
Mohs micrographic surgery for eyelid sebaceous carcinoma: A multicenter cohort of 360 patients



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Background: The decision to perform Mohs micrographic surgery (MMS) or wide local excision (WLE) for eyelid sebaceous carcinoma (SC) is controversial.

Objective: To compare local recurrence, metastasis, and tumor-related mortality of patients with eyelid SC who were initially treated with MMS versus with WLE.

Methods: A multicenter cohort study. Medical records were reviewed for factors associated with recurrence, metastasis, and tumor-related mortality. All eligible patients were followed up. The impact of initial surgical modality on the prognoses were determined by Cox analyses after control for all confounders.

Results: Of the 360 patients included in this cohort, 115 (31.9%) underwent MMS as primary resection, whereas 245 (68.1%) underwent WLE. After a median follow-up period of 60.0 months, local recurrence was observed in 18 patients (15.7%) in the MMS group and 97 patients (39.6%) in the WLE group. Metastasis occurred in 9 patients (7.8%) who underwent MMS and 38 (15.5%) who underwent WLE. In all, 6 patients in the MMS group (5.2%) and 21 in the WLE group (8.6%) died of metastatic SC. Multivariable Cox regression indicated that compared with the WLE group, the MMS group exhibited more favorable local recurrence control (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.24-0.73; $P = .002$) but a comparable metastasis rate (HR, 1.38; 95% CI, 0.60-3.18; $P = .453$) and comparable tumor-related mortality (HR, 1.70; 95% CI, 0.59-4.93; $P = .329$). However, this beneficial effect became nonremarkable for patients with pagetoid intraepithelial neoplasia (HR, 1.73; 95% CI, 0.37-8.21; $P = .488$).

Limitations: Retrospective nature of the study.

Conclusion: MMS should be proposed for eyelid SC without orbital involvement to achieve recurrence control; however, this surgical procedure did not change the long-term outcomes in terms of metastasis or tumor-related mortality. Patients with pagetoid intraepithelial neoplasia may require adjuvant measures. (J Am Acad Dermatol 2019;80:1608-17.)

Key words: eyelid sebaceous carcinoma; metastasis; Mohs micrographic surgery; recurrence; tumor-related mortality.

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Sebaceous carcinoma (SC) is not a rare eyelid tumor in China; it accounts for approximately 32.7% to 41.6% of all eyelid malignancies.^{1,2} The mainstay of curative management for eyelid SC is complete resection of the tumor.³ The surgical modalities mainly include Mohs micrographic surgery (MMS) and wide local excision (WLE).

WLE with 5- to 6-mm margins of normal-appearing tissue has traditionally been the standard therapy, and the clinical outcomes are well described and consensual. MMS has been widely used in cutaneous oncology for its accurate and staged intraoperative histologic analysis.^{4,5} The eyelid is a vital structure that maintains facial appearance and protects the eyeball; therefore, MMS is preferred in the management of eyelid tumors for its attempts to conserve tissue and preserve function.⁶ In the past few decades, the indications for MMS have been expanded from basal cell and squamous cell carcinoma to SC.⁶⁻⁹ Spencer et al performed MMS for 18 cases of eyelid SC; after 3 years of follow-up, the overall recurrence and metastatic rate were 11.1% and 5.6%, respectively.⁷ However, using MMS in all cases remains controversial because SC may grow in a noncontinuous pattern¹⁰⁻¹² and it is difficult to detect pagetoid intraepithelial neoplasia in frozen sections.^{13,14} In addition, the Mohs surgical technique relies on intraoperative analysis of frozen sections, and it is not always available in all areas.^{7,15,16} Therefore, in most parts of China, WLE remains the first-line therapy for eyelid SC. In addition, standardized guidelines for management of this disease are still lacking.

In this retrospective multicenter study, our intent was to compare in detail local recurrence, metastasis, and tumor-related death stratified by initial treatment with MMS versus WLE. We then conducted a subgroup analysis for patients with pagetoid intraepithelial neoplasia to determine whether using MMS for such patients would lead to better prognosis than using WLE.

METHODS

Patients

After approval by the research ethics committees had been obtained, a search for the term *eyelid SC* was performed in the pathologic database of Ninth People's Hospital, Shanghai Jiao Tong University

School of Medicine, the Second Affiliated Hospital of Zhejiang University School of Medicine, and Xiangya Hospital affiliated with Central South University between January 1991 and September 2017; the search resulted in the identification of 476 patients. A total of 58 patients with orbital involvement were excluded. Map biopsy was performed for patients having tumors with a diffused growth pattern. The primary treatments included MMS based on frozen-section control and WLE without intraoperative margin control. The final margins were negative intraoperatively for all patients who underwent MMS. All patients had immediate eyelid reconstruction performed by the oculoplastic surgeon. The decision about which surgical approach to perform was possibly biased

by the surgeon's experience and whether the Mohs technique was available. For patients with lymph node metastasis, combined resection of the metastatic site was carried out. We tried to contact every patient or their relatives and explained the purpose of the study. Patients participated in this study voluntarily without any additional compensation. They were interviewed about their conditions after discharge. Their vital status was also confirmed via the mandatory Chinese resident registry, and primary cause of death was recorded by checking the death certificate in the Chinese Center for Disease Control. A total of 30 patients were not reached, and 13 declined to participate in this study for other reasons such as geographic or time limitations. Of the 375 subjects who agreed to participate in the follow-up visit, 15 patients were excluded on account of incomplete data collection, leaving a final sample size of 360 eyes of 360 patients. The details of recruitment is in [Supplemental Fig 1](#) (available at <http://www.jaad.org>). The numbers of patients recruited from Ninth People's Hospital affiliated with Shanghai Jiao Tong University School of Medicine, the Second Affiliated Hospital of Zhejiang University School of Medicine, and Xiangya Hospital affiliated with Central South University were 211, 83, and 66, respectively.

