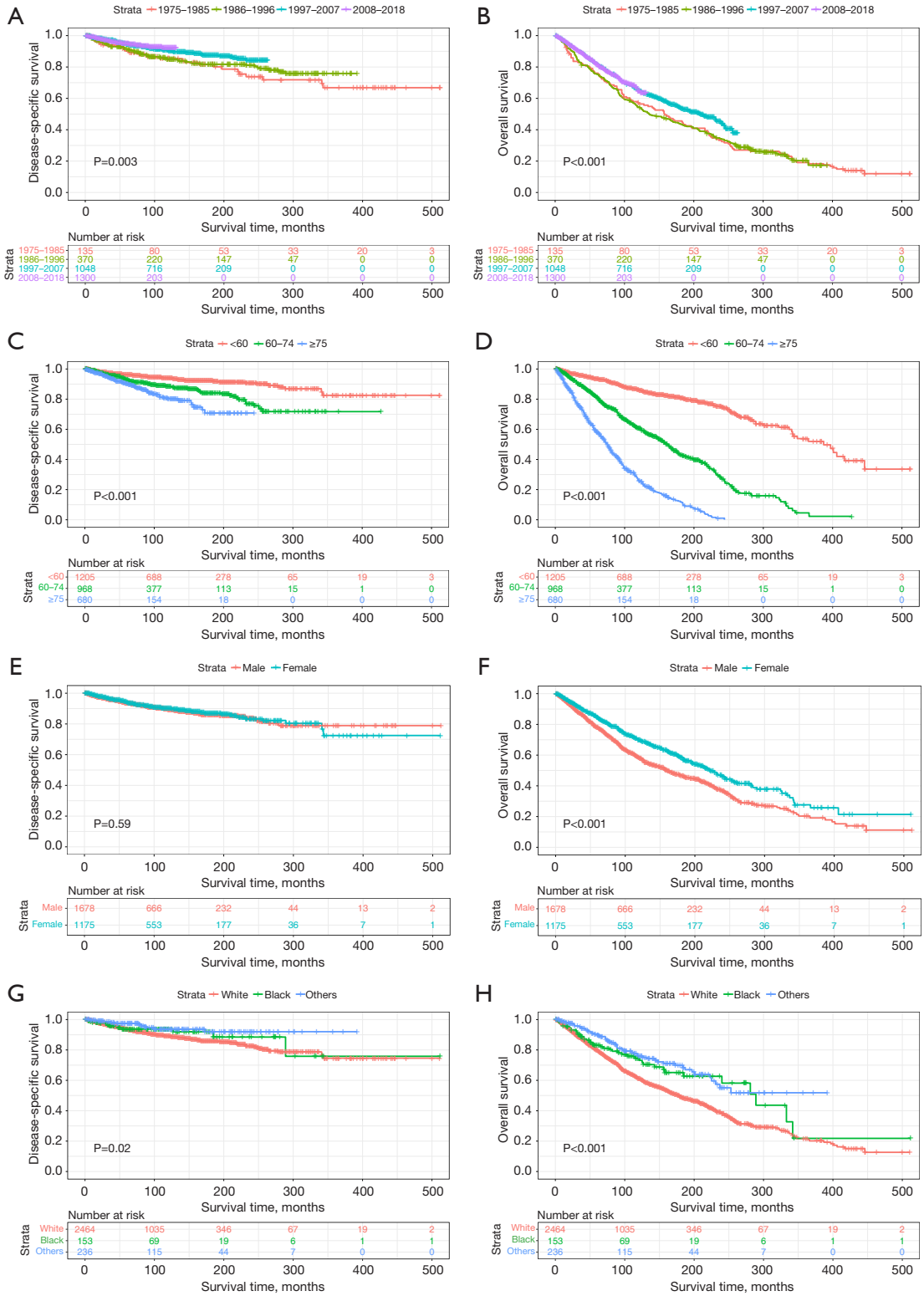

Figure 3 Disease-specific survival analysis of PMCT stratified by (A) year of diagnosis; (C) age; (E) sex; and (G) race. Overall survival analysis of PMCT stratified by (B) year of diagnosis; (D) age; (F) sex; and (H) race. SCC, squamous cell carcinoma; PMCT, primary malignant conjunctival tumor.

