

# Conjunctival Melanoma in Chinese Patients: Local Recurrence, Metastasis, Mortality, and Comparisons With Caucasian Patients

Chuandi Zhou, Yuxin Wang, Renbing Jia, and Xianqun Fan

Department of Ophthalmology, Ninth People's Hospital of Shanghai, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Correspondence: Xianqun Fan, Department of Ophthalmology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, No. 639 Zhi Zao Ju Road, Shanghai 200011, China; fanxq@sjtu.edu.cn.

Renbing Jia, Department of Ophthalmology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, No. 639 Zhi Zao Ju Road, Shanghai 200011, China; renbingjia@sjtu.edu.cn.

CZ and YW contributed equally to the work presented here and should therefore be regarded as equivalent authors.

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**PURPOSE.** To evaluate the prognosis in Chinese patients with conjunctival melanoma and determine its predictors. Further, to explore the racial differences in clinical characteristics and outcomes between Chinese and Caucasian patients.

**METHODS.** This cohort study included 57 eyes of 57 consecutive patients with pathologically verified conjunctival melanoma between 1996 and 2016. Medical records were reviewed for factors associated with the local recurrence, metastasis, and tumor-related mortality. All eligible patients were followed up for these three outcome measures. The demographic data, clinical characteristics, and outcomes were compared between Chinese and Caucasian patients.

**RESULTS.** The mean follow-up period was  $52.2 \pm 49.4$  months. Among the total 57 patients, 29 (51%) patients experienced local recurrence. The 1-, 5-, and 10-year recurrence rate was 31.0%, 59.7%, and 66.4%, respectively. Treatment complications detected in the follow-up included dry eye (32, 56.1%), irregular eyelid margin (25, 43.9%), eyelid retraction (18, 31.6%), blepharoptosis (9, 15.8%), mixed pigmentation of the tarsus reconstructed by mucosal membrane graft, corneal opacities (6, 10.5%), and symblepharon (2, 3.5%). Twenty (35%) patients developed metastasis. The 1-, 5-, and 10-year metastasis rate was 16.7%, 38.7%, and 50.9%, respectively. Fourteen (25%) patients died of conjunctival melanoma, with a median survival time of 24 months. The 1-, 5-, and 10-year tumor-related mortality was 3.8%, 30.5%, and 37.4%, respectively. Tumor hemorrhage is an independent risk factor for tumor-related death (hazard ratio [HR]: 18.81,  $P = 0.01$ ) and metastasis (HR: 4.57,  $P = 0.02$ ). Significant differences were noted between Chinese and Caucasians patients from America, Germany, and England in demographics, clinical characteristics, and outcomes. Compared to Caucasians, Chinese patients tended to have more male cases ( $P < 0.01$ ) and to be younger ( $P = 0.03$ ). At initial presentation, more Chinese patients had de novo tumor origin ( $P < 0.01$ ), epithelioid cell type ( $P < 0.01$ ), nonbulbar tumor location ( $P < 0.01$ ), greater basal diameter ( $P = 0.04$ ), multifocal tumor ( $P < 0.01$ ), feeder vessels ( $P < 0.01$ ), eyelid ( $P < 0.01$ ) and orbit involvement ( $P < 0.01$ ), and advanced T stages ( $P < 0.01$ ). Over a similar follow-up period with Caucasians patients (52.2 vs. 52 months,  $P = 0.97$ ), a significantly larger proportion of Chinese patients exhibited eyelid invasion ( $P = 0.04$ ) and orbital invasion ( $P < 0.01$ ) at follow-up, local recurrence ( $P < 0.01$ ), metastasis ( $P < 0.01$ ), and tumor-related death ( $P < 0.01$ ).

**CONCLUSIONS.** Conjunctival melanoma is a rare malignancy with great potential for mortality in Chinese. Special attention should be paid to patients with tumor hemorrhage. Compared to Caucasians, Chinese patients exhibit more aggressive clinical signs with compromised prognosis.

**Keywords:** conjunctival melanoma, local recurrence, metastasis, tumor-related mortality, racial differences

Conjunctival melanoma is an uncommon but potentially deadly tumor. It accounts for approximately 2% of all ocular malignancies.<sup>1</sup> This tumor is mostly reported in Caucasian patients, with an annual incidence of 0.2 to 0.5 cases per million people.<sup>2</sup> However, in Asia, conjunctival melanoma is a rare malignancy; the annual incidence is around 0.15 cases per million people.<sup>3</sup>

Numerous studies have explored predictors for the prognosis for conjunctival melanoma in Caucasian patients. Known

prognostic factors included greater tumor thickness, multifocal tumors, nonepibulbar location, de novo tumor origin, epithelioid cell type, lymphatic invasion, and tumor-involved surgical margin.<sup>4-8</sup> According to previous case series, the incidence of local recurrence is reported to be 26% to 60.7% at 5 years and 38% to 66.8% at 10 years.<sup>9-11</sup> The overall chances of metastasis have been reported at 15% to 66.7%.<sup>9,11-15</sup> Based on retrospective case series, the 5-year mortality rate is 7% to 26%, 10-year is 22.3% to 59%, and 15-year is 25% to



32.8%.<sup>4,8,9,11,14</sup> However, possibly due to its relative rarity in the Asian population, studies pertinent to the prognosis for conjunctival melanoma in Asians are rather limited.