Data collection

The institutional review board waived the requirement for informed consent from the patients. This study adhered to the tenets of the Declaration of

CAPSULE SUMMARY

- Whether to perform Mohs micrographic surgery or wide local excision as the primary resection for eyelid sebaceous carcinoma remains controversial.
- Compared with wide local excision, Mohs micrographic surgery exhibited a lower recurrence rate but comparable chances of metastasis and tumor-related mortality. Patients with pagetoid invasion may require adjuvant measures.

Abbreviations used:

CI:	confidence interval
HR:	hazard ratio
MMS:	Mohs micrographic surgery
SC:	sebaceous carcinoma
UM:	uveal melanoma
WLE:	wide local excision

Helsinki. The medical records and pathologic data of each patient were reviewed. The data collected included patient demographics, clinical characteristics, treatments, and final outcomes at follow-up. The demographics consisted of age and sex. The clinical characteristics comprised history of second primary tumor, diagnostic delay (the duration from the onset of symptoms until the definite diagnosis of eyelid SC), initial referral diagnoses and treatments, anatomic location, greatest tumor basal diameter, presence of intraepithelial neoplasia (confirmed by multiple map biopsy), perineural invasion and muscle infiltration, degree of histologic differentiation, surgical approaches, and adjuvant treatments. The degree of differentiation was subdivided as described elsewhere,¹⁷ and well-differentiated tumors presented as lobules with sebaceous differentiation. Moderate differentiation primarily consisted of anaplastic cells and a few areas of highly differentiated sebaceous cells. Poor differentiation was defined as tumors rich in pleomorphic nuclei, prominent nucleoli, and amphophilic-positive cytoplasm. The patients were also stratified by their clinicopathologic presentations according to the eighth edition of the American Joint Committee on Cancer staging system for eyelid SC.¹⁸ If the patient had received treatment elsewhere, his or her prior clinical details and pathologic sections before referral were retrieved for review. Local recurrence was defined as signs of new SC at the same site of the previous tumor or at any ocular site. The time of recurrence or metastasis was the date on which the dissemination was confirmed by biopsy, imaging, or clinical examination. The numbers of months from the initial diagnosis to the first recurrence, metastasis, and death were documented. In addition, the period from the first metastasis to death was calculated, and the locations of metastasis were recorded.

Statistical analysis

All analyses were performed by using SPSS software (version 21.0, IBM, Armonk, NY). The frequency (percentage) and median (interquartile range) were reported for the description of categorical and continuous variables, respectively. Demographic and preoperative clinical indicators

of the patients treated with MMS and those of the patients treated with WLE were compared by using either the nonparametric Mann-Whitney U test (continuous factors) or the chi-square test (categorical factors). Significant variates were considered confounders for the effect of surgical modality on the prognosis. The cumulative incidence of recurrence, metastasis, and tumor-related death rates was determined by the Kaplan-Meier method and compared by the log-rank test.

To explore the independent impact of MMS for eyelid SC, we first identified possible prognostic correlates by comparing baseline clinical characteristics of the patients with different outcomes by using univariate Cox regression. The Spearman rank correlation test was utilized to identify the collinearity, and a strong correlation was defined as a correlation coefficient greater than 0.4 and a *P* value less than .01. Subsequent multivariate Cox regressions included the significant parameters (*P* < .05) from the univariate analyses as the independent variables after control for all confounders and collinearity among indices, thus compensating for the deviation in the baseline parameters of the 2 groups. Initial recurrence, metastasis, and tumor-related death were set as major outcomes (dependent factors), and patients who died of other causes or who were alive at the end of follow-up were considered censored. The hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. All tests were 2 sided, and a *P* value less than .05 was considered statistically significant.

RESULTS**Descriptive statistics**

Of the 360 patients recruited in this study, 150 (41.7%) were male and 210 (58.3%) were female. The median age at diagnosis was 63.0 years, ranging from 27.0 to 96.0 years. In this cohort, 115 patients (31.9%) underwent MMS for primary resection and 245 patients (68.1%) underwent WLE as the initial surgical procedure. The demographic and clinical characteristics of the 2 groups were compared (Table I). In all, 13 patients (3.6%) had lymph node metastasis at initial presentation. Significant differences were noted between the 2 groups regarding age (*P* = .002), diagnostic delay (*P* = .001), initial diagnosis (*P* < .001), presence of perineural invasion (*P* = .010), histologic differentiation (*P* = .010), and T categories (*P* < .001). Of the patients who underwent MMS, 69 (60.0%) required more than 1 stage of Mohs surgery to achieve tumor-free margins.