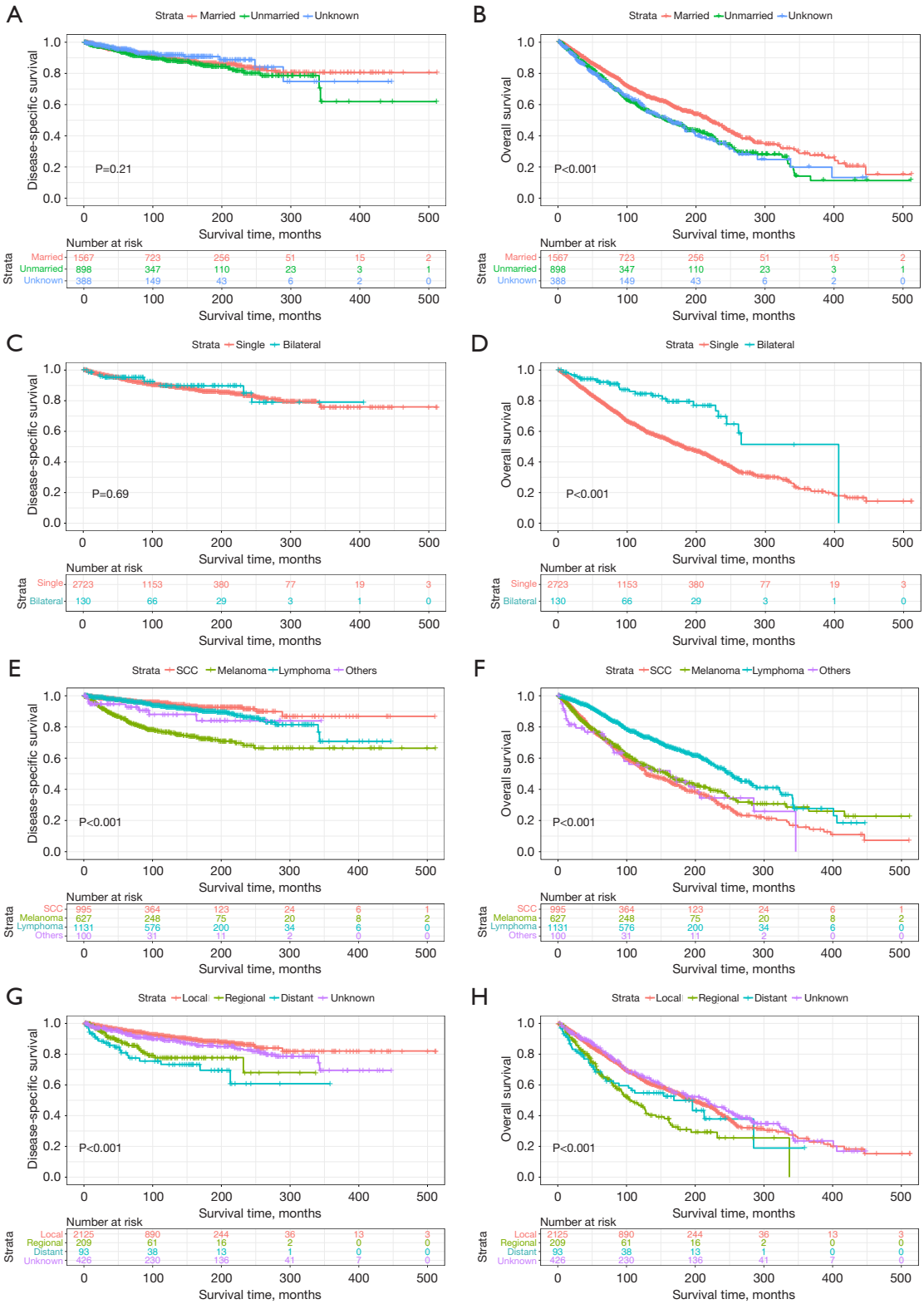

Figure 4 Disease-specific survival analysis of PMCT stratified by (A) marital status; (C) laterality; (E) histological type; and (G) SEER stage. Overall survival analysis of PMCT stratified by (B) marital status; (D) laterality; (F) histological type; and (H) SEER stage. PMCT, primary malignant conjunctival tumor; SCC, squamous cell carcinoma; SEER, Surveillance, Epidemiology, and End Results.

