Predictors of mucosal melanoma survival in a population-based setting

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Background: Mucosal melanomas are rare and aggressive neoplasms, with little published population-based data on predictors of survival.

Objective: We sought to assess the influences of race/ethnicity, sex, tumor stage, tumor thickness, and anatomic site on mucosal melanoma survival estimates.

Methods: We analyzed 132,751 cases of melanoma, including 1824 mucosal melanomas, diagnosed between 1994 and 2015 and reported to the California Cancer Registry. Kaplan−Meier survival analysis and Cox proportional hazards regression assessed the prognostic variables.

Results: The 5-year relative survival for mucosal melanomas (27.64% [95% confidence interval {CI} 25.42-29.91) was significantly lower than for cutaneous melanomas (76.28% [95% CI 76.03-76.53]). Stage independently influenced survival, and thickness did not predict survival for neoplasms of known depth. Less common anatomic sites conferred worse prognoses (hazard ratio 1.93 [95% CI 1.41-2.64]).

Limitations: The lack of a standardized staging system may have resulted in misclassification of stage for some neoplasms. The influence of genetics is unknown because our database did not contain genetic characteristics.

Conclusions: Stage and anatomic site, but not thickness (ie, Breslow depth), race, or ethnicity, determine the prognosis of mucosal melanomas. Considering the poor prognosis for all stages of mucosal melanoma, dermatologists should incorporate examination of the oropharynx and genitalia in the full body skin examination. (J Am Acad Dermatol 2019;81:136-42.)

Key words: California Cancer Registry; epidemiology; extracutaneous melanoma; mucosal melanoma; population-based; survival; treatment.

A ccounting for approximately 1% of all melanomas,[1-4] mucosal melanomas (ie, extracutaneous melanomas) are rare and poorly characterized neoplasms that can be found on any mucosal surface. Because of their occult anatomic locations and lack of early presenting signs and symptoms, they are difficult to diagnose at an early stage, resulting in a poorer prognosis than cutaneous melanomas.[3-6] Little evidence exists regarding predictors of survival from population-based survival data (ie, data obtained from geographic or national registry databases), which are necessary for the development of screening recommendations and targeted treatments.

Mucosal melanomas are pertinent to dermatologists because these neoplasms are often included in the differential for pigmented lesions in sites that dermatologists examine on full body skin examinations, including the oral mucosa and genitalia. The poor prognosis and lack of disease-specific treatment guidelines or randomized controlled trials for mucosal melanoma requires extra attention.

Treatments for mucosal melanoma are often extrapolated from data based on therapies for metastatic cutaneous melanoma. However, while Breslow depth is a well-known predictor of survival in cutaneous melanoma, population-based multivariate analyses have yet to examine the effect of thickness on survival in mucosal melanoma. Although population-based studies have shown that the 5-year relative survival proportions of mucosal melanoma are poor compared with cutaneous melanoma,[4,7] of particular interest is how survival predictors differ between mucosal melanoma and cutaneous melanoma.

This study's objective was to assess the independent influences of race/ethnicity, stage at diagnosis, and tumor thickness on mucosal melanoma survival, using a population-based database. While more detailed survival statistics on cutaneous melanoma exist elsewhere,[8] we also included information on cutaneous melanoma for comparison with mucosal melanoma, as appropriate.

MATERIALS AND METHODS
Data source

Population-based melanoma incidence data were obtained from the California Cancer Registry (CCR, available at ccrcal.org), which comprises 10 regional registries. Patients selected for analysis were residents of California who were diagnosed with invasive melanoma between January 1, 1994 and December 31, 2015 and reported to the CCR as of August 2016. Information regarding sex, race/ethnicity, tumor thickness, and other information were abstracted from the medical record within months after diagnosis.

CAPSULE SUMMARY

- This population-based study underscores that extracutaneous melanomas are rare and aggressive neoplasms.