Though melanoma is less common in Asians than in Caucasians, it is often associated with increased morbidity and mortality in people of color.<sup>5,16,17</sup> In a large retrospective study of 382 consecutive cases of conjunctival melanoma, Asian patients had a greater propensity for metastasis than Caucasians, with a crude RR (relative risk) of 372.3.<sup>5</sup> However, that study included only three patients from Asia, and the extremely small sample size might have induced deviation in the statistical analysis. Additionally, the specific reasons underlying this racial difference have not been specified.

In this case series, we intended to explore the prognostic factors for conjunctival melanoma in Chinese patients, and compare, in detail, the clinical characteristics and outcomes between Chinese patients and their Caucasian counterparts, to partially elucidate the reasons for the racial differences in prognoses.

## METHODS

### Patients

A retrospective review was performed in consecutive patients who were diagnosed with malignant conjunctival melanoma in Ninth People's Hospital of Shanghai from January 1996 to May 2016. The diagnoses were based on the typical clinical presentations and confirmed by pathologic reports. The exclusion criteria were as follows: (1) cases of precursor lesions (nevus or primary acquired melanosis [PAM]) with atypia or cases that were not histologically confirmed as malignant melanoma; (2) a follow-up period < 6 months; and (3) incomplete data collection. We contacted all patients who met the inclusion criteria or their relatives and explained the purpose of the study, and they participated in this study voluntarily without any compensation. Of the 67 patients who met the inclusion criteria, 3 patients were not reached, and 3 declined to participate in this study for reasons such as geographic or time limitations. Of the 61 subjects who agreed to return for the follow-up visit, 4 patients were excluded for incomplete data collection, leaving a final sample of 57 eyes of 57 patients.

### Data Collection

Informed consent was obtained from all patients or their relatives at the follow-up visit. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Shanghai Jiaotong University research ethics committee.

Data collected included patient demographics, clinical characteristics, treatments, and final outcomes at the follow-up. The demographics consisted of age and sex. The clinical characteristics comprised tumor origin, cell type, duration of pigmentation before diagnosis, anatomic location, greatest tumor basal diameter and tumor thickness, multifocality, tumor feeder vessels, tumor hemorrhage, surgical approaches, and adjuvant treatments. The anatomic location was subdivided as previously described<sup>4</sup>; (epi)bulbar and limbal locations were defined as "favorable site," and other conjunctival locations, including the caruncle, plica, fornices, and palpebral conjunctiva, as "unfavorable site." The patients were also stratified by their clinicopathologic presentations according to the 7th edition of American Joint Committee on Cancer (AJCC) staging system for conjunctival melanoma.<sup>18</sup> If the patient had received treatment elsewhere, his/her prior clinical details and pathologic sections before referral were retrieved for

review. For outcome measures, the months from the initial diagnosis to the first recurrence, metastasis, and death were documented, and the time from the first metastasis to death was calculated. The date of recurrence, metastasis was determined by the day on which the dissemination was confirmed by biopsy, imaging, or clinical examination. In addition, the locations of metastasis and notable complications were recorded.

### Statistical Analysis

The data were analyzed using SAS software (version 9.2; SAS Institute, Inc., Cary, NC, USA) and were reported as the mean  $\pm$  standard deviation (SD) or *n* (%). Firstly, to identify the possible correlates of recurrence, metastasis, and tumor-related death, demographic and clinical indicators at the initial presentation of the patients with different outcomes were compared using univariate Cox proportional hazards regressions. The significant factors were entered into the multivariate Cox regression models as independent variables to explore the prognostic predictors for conjunctival melanoma. Initial recurrence, metastasis, and tumor-related death were modeled as major outcomes (dependent factors), and patients who were alive at the end of follow-up or who died of other causes were considered censored. The regression coefficients and hazard ratios (HRs) with 95% confidence intervals were calculated. All tests were 2-sided, and a *P* value < 0.05 was considered statistically significant. The Kaplan-Meier method was used to analyze the patients' recurrence, metastasis, and death rate.

## RESULTS

A total of 57 eyes in 57 patients were recruited in this study, including 42 (74%) male patients and 15 (26%) female patients. The age of our patients ranged from 18 to 82 years, with an average age of  $54.4 \pm 15.6$  years. The mean follow-up period was  $52.2 \pm 49.4$  months (range, 6–216 months). Treatment before referral to our hospital was noted in 28 (49%) patients. Demographic and baseline clinical characteristics are summarized in Table 1. It is noteworthy that, in contrast to the Western studies, only three (5%) patients had melanoma that involved bulbar conjunctiva alone (T1 stage). The number of patients with T2 and T3 stage conjunctival melanoma was 25 (44%) and 29 (51%), respectively. At the time of diagnosis, one (2%) patient had exhibited regional lymph node metastasis, and none of them had exhibited distant metastasis. Varying clinical appearance of Chinese patients with conjunctival melanoma is displayed in Figure 1.