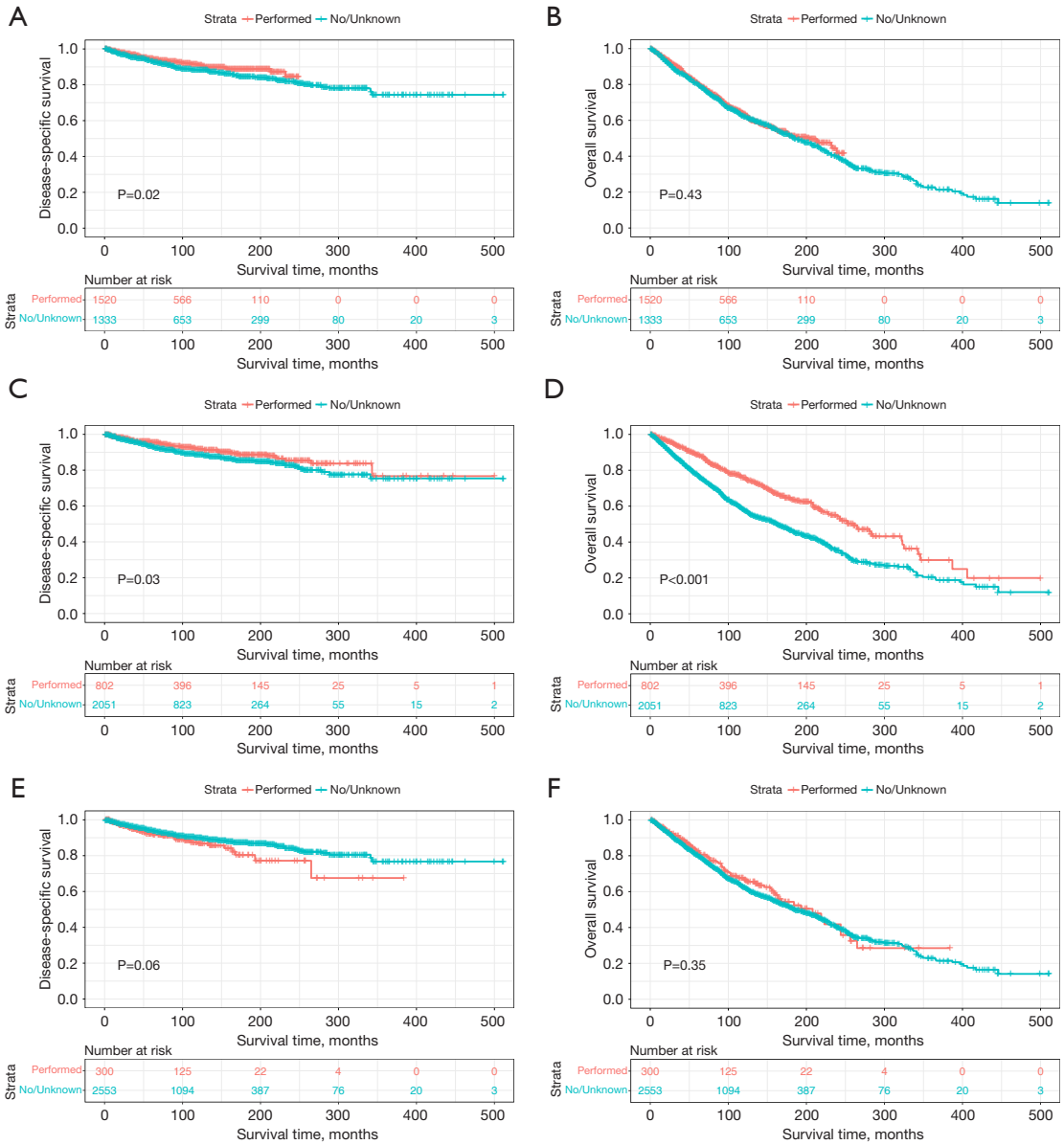

Figure 5 Disease-specific survival according to surgery (A), radiotherapy (C), and chemotherapy (E); overall survival according to surgery (B), radiotherapy (D), and chemotherapy (F).

to have different survival outcomes. Conjunctival melanoma was associated with a worse DSS, whereas conjunctival lymphoma was associated with a better OS. Conjunctival melanoma is well known for its invasive nature. It can proliferate and disseminate on the ocular surface, including the cornea, and directly invade the globe, eyelids, orbit, nasolacrimal system and sinuses (34,35). Local recurrence was observed in 50% of all cases, and metastases were detected in 16–32% of patients (35). Conjunctival melanoma has a poor prognosis. The DSS rate of conjunctival melanoma at 10 years varies from 62% to 76% (22,36,37). A Dutch study conducted by Brouwer *et al.* demonstrated that initial treatment at a large referral center enhanced the clinical outcomes of patients with conjunctival melanoma (38). Thus, they recommended that these patients should be referred as early as possible. According to disease stage, our results demonstrated that the SEER stage was related to DSS and OS. Patients with

Table 3 The results of the univariate and multivariate Cox regression analysis for DSS