- Poorer survival in patients with mucosal melanoma was observed in relation to stage and anatomic site, but not tumor thickness (ie, Breslow depth) or patient race/ethnicity.

- Because of the poor prognosis for all stages of mucosal melanoma, dermatologists should consider incorporating examination of the oropharynx and genitalia in the full body skin examination.

Tumor characteristics and patient demographics

We categorized melanomas into cutaneous and mucosal melanoma according to the methods of McLaughlin et al,[1] excluding ocular melanoma for this analysis. Invasive tumors with histology codes 8720-8790 (from the *International Classification of Diseases for Oncology, 3rd edition* [ICD-O-3]) were selected for analysis (N = 144,904).

Selected tumors were classified by their Breslow depth, anatomic site, and histologic type. Thickness was categorized in the same groups typically found in survival analyses (<1, 1-<2, 2-<4, and ≥4 mm).

Anatomic site was identified from ICD-O-2 codes and classified according to the scheme used by McLaughlin et al.[1] In the ICD-O-2 classification scheme, the skin of the anus and perianal skin are considered to be cutaneous. Cutaneous melanomas (ICD-O-2 code C44.0-C44.9) excluded the skin of the vulva, penis, and scrotum, which are instead included with mucosal melanomas. Melanomas with an unknown primary site were considered cutaneous.

We adopted the clinical and pathologic tumor, node, metastasis staging system of the Surveillance, Epidemiology and End Results program, distinguishing between localized (to the tumor boundary), regional (with lymph node or direct extension involvement only), and distant involvement.

Race/ethnicity was grouped into the mutually exclusive categories of non-Hispanic whites, non-Hispanic blacks, Hispanics, and Asian/Pacific Islanders, according to the race/ethnicity reported to the CCR. As done in other population-based studies on extracutaneous melanoma, Hispanic ethnicity was established using the North American Association of Central Cancer Registries Hispanic Identification Algorithm.[9] Patients of any other race or unknown race and patients with unknown diagnosis or follow-up dates were removed from the study population, leaving 132,751 cases for analysis.

Statistical methods

SAS software (version 9.4; SAS Institute Inc, Cary, NC) was used to perform survival analysis and

Table I. Cutaneous and mucosal melanomas by sex and race/ethnicity in California from the California Cancer Registry, 1994-2015

	Cutaneous		Mucosal	
	Cases, n (%)	**5-Year survival estimate, % (95% CI)**	**Cases, n (%)**	**5-Year survival estimate, % (95% CI)**
Sex				
Male	77,921 (59.51)	72.20 (71.86-72.55)	580 (31.80)	23.20 (19.53-27.06)
Female	53,006 (40.49)	82.28 (81.92-82.63)	1244 (68.20)	29.71 (26.96-32.50)
Race/ethnicity				
Non-Hispanic white	122,379 (93.47)	76.57 (76.31-76.83)	1261 (69.13)	28.48 (25.82-31.19)
Non-Hispanic black	470 (0.36)	56.97 (51.99-61.64)	53 (2.91)	20.54 (10.41-33.05)
Hispanic	6924 (5.29)	73.96 (72.79-75.10)	310 (17.00)	26.55 (21.20-32.18)
Asian/Pacific Islander	1154 (0.88)	66.53 (63.39-69.47)	200 (10.96)	25.82 (19.23-32.90)
Total cases	130,927		1824	

multivariate regression. Survival time was measured as the number of months between diagnosis and death. Patients still alive at last follow-up contributed their known survival time but were censored from the analysis at the date of their last follow-up without an event (death). Survival curves and univariate descriptive statistics for survival by demographic and tumor characteristics were calculated using the Kaplan–Meier method. Because tumor thickness was unknown for >70% of mucosal melanomas and tumor stage was missing for >7% of mucosal melanomas, we included an "unknown" group in all analyses involving tumor thickness or stage.