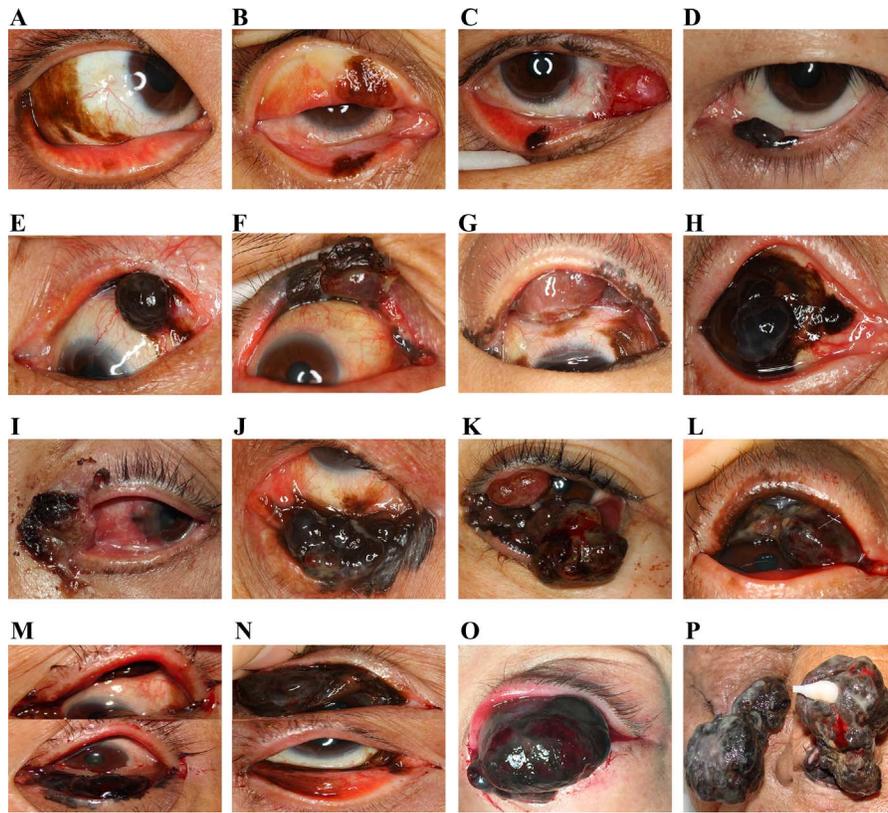
During the follow-up, more than half of our patients (29, 51%) had local recurrence; among these, 17 (30%) patients experienced recurrent melanoma within the first year after initial diagnosis. Fifteen (26%) cases had more than two recurrences. The median duration to the initial recurrence was 11 months (mean:  $15.8 \pm 18.1$  months; range, 1–84 months). However, no significant correlate was found to be associated with tumor local recurrence (Table 1). By Kaplan-Meier survival estimates, the 1-, 5-, and 10-year recurrence rate was 31.0%, 59.7%, and 66.4%, respectively.

Treatment complications detected in the follow-up included dry eye (32, 56.1%), irregular eyelid margin (25, 43.9%), eyelid retraction (18, 31.6%), blepharoptosis (9, 15.8%), mixed pigmentation of the tarsus reconstructed by mucosal membrane graft, corneal opacities (6, 10.5%), and symblepharon (2, 3.5%). Dry eye symptoms were managed by topical lubricants. Amniotic membrane was used to cover an active corneal ulcer. No patients received ocular reconstruction surgery.

TABLE 1. Univariate Analyses of Demographic and Clinical Characteristics for Tumor-Related Death, Metastasis, and Local Recurrence in Chinese Patients With Conjunctival Melanoma