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years		<0.001		<0.001
<60	Ref		Ref	
60–74	2.077 (1.537–2.807)	<0.001	2.033 (1.499–2.758)	<0.001
≥75	3.331 (2.408–4.609)	<0.001	3.211 (2.309–4.466)	<0.001
Year of diagnosis		0.003		0.68
1975–1985	Ref			
1986–1996	0.83 (0.529–1.303)	0.42		
1997–2007	0.57 (0.372–0.874)	0.01		
2008–2018	0.486 (0.303–0.78)	0.003		
Sex		0.59		
Male				
Female				
Race		0.03		0.28
White	Ref			
Black	0.742 (0.405–1.359)	0.34		
Others[#]	0.458 (0.25–0.839)	0.01		
Marital status		0.21		
Married				
Unmarried				
Unknown				
Laterality		0.69		
Single side				
Bilateral				
Histological type		<0.001		<0.001
SCC	Ref		Ref	
Melanoma	4.723 (3.309–6.741)	<0.001	4.637 (3.235–6.649)	<0.001
Lymphoma	1.425 (0.974–2.085)	0.07	1.141 (0.761–1.711)	0.52
Others	2.42 (1.174–4.987)	0.02	2.055 (0.994–4.249)	0.052
SEER stage		<0.001		<0.001
Localized	Ref		Ref	
Regional	2.599 (1.763–3.83)	<0.001	1.55 (1.04–2.309)	0.03
Distant	3.556 (2.251–5.619)	<0.001	4.318 (2.675–6.968)	<0.001
Unknown	1.376 (1.004–1.887)	0.047	1.495 (1.072–2.085)	0.02

Table 3 *(continued)*

Table 3 *(continued)*

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Surgery		0.02		0.001
Performed	Ref		Ref	
No/unknown	1.345 (1.04–1.74)		1.565 (1.187–2.062)	
Radiotherapy		0.03		0.23
Performed	Ref			
No/unknown	1.369 (1.028–1.823)			
Chemotherapy		0.058		0.11
Performed				
No/unknown				