Cox proportional hazards regression was used to perform a multivariate analysis modeling survival on age, race/ethnicity, tumor thickness and stage at diagnosis, and primary tumor site for mucosal melanomas. For categorical variables including race, stage, thickness, and primary site, the selected reference groups were non-Hispanic white, localized disease, <1 mm thickness, and oral cavity, respectively. Associations with death from disease are presented in the results as hazard ratios (HRs) with corresponding *P* values.

RESULTS

Of the 132,751 diagnoses of melanoma registered in California between 1994 and 2015 and that included race/ethnicity data, 130,927 melanomas (98.6%) were cutaneous and 1824 (1.4%) were mucosal. The 5-year survival estimate for mucosal melanoma (27.64% [95% confidence interval {CI} 25.42-29.91]) was significantly lower than that for cutaneous melanomas (76.28% [95% CI 76.03-76.53]).

Survival analysis by sex and race/ethnicity

Patients diagnosed with mucosal melanomas experienced lower 5-year survival estimates,

regardless of race/ethnicity or sex, than individuals diagnosed with cutaneous melanoma (Table I; Fig 1). For cutaneous melanoma, females had statistically significantly better survival rates than men. Similarly, for mucosal melanoma, there was a survival advantage for females, with only slightly overlapping CIs.

While non-Hispanic whites had the best survival of all racial/ethnic groups for mucosal melanomas, the difference in rates was not statistically significant. For cutaneous melanomas, the five-year survival estimates for non-Hispanic whites, Hispanics, Asian/Pacific Islanders, and non-Hispanic blacks were 76.57% (95% CI 76.3-76.8), 73.96% (95% CI 72.79-75.10), 66.53% (95% CI 63.39-69.47), and 56.97% (95% CI 51.99-61.64), respectively.

Survival analysis by stage at diagnosis

Regardless of stage, mucosal melanomas had worse survival rates than similarly staged cutaneous melanomas (Table II). Localized mucosal melanomas had worse survival rates than even regionally metastasized cutaneous melanomas (Fig 2).

Survival analysis by melanoma thickness

Mucosal melanomas of any thickness had worse survival estimates than cutaneous melanomas of any thickness, and cutaneous melanomas were more frequently thinner tumors (Supplemental Table I, available at http://www.jaad.org). While survival decreased as cutaneous melanoma thickness increased, there was less prognostic value in tumor thickness for mucosal melanomas (Fig 3).