Characteristics	Total	Recurrence		P	Metastasis		P	Tumor-Related Death		P
		(+)	(-)		(+)	(-)		(+)	(-)	
Sex										
Male, no. (%)	42 (74)	21 (72)	21 (75)	0.85	16 (80)	26 (70)	0.35	11 (79)	31 (72)	0.54
Female, no. (%)	15 (26)	8 (28)	7 (25)		4 (20)	11 (30)		3 (21)	12 (28)	
Age, y	54.4 ± 15.6	50.1 ± 13.5	58.8 ± 16.6	0.13	54.0 ± 11.9	54.5 ± 17.5	0.48	54.9 ± 12.7	54.2 ± 16.6	0.33
Duration of pigmentation, mo	6.5 ± 8.7	7.9 ± 11.5	5.1 ± 4.0	0.66	8.0 ± 8.5	5.7 ± 8.9	0.35	7.7 ± 8.8	6.1 ± 8.8	0.46
Tumor origin				0.65			0.02*			0.03*
De novo, no. (%)	23 (40)	11 (38)	12 (43)		12 (60)	11 (30)		8 (57)	15 (35)	
Nevus, no. (%)	12 (21)	5 (17)	7 (25)		4 (20)	8 (22)		4 (29)	8 (19)	
Primary acquired melanosis, no. (%)	22 (39)	13 (45)	9 (32)	0.93	4 (20)	18 (49)	0.47	2 (14)	20 (46)	0.56
Tumor location										
Favorable site, no. (%)	3 (5)	1 (3)	2 (7)		0 (0)	3 (8)		0 (0)	3 (7)	
Unfavorable site, no. (%)	54 (95)	28 (97)	26 (93)		20 (100)	34 (92)		14 (100)	40 (93)	
Tumor thickness, cm	0.6 ± 0.7	0.7 ± 0.9	0.5 ± 0.4	0.32	1.0 ± 1.0	0.4 ± 0.3	0.01*	1.2 ± 1.2	0.4 ± 0.3	<0.01*
Greatest tumor basal diameter, cm	1.6 ± 1.9	1.8 ± 2.6	1.5 ± 0.8	0.88	2.3 ± 3.1	1.3 ± 0.7	0.19	2.5 ± 3.7	1.4 ± 0.7	0.12
Cell type				0.78			0.96			0.79
Epithelioid cell type, no. (%)	37 (65)	18 (62)	19 (68)		13 (65)	24 (65)		9 (65)	28 (65)	
Spindle cell type, no. (%)	12 (21)	8 (28)	4 (14)		3 (15)	9 (24)		2 (14)	10 (23)	
Combined, no. (%)	8 (14)	3 (10)	5 (18)		4 (20)	4 (11)		3 (21)	5 (12)	
Ki 67, %	23.0 ± 19.7	23.4 ± 19.4	22.6 ± 20.3	0.97	29.3 ± 18.1	19.6 ± 19.9	0.11	29.6 ± 17.8	20.8 ± 19.9	0.18
Tumor feeder vessels				0.91			0.03*			0.09
Present, no. (%)	34 (60)	18 (62)	16 (57)		20 (100)	14 (38)		14 (100)	20 (47)	
Absent, no. (%)	23 (40)	11 (38)	12 (43)		0 (0)	23 (62)		0 (0)	23 (53)	
Tumor hemorrhage				0.78			<0.01*			<0.01*
Present, no. (%)	25 (44)	14 (48)	11 (39)		16 (80)	9 (24)		13 (93)	12 (28)	
Absent, no. (%)	32 (56)	15 (52)	17 (61)		4 (20)	28 (76)		1 (7)	31 (72)	
Multifocality				0.78			<0.01*			0.04*
Unifocal tumor, no. (%)	24 (42)	11 (38)	13 (46)		2 (10)	22 (60)		1 (7)	23 (54)	
Multifocal tumor, no. (%)	33 (58)	18 (62)	15 (54)		18 (90)	15 (40)		13 (93)	20 (46)	
Tumor involvement of surgical margins				0.66			0.01*			0.19
Tumor-free margins, no. (%)	24 (42)	11 (38)	13 (46)		4 (20)	20 (54)		4 (29)	20 (47)	
Tumor-involved margins, no. (%)	33 (58)	18 (62)	15 (54)		16 (80)	17 (46)		10 (71)	23 (53)	
Had adjuvant therapy				0.95			0.38			0.30
Yes, no. (%)	18 (32)	9 (31)	9 (32)		8 (40)	10 (27)		6 (43)	12 (28)	
No, no. (%)	39 (68)	20 (69)	19 (68)		12 (60)	27 (73)		8 (57)	31 (72)	
Eyeball preservation				0.76			0.84			0.51
Yes, no. (%)	35 (61)	17 (59)	18 (64)		13 (65)	22 (60)		10 (71)	25 (58)	
No, no. (%)	22 (39)	12 (41)	10 (36)		7 (35)	15 (40)		4 (29)	18 (42)	

\* Statistically significant.



**FIGURE 1.** Clinical appearance in Chinese patients with conjunctival melanoma. (A) Conjunctival melanoma originating from primary acquired melanosis (PAM). (B) Multifocal, recurrent conjunctival melanoma originating from PAM. (C) Recurrence presenting with both amelanotic caruncular (having large intrinsic vasculature) and pigmented palpebral melanoma. (D) Nodular tarsal conjunctival melanoma with intrinsic vessels. (E) Nodular tarsal recurrence with feeder vessels. (F) Multifocal, tarsal melanoma with hemorrhage. (G) Recurrent conjunctival melanoma with a mixed pigmentation. (H) Bulbar conjunctival melanoma involving a large area with feeder vessels. (I) Mixed pigmented recurrence in caruncular and limbal locations exhibited with tumor hemorrhage and ulceration. (J) Relapsed conjunctival melanoma with intrinsic vessels and eyelid skin invasion. (K) Multiple, mixed pigmented melanoma with tumor hemorrhage. (L) Large nodular conjunctival melanoma with hemorrhage, ulceration, and purulent discharge. (M) Multifocal, recurrent melanomas with tumor hemorrhage and orbital invasion. (N) Large hemorrhagic nodular tumor originating from PAM. (O) Large nodular recurrence with severe hemorrhage. (P) Extremely large conjunctival melanoma with nasal cavity invasion, presenting with tumor hemorrhage, ulceration, and purulent discharge.