Others[#], American Indian/Alaska Native, and Asian/Pacific Islander. DSS, disease-specific survival; HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; SEER, Surveillance, Epidemiology, and End Results.

distant SEER stages exhibited poor survival outcomes. Due to incomplete data on TNM in the SEER database, we could not obtain sufficient information to calculate the TNM stage of primary conjunctival malignant tumors. SEER stage is a standardized and simplified code that documents consistent tumor stage definitions over time (39). Most PMCT cases in our study were diagnosed at an early stage of the disease. In contrast to other mucous membranes throughout the body, the conjunctiva is readily observable. Due to the typical clinical features of conjunctival tumors, diagnoses are often achievable through routine ophthalmic examination and slit-lamp biomicroscopy performed by a skilled ophthalmologist. Consequently, tumors and associated lesions originating in the conjunctiva are typically detected at a comparatively early phase (40).

Surgical excision is the conventional therapy for the majority of cases of conjunctival malignancies. Except for lymphoma, surgery was the predominant intervention in patients with PMCT in our study. Surgery was also notably linked to prolonged DSS and OS. Incisional biopsy is performed for extensive suspicious malignancies, such as large melanoma, SCC, and primary acquired melanosis (2). However, incisional biopsy should be avoided for conjunctival melanoma, as it may increase the risk of recurrence (29,41). It is important to notice that if the conjunctival tumor occupies 4 hours or less on the bulbar or ≤15 mm basal dimension, excisional surgery and biopsy is usually preferable over incisional biopsy (42). In cases of SCC, epibulbar osseous choristoma, and melanoma, excisional biopsy is the preferred option to avoid inattentive tumor seeding. Complete excision and conjunctival reconstruction are feasible for tumors arising in the conjunctival fornix. However, most PMCTs, including SCC and melanoma, invade the intervertebral area near the limbus (8). Malignant limbal tumors probably invade the corneal epithelium and sclera that surround the tumor into the anterior chamber and disseminate through soft tissues into the orbit (35,43). Therefore, resecting a thin lamella of the sclera to obtain tumor-free margins could reduce the risk of tumor recurrence by avoiding friable tumor seeding into adjacent tissues. It is wise to use a delicate surgical technique, refraining from direct contact with the tumor, as well as to use microscopic techniques and keep a dry operative field to minimize the seeding of tumor cells (2).

In the present study, although radiotherapy was less common than surgery in patients with PMCT, more than half of the patients with conjunctival lymphoma received radiotherapy. Conjunctival tumors can be treated with two forms of radiotherapy: external beam radiotherapy and brachytherapy. External beam radiotherapy is often the preferred treatment option for conjunctival lymphoma, especially for lymphoma confined to the conjunctiva (27,44). A traditional radiation dosage of 20–30 Gy has been widely recommended for addressing such lesions, while studies also indicate that much lower doses may be sufficient (45,46). Brachytherapy directly sends a radioactive source to the tumor surface through various applicators, including plaques and seeds, and is used after

Table 4 The results of the univariate and multivariate Cox regression analysis for OS