Survival analysis by anatomic site

When mucosal melanomas of known primary sites were categorized by primary anatomic site, their 5-year survival estimates were 37.41% for genitourinary, 27.85% for oral cavity, 23.77% for nasal and sinus,
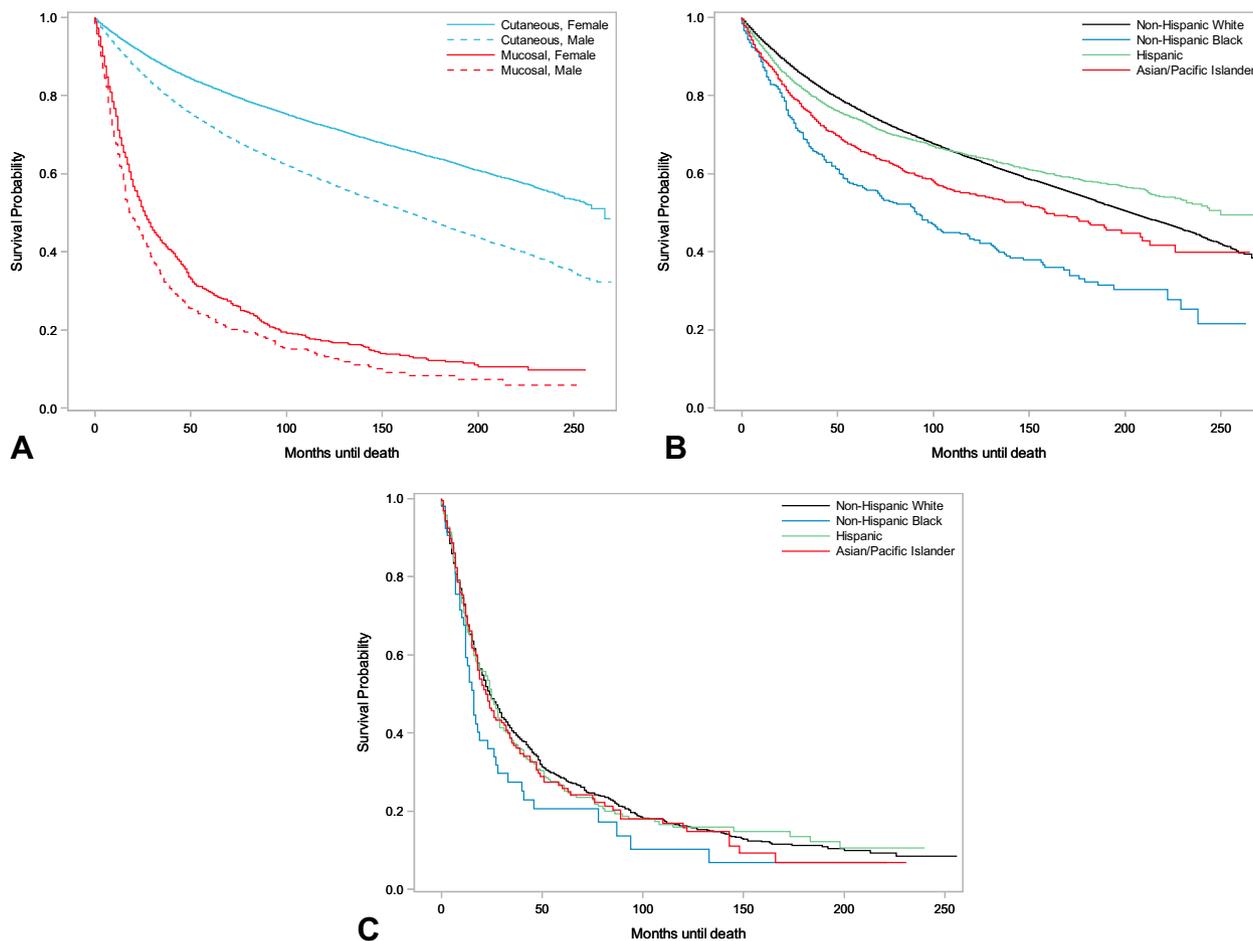
Fig 1. Survival for cutaneous and mucosal melanoma by sex and race/ethnicity in California. California Cancer Registry, 1994-2015. **A**, Cutaneous vs mucosal melanoma survival by sex. **B**, Cutaneous melanoma survival by race/ethnicity. **C**, Mucosal melanoma survival by race/ethnicity.

Table II. Survival for cutaneous and mucosal melanoma in California, by tumor stage at diagnosis, California Cancer Registry, 1994-2015

	Cutaneous		Mucosal	
	Cases, n (%)	5-Year survival estimate, % (95% CI)	Cases, n (%)	5-Year survival estimate, % (95% CI)
Stage at diagnosis				
Localized	109,982 (84.00)	82.87 (82.62-83.12)	790 (43.31)	43.93 (40.13-47.67)
Regional	10,515 (8.03)	50.58 (49.52-51.64)	518 (28.40)	18.76 (15.20-22.62)
Remote	5773 (4.41)	13.50 (12.54-14.50)	384 (21.05)	7.84 (5.13-11.29)
Unknown	4657 (3.56)	55.65 (54.09-57.19)	132 (7.24)	20.97 (13.98-28.93)
Total cases	130,927		1824	

20.94% for gastrointestinal, 16.68% for anorectal, and 13.57% for other sites (Supplemental Table I, available at http://www.jaad.org).