Local recurrence

After a median follow-up period of 60.0 months (range, 12.0-342.0 months), 115 patients (31.9%) had

Table I. Baseline demographic and clinical characteristics for patients with eyelid sebaceous carcinoma

Variables	Total (N = 360)	MMS (n = 115)	WLE (n = 245)	P value
Sex, n (%)				.834
Male	150 (41.7)	47 (40.9)	103 (42.0)	
Female	210 (58.3)	68 (59.1)	142 (58.0)	
Median age, y (range)	63.0 (54.0-73.8)	65.0 (59.0-77.0)	62.0 (52.0-72.0)	.002*
Second primary tumor, n (%)	16 (4.4)	7 (6.1)	9 (3.7)	.300
Median diagnostic delay, mo (range)	13.9 (6.0-30.0)	12.0 (6.0-24.0)	16.0 (8.0-36.0)	.001*
Initial diagnosis, n (%)				<.001*
Sebaceous carcinoma	225 (62.5)	90 (78.3)	135 (55.1)	
Squamous cell carcinoma	34 (9.4)	7 (6.1)	27 (11.0)	
Basal cell carcinoma	21 (5.8)	8 (7.0)	13 (5.3)	
Chalazion	20 (5.6)	3 (2.6)	17 (6.9)	
Blepharitis	43 (11.9)	7 (6.1)	36 (14.7)	
Dermoid	9 (2.5)	0 (0)	9 (3.7)	
Nevus	8 (2.2)	0 (0)	8 (3.3)	
Tumor location, n (%)				NA
Upper eyelid	216 (60.0)	67 (58.3)	149 (60.8)	
Lower eyelid	115 (31.9)	39 (33.9)	76 (31.0)	
Both upper and lower eyelid	8 (2.2)	2 (1.7)	6 (2.4)	
Caruncle	26 (7.2)	7 (6.1)	19 (7.8)	
Bulbar conjunctiva	18 (5.0)	2 (1.7)	16 (6.5)	
Median greatest basal diameter, mm (range)	10.0 (8.0-15.0)	10.0 (7.0-13.0)	10.0 (8.0-15.0)	.087
Multifocal tumor, n (%)	34 (9.4)	14 (12.2)	20 (8.2)	.225
Pagetoid intraepithelial neoplasia, n (%)	59 (16.4)	13 (11.3)	46 (18.8)	.074
Perineural invasion, n (%)	24 (6.7)	2 (1.7)	22 (9.0)	.010*
Muscle infiltration, n (%)	44 (12.2)	14 (12.2)	30 (12.2)	.985
Median Ki-67 percentage (range)	30.0 (20.0-50.0)	30.0 (15.0-50.0)	30.0 (20.0-50.0)	.070
Histologic differentiation, n (%)				.010*
Well	54 (15.0)	19 (16.5)	35 (14.3)	
Moderate	220 (61.1)	80 (69.6)	140 (57.1)	
Poor	86 (23.9)	16 (13.9)	70 (28.6)	
T stage, n (%)				<.001*
T1	150 (41.7)	66 (57.4)	84 (34.3)	
T2	151 (41.9)	35 (30.4)	116 (47.3)	
T3	59 (16.4)	14 (12.2)	45 (18.4)	
N stage, n (%)				.485
N0	347 (96.4)	112 (97.4)	235 (95.9)	
N1	13 (3.6)	3 (2.6)	10 (4.1)	

MMS, Mohs micrographic surgery; NA, not available for dependent samples; WLE, wide local excision.

*Statistically significant.

local recurrence. Among these relapsed patients, 21 (18.3%) had 2 or more kinds of recurrences and 9 (7.8%) experienced orbital recurrence. Of the patients who underwent MMS, 18 (15.7%) experienced recurrence, and their 1- and 5-year cumulative recurrence rates were 4.3% and 16.8%, respectively. These rates were significantly lower than those in the WLE group (overall recurrence, 39.6%; 1-year, 12.7%; and 5-year, 39.7% [$P < .001$]) (Fig 1, A). The median interval from diagnosis to the initial recurrence was 16.0 months (range, 7.0-120.0 months). This duration was 19.0 months (range, 8.0-120.0 months) for the MMS group and 15.0 months (range, 7.0-120.0 months) for the WLE group. Second primary tumor, muscle infiltration,

and greatest basal diameter were excluded for their strong correlation with other factors. Multivariate Cox analyses indicated that patients who had initially received MMS had significantly lower chances of recurrence (HR, 0.42; 95% CI, 0.24-0.73; $P = .002$), even after control for all confounders and collinearity among variables (the details are summarized in Table II).