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years		<0.001		<0.001
<60	Ref		Ref	
60–74	3.833 (3.236–4.54)	<0.001	3.725 (3.139–4.421)	<0.001
≥75	10.191 (8.57–12.118)	<0.001	9.399 (7.876–11.216)	<0.001
Year of diagnosis		<0.001		0.69
1975–1985	Ref			
1986–1996	1.01 (0.805–1.267)	0.93		
1997–2007	0.742 (0.597–0.923)	0.007		
2008–2018	0.73 (0.572–0.931)	0.01		
Sex		<0.001		<0.001
Male	Ref		Ref	
Female	0.704 (0.622–0.797)		0.701 (0.612–0.803)	
Race		<0.001		0.13
White	Ref			
Black	0.665 (0.49–0.902)	0.009		
Others[#]	0.532 (0.407–0.696)	<0.001		
Marital status		<0.001		<0.001
Married	Ref		Ref	
Unmarried	1.354 (1.188–1.542)	<0.001	1.342 (1.17–1.538)	<0.001
Unknown	1.373 (1.153–1.634)	<0.001	1.204 (1.008–1.439)	0.04
Laterality		<0.001		0.09
Single side	Ref			
Bilateral	0.402 (0.27–0.598)			
Histological type		<0.001		<0.001
SCC	Ref		Ref	
Melanoma	0.878 (0.756–1.02)	0.09	1.022 (0.873–1.197)	0.78
Lymphoma	0.496 (0.43–0.571)	<0.001	0.628 (0.533–0.74)	<0.001
Others	1.025 (0.752–1.397)	0.88	0.866 (0.633–1.184)	0.37
SEER stage		<0.001		<0.001
Localized	Ref		Ref	
Regional	1.724 (1.399–2.125)	<0.001	1.26 (1.017–1.561)	0.04
Distant	1.351 (0.986–1.85)	0.06	2.077 (1.498–2.881)	<0.001
Unknown	0.94 (0.805–1.098)	0.44	1.114 (0.944–1.314)	0.20

Table 4 *(continued)*

Table 4 *(continued)*

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Surgery		0.43		0.03
Performed			Ref	
No/unknown			1.16 (1.018–1.322)	
Radiotherapy		<0.001		0.70
Performed	Ref			
No/unknown	1.755 (1.517–2.031)			
Chemotherapy		0.35		0.86
Performed				
No/unknown				

Others[#], American Indian/Alaska Native, and Asian/Pacific Islander. OS, overall survival; HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; SEER, Surveillance.

conjunctival epithelial healing from lesion resection (47). Generally, brachytherapy is employed for patients with diffuse tumors that cannot be resected completely, and those with multiple recurrences (2). Increasing evidence demonstrates that topical chemotherapy, which has the potential to eliminate subclinical tumor cells, is a prominent therapy for conjunctival tumors, both in combination with surgical procedures and as a standalone therapy (48,49). It is preferable for diffuse, multifocal tumors invading the cornea and limbus, or when surgical resection margins test positive. However, owing to the relative rarity of PMCT, which limits the conducting of comparable studies, at present no standard guidelines exist for the utilization of diverse drugs across different types of conjunctival tumors.

There are several limitations in this study. First, as this was a retrospective study, bias was inevitable. Although we enrolled as many eligible patients as possible, the relationship between risk factors and prognosis may not have been well-identified due to the insufficient number of patients in the Cox regression model. However, to the best of our knowledge, the number of patients with PMCT in this study is the highest yet to be evaluated in the literature. Second, many factors that could impact survival outcomes are not available in the SEER database, including various laboratory indicators, vision preservation, and some potential prognostic variables could not be included. Third, the patients enrolled in our study may be unrepresentative, owing to an imbalance in race distribution in the SEER database. Further research based on different regions and races is required to obtain generalized results. Despite these limitations, the SEER database remains a reliable and valuable resource for researching uncommon malignancies.

Conclusions

The findings presented in this study indicate that PMCT is relatively uncommon, with an increasing incidence rate after 1975 up until 1997, followed by a slightly decreasing trend. Age, histological type, SEER stage, and surgery were all significantly associated with DSS and OS, while age ≥75 years, melanoma, and distant SEER stage were found to potentially lead to worse DSS. Similarly, age ≥75 years, male, unmarried status, and distant SEER stage were associated with worse OS, while lymphoma was related to better OS. Surgery is likely to improve the survival outcomes of patients. Taken together, these results provide a new perspective for improving the management and healthcare of patients with PMCT.

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Footnote

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