Multivariate analysis

After accounting for age, sex, race/ethnicity, and tumor stage at diagnosis, tumor thickness did not predict mucosal melanoma survival from tumors of known depth. The risk of death was increased for mucosal melanomas of unknown thickness (HR 1.47 [95% CI 1.15-1.89]; Supplemental Table II, available at http://www.jaad.org). Thickness was a statistically significant prognostic factor of death from cutaneous melanomas of all depths.
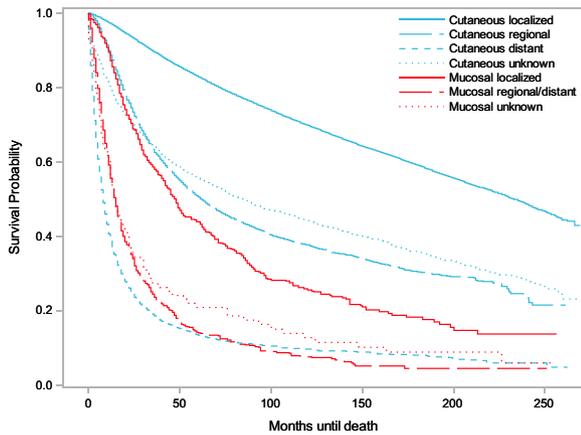
Fig 2. Survival for cutaneous and mucosal melanoma in California, by tumor stage at diagnosis. California Cancer Registry, 1994-2015.

After controlling for the above factors in addition to thickness, stage at diagnosis was a statistically significant predictor of survival for both mucosal and cutaneous melanomas. For cutaneous melanoma, risk of death for distantly metastasized disease was almost 8 times as high as for localized disease (HR 7.64 [95% CI 7.37-7.92]). The effect was mirrored, although not to the same degree, for mucosal melanomas, because distantly metastasized mucosal melanomas increased risk of death by >3 times (HR 3.36 [95% CI 2.9-3.92]).

While race/ethnicity had minimal effect on death from cutaneous melanomas, with HRs ranging from 1.15 to 1.41, this factor did not affect risk of death for mucosal melanomas (Supplemental Table II, available at http://www.jaad.org). There remained a small a survival advantage for females with cutaneous melanoma (HR 0.75 [95% CI 0.74-0.77]) and mucosal melanoma.

Mucosal melanomas from less common anatomic sites (eg, the spine/central nervous system, lung and pleura, liver, and pancreas) conferred the worst prognosis (HR 1.93 [95% CI 1.41-2.64]). Oral, anorectal, and gastrointestinal sites also negatively affected survival, with HRs of 1.37 (95% CI 1.10-1.70) and 1.65 (95% CI 1.19-2.27), respectively.

DISCUSSION

Because of the rarity of mucosal melanomas, few population-based studies have reported predictors of survival from these neoplasms. Our population-based analysis of survival outcomes over a 21-year period found that stage at diagnosis is an independent risk factor for survival from mucosal melanoma, while tumor thickness and race/ethnicity are not. Consistent with previous population-based reports,[1-4] we found that mucosal melanomas comprised

approximately 1% of all melanomas. Our aggregate 5-year survival estimate of approximately 28% was similar to a previously reported U.S. population—based estimate,[10] thereby underscoring the current knowledge that mucosal melanoma continues to be an aggressive disease that carries a poor prognosis.

Stage at diagnosis modified survival rates for cutaneous melanomas more than mucosal melanomas. This is likely because the risk of death from even a localized mucosal melanoma is even higher than for regionally metastatic cutaneous melanoma, possibly because these 2 types of melanomas are genetically distinct.[11,12]