Metastasis

From our observation, 47 patients (13.1%) developed metastasis after a median of 17.0 months (range, 0-100.0 months) from initial diagnosis. Among them, 9 patients (7.8%) underwent MMS whereas 38 (15.5%) underwent WLE. The metastasis

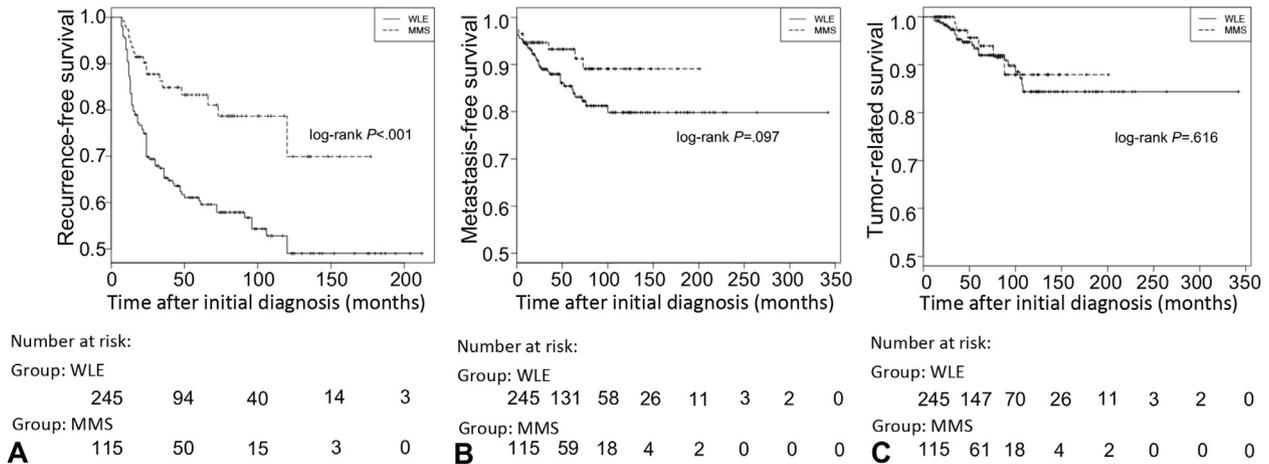


Fig 1. The prognosis of eyelid sebaceous carcinoma based on initial surgical modality of Mohs micrographic surgery (MMS) versus wide local excision (WLE). Compared with initial treatment with WLE, initial treatment with MMS was associated with a lower cumulative incidence of local recurrence (log-rank $P < .001$) (A) but a comparable metastatic rate (log-rank $P = .097$) (B) and tumor-related mortality (log-rank $P = .616$) (C).

locations included parotid lymph node ($n = 33$ [70.2%]), cervical lymph node ($n = 9$ [19.1%]), submandibular lymph node ($n = 7$ [14.9%]), lung ($n = 7$ [14.9%]), brain ($n = 3$ [6.4%]), skull base ($n = 2$ [4.3%]), and mediastinal lymph node ($n = 1$ [2.1%]). Among these patients, 15 (31.9%) presented with metastases involving multiple sites. The time from diagnosis to initial metastasis was 7.0 months (range, 0-73.0 months) for the MMS group and 18.5 months (range, 0-100.0 months) for the WLE group. According to the Kaplan-Meier estimates at 5 and 10 years, metastasis occurred in 6.8% and 10.9% of patients who underwent MMS, respectively. These rates were lower than those for the WLE group (5-year rate, 14.6%; 10-year rate, 20.2%) but did not reach statistical significance ($P = .097$) (Fig 1, B). Multivariate Cox analyses did not demonstrate any significant differences in metastasis between patients initially treated with MMS and those initially treated with WLE after control for all confounders (HR, 1.38; 95% CI, 0.60-3.18; $P = .453$) (Table II).

Tumor-related death

In this study, 71 patients (19.7%) died, with 27 (7.5%) dying of eyelid SC; among them, 6 (5.2%) had undergone MMS and 21 (8.6%) had undergone WLE. The median survival time for participants who experienced tumor-related death was 48.0 months (range, 12.0-108.0 months). This period was 54.0 months (range, 34.0-88.0 months) for the MMS group and 42.0 months (range, 12.0-108.0 months) for the WLE group. The median duration after initial metastasis to death was 35.0 months (range, 12.0-58.0 months) for the MMS group and

20.0 months (range, 5.0-60.0 months) for the WLE group. In the MMS group the 5- and 10-year tumor-related mortality rates were 6.1% and 12.1%, respectively, whereas in the WLE group these rates were slightly higher (5-year rate, 8.0%; 10-year rate, 15.6%) without reaching statistical significance ($P = .616$, Fig 1, C). Multivariate Cox analyses indicated that the initial surgical modality was not an independent risk factor for tumor-related mortality (HR, 1.70; 95% CI, 0.59-4.93; $P = .329$) (Table II).

MMS for patients with pagetoid intraepithelial neoplasia

In this cohort, 59 patients (16.4%) exhibited pagetoid intraepithelial neoplasia, and a subgroup analysis was conducted for such patients (Table III). Multivariate Cox analyses suggested that no significant difference in terms of local recurrence (HR, 1.73; 95% CI, 0.37-8.21; $P = .488$), metastasis (HR, 5.44; 95% CI, 0.66-44.74; $P = .115$), or tumor-related mortality (HR, 11.67; 95% CI, 0.61-221.81; $P = .102$) exists for patients with pagetoid intraepithelial neoplasia regardless of whether they were initially treated with MMS or WLE.