During the follow-up, 20 (35%) patients developed metastasis. The initial metastasis locations included lymph node (10, 50%), brain (5, 25%), liver (2, 10%), lung (1, 5%), bone (1, 5%), and systemic dissemination (1, 5%). Among these, seven (35%) patients presented metastases involving multiple sites. The median duration between the initial diagnosis and first metastasis was 17.5 months (mean:  $24.8 \pm 25.2$  months; range, 0–93 months). By Kaplan-Meier survival estimates, the

1-, 5-, and 10-year metastasis rate was 16.7%, 38.7%, and 50.9%, respectively. Univariate Cox analysis indicated that tumor origin ( $P = 0.02$ ), thickness ( $P = 0.01$ ), multifocality ( $P < 0.01$ ), T stage ( $P < 0.01$ ), tumor involvement in resection ( $P = 0.01$ ), the presence of feeder vessels ( $P = 0.03$ ), and tumor hemorrhage ( $P < 0.01$ ) were the potential predictors for metastasis (Table 1). In multivariate Cox proportional hazard regression analysis, tumor hemorrhage (HR: 4.57,  $P = 0.02$ )

**TABLE 2.** Cox Proportional Hazards Regression Analysis for the Predictors of Metastasis in Chinese Patients With Conjunctival Melanoma

Variables	Regression Coefficient (SE)	Hazard Ratio (95% CI)	P
Tumor origin			
Primary acquired melanosis	Reference		
De novo	0.93 (0.64)	2.54 (0.72–8.96)	0.15
Nevus	–0.02 (0.74)	0.98 (0.23–4.21)	0.98
Tumor thickness, mm	–0.14 (0.24)	0.87 (0.55–1.38)	0.55
Feeder vessels, yes vs. no	11.26 (171.42)	7.80E4 (0–6.43E150)	0.95
Tumor hemorrhage, yes vs. no	1.52 (0.66)	4.57 (1.25–16.76)	0.02*
Multifocality, multifocal vs. unifocal	1.19 (0.78)	3.28 (0.71–15.06)	0.13
Tumor involvement of surgical margins, tumor-involved vs. tumor-free margins	–0.21 (0.60)	0.81 (0.25–2.64)	0.73

SE, standard error; CI, confidence interval.

\* Statistically significant.

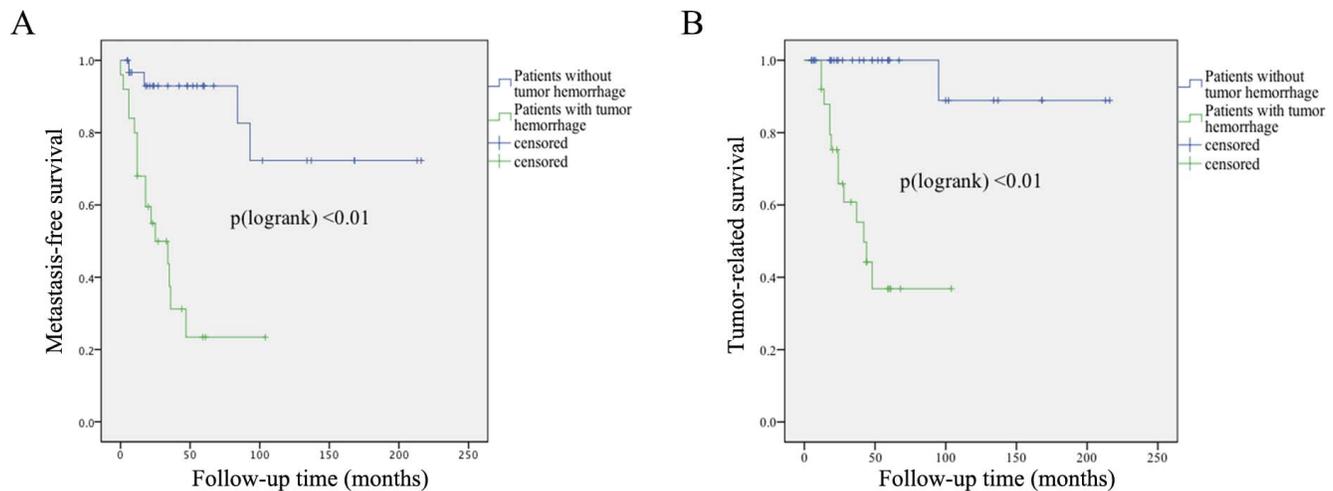


FIGURE 2. The presence of tumor hemorrhage and prognosis in Chinese patients with conjunctival melanomas. Significantly lower metastasis-free (A) and tumor-related (B) survival rates were exhibited in patients with tumor hemorrhage than in patients without this clinical sign (all  $P < 0.01$ ).

was the only independent risk factor for metastasis in Chinese patients with conjunctival melanoma (Table 2). The metastasis-free survival curves of the patients with and without tumor hemorrhage are shown in Figure 2A.