While tumor thickness (ie, Breslow depth) is the most important prognostic indicator for cutaneous melanomas,[12] our results suggest that the same principle cannot be applied to mucosal melanomas. We found that tumor thickness conferred little prognostic value for survival from mucosal melanomas of known thicknesses, once we accounted for stage. Thickness likely had a smaller prognostic effect for mucosal melanomas because of their overall worse prognosis compared with cutaneous melanomas. Notably, most (70%) of mucosal melanomas were of unknown depth, likely because they are difficult to detect and are likely to be metastatic at the time of diagnosis. Accordingly, the worst survival estimates were for patients with mucosal melanomas of unknown thickness. Thickness was not a predictor of survival for mucosal melanomas of known thickness, and it could not be measured in many mucosal melanomas, thus further reducing its utility as a basis for clinical decision-making for mucosal melanomas. The lack of difference in survival estimates between thin and thick mucosal melanomas suggests that even thin tumors should be aggressively treated with systemic therapy.

Consistent with previous population-based multivariate analyses,[4] we found that race/ethnicity is not an independent risk factor for mucosal melanoma survival. Regardless of race/ethnicity, patients with mucosal melanoma had worse prognoses than individuals who were diagnosed with cutaneous melanoma.

We showed that anatomic site influences survival because mucosal melanomas in the most occult anatomic sites (eg, spine/central nervous system, lung and pleura, liver, and pancreas) had the worst prognosis, likely because they have already metastasized by the time they are diagnosed. Overall, our survival estimates based on anatomic site parallel the poor prognosis described in other population-based studies that have provided 5-year survival estimates
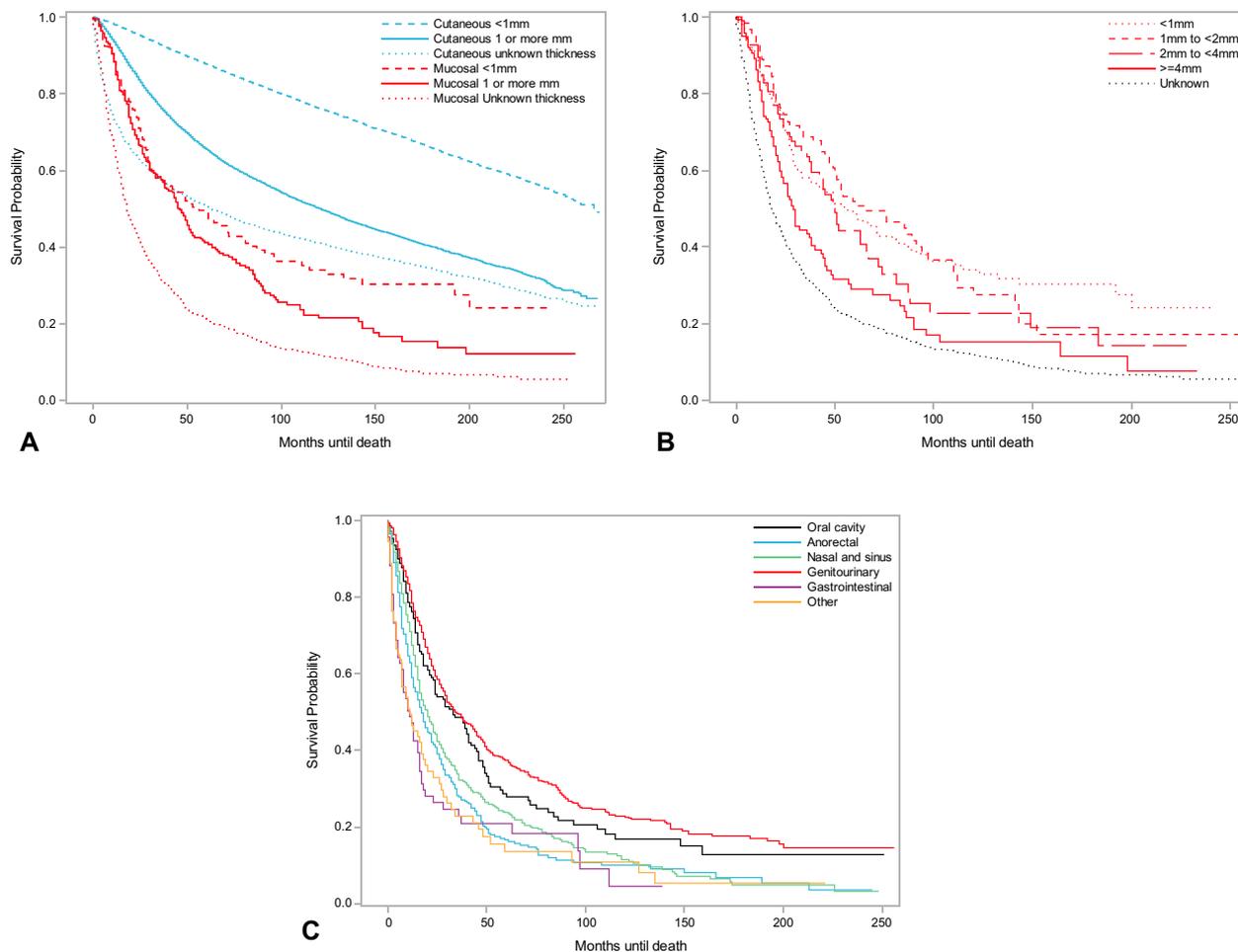
Fig 3. Survival for cutaneous and mucosal melanomas in California by tumor thickness and anatomic site. California Cancer Registry, 1994-2015. **A**, Cutaneous versus mucosal melanoma survival by thickness. **B**, Mucosal melanoma survival by thickness. **C**, Mucosal melanoma survival by primary anatomic site.