DISCUSSION

This multicenter comparative study of 360 consecutive patients with eyelid SC confirmed the benefit of MMS in preventing local recurrence; however, this protective effect was not prominent in cases of pagetoid intraepithelial neoplasia. Nevertheless, MMS did not have a remarkable impact on the long-term prognosis of metastasis and

Table II. Univariable and multivariable Cox proportional hazards regression analysis for the predictors of local recurrence, metastasis, and tumor-related mortality

Variables	Univariable				Multivariable				Univariable				Multivariable					
	Recurrence (+) (n = 115)	Recurrence (-) (n = 245)	HR (95% CI)	P value	HR (95% CI)	P value	Metastasis (+) (n = 47)	Metastasis (-) (n = 313)	HR (95% CI)	P value	HR (95% CI)	P value	Tumor-related death (+) (n = 27)	Tumor-related death (-) (n = 333)	HR (95% CI)	P value	HR (95% CI)	P value
Initial surgical modality			0.40 (0.24-0.66)	<.001*	0.42 (0.24-0.73)	.002*			0.55 (0.26-1.13)	.103	1.38 (0.60-3.18)	.453			0.79 (0.32-1.97)	.617	1.70 (0.59-4.93)	.329
WLE [†]	97 (84.3)	148 (60.4)					38 (80.9)	207 (66.1)					21 (77.8)	224 (67.3)				
MMS	18 (15.7)	97 (39.6)					9 (19.1)	106 (33.9)					6 (22.2)	109 (32.7)				
Sex			1.02 (0.71-1.48)	.905					1.00 (0.56-1.78)	.996					0.78 (0.37-1.67)	.528		
Male [†]	47 (40.9)	103 (42.0)					20 (42.6)	130 (41.5)					13 (48.1)	137 (41.1)				
Female	68 (59.1)	142 (58.0)					27 (57.4)	183 (58.5)					14 (51.9)	196 (58.9)				
Age, y	62.0 (49.0-73.0)	64.0 (56.0-74.0)	0.99 (0.97-1.00)	.068	1.00 (0.99-1.02)	.657	59.0 (46.0-68.0)	64.0 (55.0-75.0)	0.97 (0.95-0.99)	.008*	0.98 (0.96-1.00)	.058	61.0 (48.0-70.0)	63.0 (54.0-74.0)	0.99 (0.96-1.02)	.400	1.00 (0.97-1.03)	.755
Second primary tumor	6 (5.2)	10 (4.1)	1.21 (0.53-2.76)	.646			3 (6.4)	13 (4.2)	1.45 (0.45-4.68)	.533			3 (11.1)	13 (3.9)	3.06 (0.92-10.24)	.069		
Diagnostic delay, mo (months)	30.0 (13.7-54.0)	12.0 (6.0-24.0)	1.01 (1.00-1.01)	<.001*	1.01 (1.01-1.02)	<.001*	16.0 (8.0-48.0)	13.0 (6.0-30.0)	1.01 (0.99-1.01)	.154	1.00 (0.99-1.01)	.708	16.0 (8.0-44.0)	13.0 (6.0-30.0)	1.00 (0.99-1.01)	.856	0.99 (0.98-1.01)	.443
Initial diagnosis			2.01 (1.40-2.90)	<.001*	1.37 (0.92-2.02)	.121			2.00 (1.13-3.55)	.018*	1.89 (1.00-3.59)	.052			2.51 (1.15-5.49)	.021*	3.14 (1.29-7.66)	.012*
Sebaceous carcinoma [†]	55 (47.8)	170 (69.4)					21 (44.7)	204 (65.2)					10 (37.0)	215 (64.6)				
Others	60 (52.2)	75 (30.6)					26 (55.3)	109 (34.8)					17 (63.0)	118 (35.4)				
Caruncular involvement	11 (9.6)	15 (6.1)	1.65 (0.89-3.08)	.114			9 (19.1)	17 (5.4)	3.27 (1.58-6.76)	.001*	1.20 (0.55-2.61)	.652	6 (22.2)	20 (6.0)	3.34 (1.34-8.29)	.009*	1.79 (0.63-5.09)	.274
Bulbar conjunctival involvement	9 (7.8)	9 (3.7)	2.09 (1.06-4.14)	.034*	1.75 (0.83-3.69)	.140	8 (17.0)	10 (3.2)	4.17 (1.95-8.93)	<.001*	1.56 (0.66-3.73)	.314	5 (18.5)	13 (3.9)	3.95 (1.49-10.48)	.006*	1.68 (0.54-5.26)	.370
Greatest basal diameter, mm	10.0 (8.0-15.0)	10.0 (7.0-15.0)	1.01 (0.98-1.04)	.471			13.0 (10.0-20.0)	10.0 (7.0-15.0)	1.06 (1.03-1.09)	<.001*			14.0 (8.0-22.0)	10.0 (7.5-15.0)	1.05 (1.01-1.10)	.026*		
Multifocal tumor	15 (13.0)	19 (7.8)	1.66 (0.96-2.86)	.070			8 (17.0)	26 (8.3)	2.13 (0.99-4.55)	.052			5 (18.5)	29 (8.7)	2.52 (0.95-6.67)	.064		
Pagetoid intraepithelial neoplasia	26 (22.6)	33 (13.5)	1.58 (1.02-2.44)	.041*	1.27 (0.78-2.06)	.337	23 (48.9)	36 (11.5)	5.16 (2.91-9.15)	<.001*	3.11 (1.59-6.09)	.001*	13 (48.1)	46 (13.8)	4.12 (1.94-8.77)	<.001*	2.25 (0.86-5.87)	.098
Perineural invasion	13 (11.3)	11 (4.5)	2.11 (1.18-3.75)	.012*	1.57 (0.86-2.87)	.142	11 (23.4)	13 (4.2)	4.79 (2.44-9.41)	<.001*	2.33 (1.06-5.11)	.035*	6 (22.2)	18 (5.4)	3.40 (1.37-8.44)	.008*	1.73 (0.57-5.32)	.335
Muscle infiltration	17 (14.8)	27 (11.0)	1.31 (0.78-2.19)	.305			9 (19.1)	35 (11.2)	1.66 (0.80-3.44)	.173			5 (18.5)	39 (11.7)	1.35 (0.51-3.56)	.547		
Median Ki-67 percentage (range)	35.0 (20.0-50.0)	30.0 (20.0-40.0)	1.01 (1.00-1.02)	.006*	1.02 (1.01-1.03)	.004*	40.0 (30.0-55.0)	30.0 (20.0-45.5)	1.03 (1.01-1.04)	.001*	1.01 (0.99-1.03)	.277	30.0 (30.0-50.0)	30.0 (20.0-50.0)	1.01 (0.99-1.03)	.264		
Histologic differentiation																		
Well [†]	17 (14.8)	37 (15.1)					2 (4.3)	52 (16.6)					2 (7.4)	52 (15.6)				
Moderate	69 (60.0)	151 (61.6)	0.96 (0.57-1.63)	.880	0.88 (0.51-1.52)	.654	20 (42.6)	200 (63.9)	2.48 (0.58-10.59)	.222	2.29 (0.53-9.95)	.268	11 (40.7)	209 (62.8)	1.31 (0.29-5.91)	.725	1.14 (0.25-5.22)	.871