In this follow-up, 14 (25%) patients had died of conjunctival melanoma, with a median survival time of 24 months (mean:  $31.1 \pm 22.0$  months; range, 12–95 months). The median survival after initial metastasis up to mortality was 7 months (mean:  $9.1 \pm 8.4$  months; range, 2–36 months). By Kaplan-Meier survival estimates, the 1-, 5-, and 10-year tumor-related mortality was 3.8%, 30.5%, and 37.4%, respectively. Demographic and clinical indices were compared between the patients with and without tumor-related death (Table 1). The two groups had significant differences in tumor origin ( $P = 0.03$ ), thickness ( $P < 0.01$ ), the presence of tumor hemorrhage ( $P < 0.01$ ), and multifocality ( $P = 0.04$ ). Multivariate Cox proportional hazards regression analysis indicated that tumor hemorrhage (HR: 18.81,  $P = 0.01$ ) was significantly associated with tumor-related death (Table 3). Metastasis-free survival curves of the patients with and without tumor hemorrhage are shown in Figure 2B.

To elucidate the racial diversity of conjunctival melanoma in detail, consecutive White patients with detailed clinical information from four large studies were chosen as the control.<sup>4,5,19,20</sup> Then, our patients were divided according to the stratification in these four studies, which were conducted by Shields et al.<sup>5,20</sup> in 2011 and 2012 (America, 382 patients; America, 343 patients), Heindl et al.<sup>19</sup> in 2011 (Germany, 109 patients), and Paridaens et al.<sup>4</sup> in 1994 (England, 256 patients), respectively. The baseline characteristics and clinical outcomes

between Caucasian and Chinese patients were compared, and the results are summarized in Table 4. Obviously, our case series tended to have more male patients ( $P < 0.01$ ) and to be younger ( $P = 0.03$ ). And at initial presentation, more Chinese patients had de novo tumor origin ( $P < 0.01$ ), epithelioid cell type ( $P < 0.01$ ), unfavorable tumor location ( $P < 0.01$ ), greater basal diameter ( $P = 0.04$ ), multifocal tumor ( $P < 0.01$ ), feeder vessels ( $P < 0.01$ ), eyelid ( $P < 0.01$ ) and orbit involvement ( $P < 0.01$ ), and advanced T stages ( $P < 0.01$ ). In addition, regarding the surgical approaches, the proportion of Chinese patients who underwent resections with tumor-free margins was much smaller than that of White patients ( $P < 0.01$ ). However, orbital exenteration rate was much higher in our sample ( $P < 0.01$ ). Over a follow-up period similar to that of the study conducted by Shields et al.,<sup>5</sup> (52.21 vs. 52 months,  $P = 0.97$ ), a significantly larger proportion of Chinese patients exhibited eyelid invasion ( $P = 0.04$ ) and orbital invasion ( $P < 0.01$ ) at follow-up, local recurrence ( $P < 0.01$ ), metastasis ( $P < 0.01$ ), and tumor-related death ( $P < 0.01$ ).

DISCUSSION

The findings of our study indicated that Chinese patients exhibited more aggressive conjunctival melanoma with a compromised prognosis when compared to the Caucasian patients. In our study, the 5- and 10-year melanoma relapse rates in Chinese patients (5-year: 59.7%; 10-year: 66.4%) were notably higher than those of patients in America (5-year: 26%; 10-year: 51%)<sup>9</sup> and Finland (5-year: 36%; 10-year: 38%),<sup>10</sup> but

TABLE 3. Cox Proportional Hazards Regression Analysis for the Predictors of Tumor-Related Survival in Chinese Patients With Conjunctival Melanoma

Variables	Regression Coefficient (SE)	Hazard Ratio (95% CI)	P
Tumor origin			
Primary acquired melanosis	Reference		
De novo	1.45 (0.87)	4.26 (0.77–23.52)	0.10
Nevus	1.18 (0.93)	3.25 (0.53–20.06)	0.21
Tumor thickness, mm	0.07 (0.21)	1.07 (0.70–1.63)	0.76
Tumor hemorrhage, yes vs. no	2.93 (1.15)	18.81 (1.97–179.90)	0.01*
Multifocality, multifocal vs. unifocal	1.72 (1.06)	5.57 (0.70–44.49)	0.11

SE, standard error; CI, confidence interval.  
\* Statistically significant.