ranging from 4% to 60%, depending on site.[3,13] Although mucosal melanomas are infrequently encountered by dermatologists, they are often considered during differential diagnosis for pigmented mucosal lesions in sites that dermatologists can see, including the mouth and female genital tract. There are currently no mucosal melanoma consensus treatment guidelines or randomized controlled trials,[14] and treatment regimens are often extrapolated from data based on therapies used to treat metastatic cutaneous melanoma.

Considering these findings, we recommend that dermatologists examine the oropharynx and the genitalia when performing a full body skin examination. The examination of the oropharynx includes asking the patient to lift their upper lip, pull down their lower lip, and open their mouth so that the clinician can examine the palate. If a suspicious lesion in the oral mucosa is identified, we recommend referral to a dentist for further evaluation

including the possibility of obtaining a biopsy specimen. We also discuss with our patients that examination of the genital areas is recommended for full body skin examinations, but patients can defer if they choose or if they have regular follow-up with a gynecologist or urologist. These added steps are easy to incorporate into the full body skin examination and do not significantly prolong the encounter. Using these methods, the authors have identified mucosal melanomas in the oral cavity and genital areas. Given the poor prognosis of mucosal melanomas, we recommend that dermatologists consider implementing a comprehensive method of performing full body skin examinations.

Limitations include the lack of a standardized staging system for mucosal melanomas, which may have resulted in potential misclassification of the extent of spread of some mucosal melanomas. Because our database did not have data on the genetic characteristics of the cases or their tumors, it

is difficult to determine whether these factors modify our observations. Despite these limitations, this study has several strengths. Most importantly, we used a population-based dataset with a large enough sample size to explore relationships between multiple variables. Compared with data from a single clinical institution, in which patient participation could represent a biased selection of mucosal melanomas, our data from a population-based registry is more generalizable to the U.S. population.

In conclusion, this study of 21 years of population-based CCR data showed that mucosal melanoma continues to be an aggressive disease with a poor prognosis. We found that stage at diagnosis is an independent risk factor for survival from mucosal melanoma, but tumor thickness and race/ethnicity are not. Anatomic site affects survival from mucosal melanomas, with tumors of less common anatomic sites conferring the worst prognosis. Because of the poor prognosis for mucosal melanomas of all stages, clinicians should consider treating more aggressively at the time of diagnosis and advocating for the development of treatments that are specific to mucosal melanoma.