Continued

Table II. Cont'd

Variables	Univariable			Multivariable			Univariable			Multivariable						
	Recurrence (+) (n = 115)	Recurrence (-) (n = 245)	HR (95% CI) P value	Metastasis (+) (n = 47)	Metastasis (-) (n = 313)	HR (95% CI) P value	HR (95% CI) P value	HR (95% CI) P value	Tumor-related death (+) (n = 27)	Tumor-related death (-) (n = 333)	HR (95% CI) P value	HR (95% CI) P value				
Poor	29 (25.2)	57 (23.3)	1.13 (0.62-2.05)	.697	0.67 (0.35-1.30)	.235	25 (53.2)	61 (19.5)	8.80 (2.08-37.17)	.003*	4.00 (0.89-17.97)	14 (51.9)	72 (21.6)	4.46 (1.01-19.62)	.048*	2.05 (0.42-9.92)
T stage																
T1†	39 (33.9)	111 (45.3)					10 (21.3)	140 (44.7)				7 (25.9)	143 (42.9)			
T2	55 (47.8)	96 (39.2)	1.41 (0.93-2.13)	.102	1.05 (0.68-1.64)	.814	18 (38.3)	133 (42.5)	1.70 (0.78-3.67)	.181	1.31 (0.59-2.93)	9 (33.3)	142 (42.6)	1.04 (0.39-2.80)	.934	0.83 (0.29-2.40)
T3	21 (18.3)	38 (15.5)	1.32 (0.78-2.24)	.307	0.70 (0.39-1.26)	.231	19 (40.4)	40 (12.8)	4.87 (2.27-10.48)	<.001*	2.43 (0.99-6.01)	11 (40.7)	48 (14.4)	3.40 (1.32-8.79)	.011*	2.44 (0.73-8.16)

Data are presented as median (interquartile range) or n (%).

CI, Confidence interval; HR, hazard ratio; MMS, Mohs microscopic surgery; WLE, wide local excision.

*Statistically significant.

†Reference variable.

tumor-related mortality. It was somewhat surprising to discover this phenomenon; however, the prognostic factors of cancer are generally multifactorial, consisting of tumor-, patient-, and treatment-related parameters. The initial surgical modality, although important, was not the dominant determinant for prognosis. An appropriate choice for primary excision might achieve favorable control of tumor for a short period; however, it could hardly change the entire long-term outcomes independently. This is often the case in other ocular tumors, such as uveal melanoma (UM). Targeted therapies are booming in the current era of UM management. In a randomized clinical trial that included 120 patients with advanced UM, when the mitogen-activated protein kinase/ERK kinase inhibitor selumetinib was compared with chemotherapy, it resulted in a modestly improved progression-free survival; however, no improvement in overall survival was noted.¹⁹