TABLE 4. Comparisons of Baseline Characteristics and Clinical Outcomes Between Caucasian and Chinese Patients With Conjunctival Melanoma

Characteristics	White Patients	Chinese Patients	P
Sex†	n = 382	n = 57	<0.01*
Male, no. (%)	186 (49)	42 (74)	
Female, no. (%)	196 (51)	15 (26)	
Age‡, y (n)	59 (n = 382)	54.4 (n = 57)	0.03*
Clinical origin†	n = 382	n = 57	<0.01*
De novo, no. (%)	72 (19)	23 (40)	
Nevus, no. (%)	26 (7)	12 (21)	
Primary acquired melanosis, no. (%)	284 (74)	22 (39)	
Tumor topography†	n = 280	n = 57	0.40
Flat, no. (%)	105 (38)	18 (32)	
Nodular, no. (%)	175 (63)	39 (68)	
Greatest tumor basal diameter, cm† (n)	1.1 (n = 382)	1.6 (n = 57)	0.04*
Cell type‡	n = 109	n = 57	<0.01*
Epithelioid cell type, no. (%)	31 (28)	37 (65)	
Spindle cell type, no. (%)	26 (24)	12 (21)	
Combined, no. (%)	39 (36)	8 (14)	
Indeterminate cell type, no. (%)	13 (12)	0 (0)	
Tumor location§	n = 256	n = 57	<0.01*
Favorable site, no. (%)	143 (56)	3 (5)	
Unfavorable site, no. (%)	113 (44)	54 (95)	
Ki 67, %‡ (n)	19 (n = 109)	23.0 (n = 57)	0.13
With tumor feeder vessels†, no. (%) (n)	101 (26) (n = 382)	34 (60) (n = 57)	<0.01*
Multifocality‡	n = 109	n = 57	<0.01*
Unifocal tumor, no. (%)	90 (83)	24 (42)	
Multifocal tumor, no. (%)	19 (17)	33 (58)	
T stage	n = 343	n = 57	<0.01*
T1, no. (%)	196 (57)	3 (5)	
T2, no. (%)	110 (32)	25 (44)	
T3, no. (%)	37 (11)	29 (51)	
Eyelid invasion at presentation†, no. (%) (n)	4 (1) (n = 382)	10 (18) (n = 57)	<0.01*
Orbital invasion at presentation†, no. (%) (n)	8 (2) (n = 382)	10 (18) (n = 57)	<0.01*
Tumor-free margins in resection‡, no. (%) (n)	104 (95) (n = 109)	24 (42) (n = 57)	<0.01*
Underwent exenteration†, no. (%) (n)	39 (10) (n = 382)	21 (37) (n = 57)	<0.01*
Follow-up period, mo†, no. (n)	52 (n = 382)	52.2 (n = 57)	0.97
Eyelid invasion at follow-up†, no. (%) (n)	81 (21) (n = 382)	19 (33) (n = 57)	0.04*
Orbital invasion at follow-up†, no. (%) (n)	50 (13) (n = 382)	25 (44) (n = 57)	<0.01*
Local recurrence†, no. (%) (n)	106 (28) (n = 382)	29 (51) (n = 57)	<0.01*
Metastasis†, no. (%) (n)	71 (19) (n = 382)	20 (35) (n = 57)	<0.01*
Tumor-related death†, no. (%) (n)	20 (5) (n = 382)	14 (25) (n = 57)	<0.01*

\* Statistically significant.

† Shields et al.<sup>5</sup>

‡ Heindl et al.<sup>19</sup>

§ Paridaens et al.<sup>4</sup>

|| Shields et al.<sup>20</sup>

slightly lower than the findings in The Netherlands (5-year: 60.7%; 10-year: 66.8%).<sup>11</sup> From our observation, the 5- and 10-year metastasis rate was 38.7% and 50.9%, respectively, which is much higher than the results from America (5-year: 16%; 10-year: 26%)<sup>9</sup> and Finland (10-year: 18%).<sup>12</sup> Regarding mortality, the 5- and 10-year tumor-related death rate for Chinese patients was 30.5% and 37.4%, respectively. This mortality is much higher than that in America (5-year: 7%,<sup>9</sup> 26%,<sup>14</sup>), The Netherlands (5-year: 13.7%; 10-year: 28.8%),<sup>11</sup> England (5-year: 17%; 10-year: 30.7%),<sup>4</sup> Germany (5-year: 13.4%,<sup>21</sup> 15.2%,<sup>8</sup>; 10-year: 23.7%,<sup>21</sup> 22.3%,<sup>8</sup>), Sweden (10-year: 30%,<sup>22</sup>), and Finland (5-year: 20%,<sup>10</sup>; 10-year: 32%,<sup>23</sup>). However, in the studies conducted by Tuomaala et al.<sup>10</sup> and Esmaeli et al.,<sup>14</sup> the 10-year tumor-related death rate was 38% and 59%, respectively, which was higher than that of Chinese patients. The above findings demonstrated that Chinese patients with conjunctival melanoma exhibited a higher 5-year mortality and a comparable 10-year mortality when compared to their Western counterparts.