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Dr Cockburn. Acquisition of data: Dr Cockburn. Analysis and interpretation of data: All authors. Drafting of the manuscript: Drs Altieri, Eguchi, and Cockburn. Critical revision of the manuscript for important intellectual content: All authors.

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Supplemental Table I. Survival for cutaneous and mucosal melanoma in California, by tumor thickness and primary site at diagnosis, California Cancer Registry, 1994-2015

	Cutaneous		Mucosal	
	Cases, n (%)	5-Year survival estimate, % (95% CI)	Cases, n (%)	5-Year survival estimate, % (95% CI)
Thickness at diagnosis				
<1 mm	74,885 (57.20)	87.70 (87.44-87.96)	161 (8.83)	48.83 (40.28-56.82)
1-<2 mm	20,413 (15.59)	77.38 (76.74-78.00)	126 (6.91)	51.94 (41.83-61.12)
2-<4 mm	11,777 (9.00)	61.10 (60.12-62.06)	98 (5.37)	44.28 (32.80- 55.14)
≥4 mm	8642 (6.60)	43.10 (41.94-44.26)	142 (7.79)	29.01 (20.62-37.91)
Unknown	15,210 (11.62)	50.56 (49.73-51.40)	1297 (71.11)	21.29 (18.92-23.75)
Primary site				
Oral cavity			174 (9.54)	27.85 (20.58-35.57)
Anorectal			358 (19.63)	16.68 (12.58-21.28)
Nasal and sinus			452 (24.78)	23.77 (19.65-28.13)
Genitourinary			700 (38.38)	37.41 (33.53-41.29)
Gastrointestinal			68 (3.73)	20.94 (11.82-31.84)
Other			72 (3.95)	13.57 (6.32-23.58)
Total cases	130,927		1824	

Supplemental Table II. Multivariate models predicting cutaneous and mucosal melanoma death in the population of California, California Cancer Registry, 1994-2015

	Cutaneous, n = 130,927	Mucosal, n = 1824
	HR (95% CI)	HR (95% CI)
5-year age group	1.33* (1.33-1.34)	1.12* (1.09-1.14)
Sex		
Male	Reference	Reference
Female	0.75* (0.74-0.77)	0.92 (0.81-1.04)
Race		
Non-Hispanic white	Reference	Reference
Non-Hispanic black	1.41* (1.24-1.60)	1.06 (0.77-1.44)
Hispanic	1.15* (1.10-1.20)	1.03 (0.89-1.20)
Asian/Pacific Islander	1.17[†] (1.07-1.29)	0.93 (0.78-1.11)
Stage		
Localized	Reference	Reference
Regional	1.96* (1.90-2.02)	1.76* (1.54-2.02)
Distant	7.64* (7.37-7.92)	3.36* (2.90-3.92)
Unknown	1.74* (1.66-1.82)	1.71* (1.38-2.13)
Thickness		
<1 mm	Reference	Reference
1-<2 mm	1.47* (1.43-1.51)	0.93 (0.68-1.26)
2-<4 mm	1.95* (1.89-2.01)	1.08 (0.78-1.51)
≥4 mm	2.27* (2.19-2.35)	1.18 (0.88-1.58)
Unknown	1.92* (1.85-1.98)	1.47[†] (1.15-1.89)
Primary site		
Oral cavity		Reference
Anorectal		1.37[†] (1.10-1.69)
Nasal and sinus		1.08 (0.88-1.33)
Genitourinary		1.20 (0.96-1.50)
Gastrointestinal		1.65[†] (1.19-2.27)
Other		1.93* (1.42-2.64)

CI, Confidence interval; *HR*, hazard ratio.

Covariates include age, sex, race/ethnicity, tumor stage at diagnosis, tumor thickness at diagnosis, and mucosal primary site.

*$P < .0001$.

[†]$P < .01$.