Early in the 1930s, MMS was initially described by Frederic E. Mohs. In the next few decades, the Mohs technique developed rapidly.^{20,21} MMS is an ideal surgical approach for sparing maximal normal tissue, and it offers the potential advantages for immediate reconstruction surgery.²² It was considered the criterion standard for the excision of periocular nonmelanoma skin cancer.^{23,24} In basal cell and squamous cell carcinoma, Mohs reported 5-year cure rates of 98.0%.²³ Therefore, in recent years, MMS has been applied to eradicate eyelid SC. Spencer et al conducted a retrospective study of 18 patients with eyelid SC who underwent MMS; after a follow-up period of 37 months, the recurrence, metastasis, and mortality probabilities were 11.1%, 5.6%, and 0%, respectively.⁷ Another report collected 49 patients from 10 studies who underwent MMS; the report showed a relapse rate of 12.2%, a regional metastatic likelihood of 8.0%, and no death after a mean follow-up of 3.1 years.²⁵ In our cohort, of the 115 patients who underwent MMS as the initial treatment, 18 (15.7%) exhibited recurrence, 9 (7.8%) had metastasis, and 6 (5.2%) died of SC after a median follow-up of 60.0 months. All participants of our cohort were collected from tertiary hospitals, and the proportions of patients with advanced disease were higher in these centers than in other medical settings. Other possible explanations for the disparities in prognosis may lie in the following factors. First, the sample size differed greatly. The numbers of patients in the previous studies did not exceed 50; however, small sample sizes probably could not capture the true characteristics of an entire SC population. Second, the follow-up durations were dissimilar, and our

Table III. Multivariable Cox proportional hazards regression analysis for prognostic factors in patients of pagetoid intraepithelial neoplasia

Variables	Recurrence		Metastasis		Tumor-related death	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Initial surgical approach (MMS vs WLE)	1.73 (0.37-8.21)	.488	5.44 (0.66-44.74)	.115	11.67 (0.61-221.81)	.102
Age, y	0.97 (0.94-1.01)	.144	0.96 (0.93-1.00)	.028*	0.99 (0.94-1.03)	.520
Diagnostic delay, mo	1.02 (0.99-1.04)	.065	1.00 (0.98-1.02)	.921	0.99 (0.96-1.02)	.630
Initial diagnosis (others vs sebaceous carcinoma)	1.57 (0.59-4.17)	.368	6.78 (1.85-24.78)	.004*	14.35 (1.91-107.79)	.010*
The presence of perineural invasion (yes vs no)	7.05 (1.67-29.83)	.008*	14.47 (2.89-72.33)	.001*	15.72 (1.37-179.77)	.027*
Histologic differentiation						
Well [†]						
Moderate	1.33 (0.26-6.70)	.732	2.19 (0.21-23.08)	.515	1.75 (0.11-27.41)	.689
Poor	1.59 (0.33-7.51)	.562	3.64 (0.35-37.99)	.280	1.79 (0.13-25.45)	.669
T stage						
T1 [†]						
T2	1.25 (0.39-3.95)	.709	1.40 (0.41-4.82)	.597	1.31 (0.30-5.86)	.720
T3	0.56 (0.13-2.42)	.435	2.70 (0.55-13.19)	.221	0.93 (0.11-8.12)	.945

CI, Confidence interval; MMS, Mohs microscopic surgery; WLE, wide local excision.

*Statistically significant.

[†]Reference variable.

study covered a longer follow-up period than the others did. In addition, other discrepancies may relate to racial differences and multiple surgeons with diverse experiences.

Our study corroborates published reports that pagetoid intraepithelial neoplasia limited the beneficial effect of MMS in recurrence control.^{14,26} MMS becomes unreliable when discontinuous lesions exist. Microscopically, tumors grown in multicentric patterns tend to extend far beyond their assessed clinical margins. Patients with intraepithelial invasion have been reported to have displayed more ill-defined and fewer localized symptoms than those without this sign.¹⁰ For patients without pagetoid intraepithelial neoplasia in our cohort, the rates of recurrence, metastasis, and tumor-related mortality were 29.6%, 8.0%, and 4.7%, respectively. However, for patients with pagetoid intraepithelial neoplasia, these chances were much higher (recurrence, 44.1%; metastasis, 39.0%, and tumor-related mortality, 22.0%). Therefore, pagetoid intraepithelial neoplasia had conventionally been an indication for exenteration, but now, this strategy is controversial.^{10,27} The use of epithelial membrane antigens and simple epithelial keratins in the rapid immunohistochemistry Mohs technique were proposed to discriminate the noncontinuous foci of SC.^{28,29} Multiple map biopsies of the conjunctiva have been recommended to delineate the extent of the tumor, and adjuvant therapies such as cryotherapy³⁰ and topical

application of mitomycin C might be effective to eradicate SC with pagetoid intraepithelial neoplasia.³¹

Of note, incorrect initial diagnosis was the only common independent risk factor for metastasis and tumor-related death. In this cohort, 135 patients (37.5%) were misdiagnosed at initial referral. The most common misdiagnosis was blepharitis (n = 43 [11.9%]). Patients with SC often have diffuse tarsus and conjunctival epithelium infiltration, which tends to present with inflammatory signs that confound ophthalmologists.^{32,33} In this condition, SC has usually been misdiagnosed as chronic blepharoconjunctivitis.³² In our cohort, the median diagnostic delay was 13.9 months and 146 patients (40.56%) needed more than twice the number of surgical procedures to establish the diagnosis of SC. Consequently, heightened awareness and early recognition of SC are critical, and the clinician should possess adequate suspicion for SC, especially when encountering elderly patients with refractory unilateral blepharoconjunctivitis; map biopsy is recommended for such patients.