Potential explanations for these discrepancies may lie in the following aspects. First, Chinese patients were more likely to be predisposed to the reported risk factors, such as de novo tumor origin, greatest tumor basal diameter, epithelioid cell type, and non-epibulbar location. Secondly, patients in China, especially those living in rural areas, have limited access to standard medical treatment for melanoma. Nearly half of our patients (28, 49%) had received surgery elsewhere before referral to our hospital. As to primary resection, 33 (58%) participants in our study did not have a pathologically confirmed tumor-free margin intraoperatively. Among these patients, 18 (55%) had recurrent conjunctival melanoma, 16 (48%) patients developed metastasis, and 10 (30%) cases died of melanoma. In addition, ethnicity-specific genetic factors might also play a role in these racial variations. *BRAF* mutations were identified in around 40% of Caucasian cases,<sup>24,25</sup> whereas in Chinese patients, the mutation rate was reported as only 8% to 14.7%.<sup>26,27</sup> Genetic mutations of *c-kit* were detected in approximately 10.8% of Chinese melanoma patients,<sup>28</sup> which

was also lower than in Caucasian patients.<sup>29</sup> Although this gene diversity does exist, its explanatory effect on the behavior of conjunctival melanomas remains largely unpredictable. Furthermore, infrequent screening and poor melanoma awareness in China might also contribute to these disparities. Due to the low morbidity of conjunctival melanoma in the Chinese population, most patients have a poor knowledge base for recognizing melanoma. Additionally, doctors did not have adequate suspicion concerning melanoma when encountering patients with ocular pigmentations. The significantly greater number of patients with multifocal tumors and higher T stages (all  $P < 0.01$ ) can be partially attributable to delay in standard treatment of melanoma. Consequently, to achieve better survival in Chinese patients with conjunctiva melanoma, the following measures could be recommended: (1) raising awareness of conjunctiva melanoma among the public as well as among ocular physicians; (2) frequent screening of patients for nevus or PAM with atypia; (3) applying the surgical technique of complete resection with pathologically confirmed tumor-free margin intraoperatively<sup>19</sup>; (4) appropriate adjuvant therapies<sup>27,30</sup>; and (5) the application of BRAF inhibitor (vemurafenib) for metastatic *BRAF*-mutated patients.<sup>31</sup>

The multivariate Cox regression model showed that tumor hemorrhage is an ominous sign with regard to predicting metastasis and tumor-related death in Chinese patients with conjunctival melanoma. In this study, 25 (44%) eyes exhibited tumor hemorrhage; among these, 16 (64%) metastasized and 13 (52%) of the patients died. Intrinsic and feeder vascularity are common signs of conjunctival melanoma.<sup>32</sup> Therefore, malignant tumors of advanced stages have a propensity to hemorrhage for their rich blood supply. Experiences from other medical centers also gave credence to this finding from different perspectives. Shields et al.<sup>33</sup> conducted a retrospective study in 806 children with conjunctival tumor.<sup>33</sup> It was proven that compared to nevus, a child with malignant conjunctival melanoma had a 25.3-fold increase in chances of hemorrhage in the tumor. And in another large series of 5002 patients with conjunctival tumors, tumor hemorrhage was a significant predictor for malignant melanoma compared with PAM lesions.<sup>32</sup>

This study should be regarded as an initial exploration regarding the racial differences between Chinese and Caucasian patients with conjunctival melanoma. However, caution should be exercised when interpreting the findings due to a number of limitations. First, compared to the case series with Caucasians, our sample size was small, and all the patients were recruited from a single tertiary hospital. The sample size might produce large confidence intervals for hazard ratios in Cox analysis. However, the extremely low incidence of this disease makes it difficult to gather a large number of patients in China. Another bias may relate to the recruitment of the patients. Higher mortality, metastasis, and recurrence rate may result from the fact that more patients with advanced disease were admitted to our hospital than to other medical settings. All these factors might have caused selection bias, and our results might not generalize to the entire Chinese conjunctival melanoma patient population. Second, comparisons between Chinese and Caucasians might have been confounded by other factors not taken into consideration, for example, the evaluations made by different doctors and the interactions between these clinical indices. However, our data are not sufficient to allow further detailed exploration. Nevertheless, it is noteworthy that this study constitutes the largest report on conjunctival melanoma in an Asian population to date.

Although conjunctival melanoma is less prevalent in Chinese than in the White population, when it does occur in Chinese, it is more likely to present advanced melanoma at diagnosis and lower survival. Consequently, to raise awareness

and enhance screening among the public is of great significance in China. However, to our knowledge, this study is the first and only evaluation comparing detailed clinical characteristics and outcomes between Chinese and Caucasian patients with conjunctival melanoma. Therefore, a large series from multiple clinical centers with long-term follow-up is needed to fully validate our findings.

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