This study should be regarded as an initial report that specifically compared the long-term outcomes of patients with eyelid SC who underwent MMS and WLE. However, caution should be exercised when interpreting the findings owing to a number of limitations. First, key drawbacks of this study were its retrospective nature and the fact that the baseline conditions of the 2 groups were not

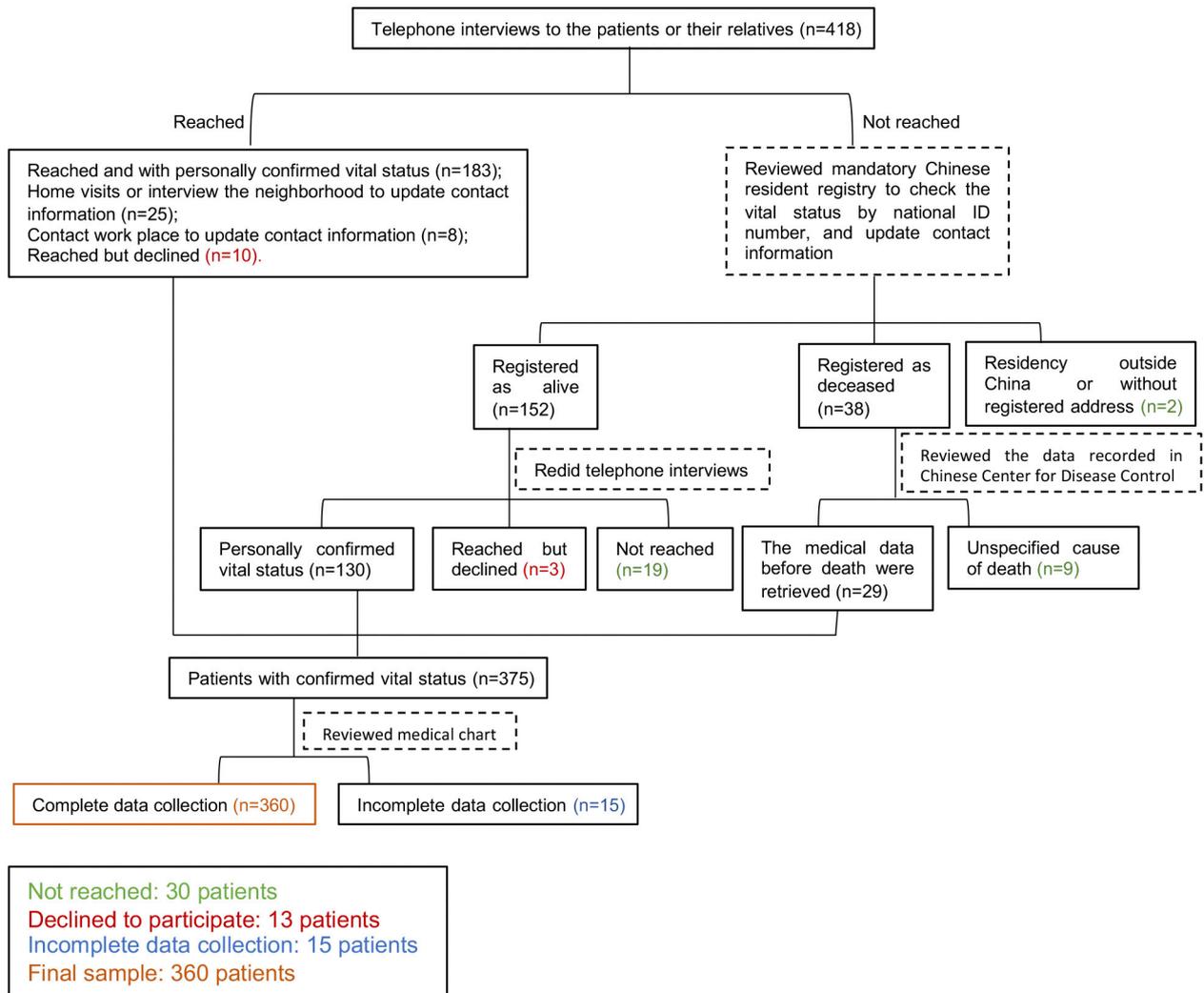
parallel. Second, the small number of patients with pagetoid intraepithelial neoplasia and limited number of outcome events produced large confidence intervals of HRs in the subgroup analyses. In addition, we did not carry out DNA mismatch and microsatellite instability tests for patients with second primary tumor. Nevertheless, the use of rigorous statistical methodology and adjustment of various confounders and interactions enabled us to maximally eliminate bias. Additionally, to our knowledge, our cohort constitutes the largest report of eyelid SC to date, and the long follow-up time made our results more convincing.

In summary, MMS played an important role in preventing local recurrence; however, it did not independently change the long-term outcomes of metastasis and tumor-related mortality. Nonetheless, we propose MMS as the primary surgical modality for eyelid SC without orbital involvement, whereas patients with pagetoid intraepithelial neoplasia may require adjuvant measures. To our knowledge, this is the first and only evaluation of the efficacy of MMS versus WLE in a large multicenter sample of eyelid SC. Nevertheless, a prospective, randomized trial is needed to fully validate our findings.

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Supplemental Fig 1. Cohort sample size flowchart.