



## Predictors of survival in head and neck mucosal melanoma



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### ABSTRACT

**Objectives:** To evaluate hospital-based data of head and neck mucosal melanoma patients in order to identify predictors of survival.

**Materials and methods:** The National Cancer Data Base was used to identify 1368 patients with head and neck mucosal melanoma diagnosed between the years of 2004 and 2012. The Kaplan-Meier method was utilized to estimate overall survival, and multivariate Cox regression analyses were performed to assess the impact of covariates on survival after adjusting for confounding variables.

**Results:** Median follow-up was 55.2 months. Median survival of all patients was 29.3 months, and the 5-year survival was 27.4%. After adjusting for other prognostic factors in multivariate analysis, paranasal sinus location [hazard ratio (HR) = 1.54, 95% Confidence Interval (CI) = 1.30–1.82,  $P < 0.001$ ] and the use of radiotherapy alone for definitive local treatment (HR = 2.27, 95% CI = 1.72–2.98,  $P < 0.001$ ) were associated with worse survival. Similar results were seen in the subgroup of patients with complete clinical staging information. In terms of patterns of care, the use of combined surgery and radiotherapy as the primary local treatment modality has significantly increased from 2004 and 2012 ( $P = 0.03$ ).

**Conclusion:** Outcomes in mucosal melanoma of the head and neck remain suboptimal, despite increased use of multimodality local therapy, likely due to the high risk of distant metastases. Mucosal melanomas arising from the paranasal sinuses have particularly poor prognosis. Novel therapeutic paradigms for head and neck mucosal melanoma, incorporating systemic therapies to decrease the risk of distant relapse, should be pursued in clinical trials.

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### Introduction

Mucosal melanomas are among the most lethal of head and neck cancers. Although they can arise from any mucosa-lined surface, mucosal melanomas most commonly occur in the sinonasal regions of the head and neck [1]. In comparison to cutaneous, acral, and ocular melanomas, mucosal melanoma exhibits an aggressive clinical course with poor prognosis [2–5]. Diagnosis is often delayed given few and nonspecific presenting symptoms mimicking more common benign processes [6]. Furthermore, head and neck mucosal melanomas (HNMMs) have relatively high rates of

local, regional, and distant metastases despite aggressive multimodality therapy [7].

Due to the rarity of the disease, HNMM literature mainly consists of case reports and retrospective, single institution studies with limited patient numbers and heterogeneous anatomic sites. Thus, there is no clear consensus on treatment guidelines. Primary resection is a current standard therapy for resectable stage III-IVA disease, but the role of adjuvant or definitive radiotherapy is less certain [5,8]. Numerous studies have demonstrated improved locoregional control with adjuvant radiotherapy [9–17], but generally with no impact on overall survival. Thus, the optimal treatment paradigm in HNMM remains to be defined.

Given the limited knowledge about prognostic factors and optimal therapeutic paradigms, we sought to use the National Cancer Data Base to analyze the impact of clinicopathologic, demographic, and treatment-related factors in a relatively large cohort of HNMM patients.

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## Materials and methods

We retrospectively reviewed patients with head and neck mucosal melanoma (HNMM) using the National Cancer Data Base, a hospital-based cancer database sponsored by the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The database includes approximately 70% of newly-diagnosed cancer patients from approximately 1600 accredited cancer care programs in the United States and Puerto Rico. This study was deemed to be exempt from full institutional review board review by Cedars-Sinai Medical Center.

The Consolidated Standards of Reporting Trials (CONSORT) diagram details the study inclusion criteria (Supplementary Fig. 1). Patients with non-mucosal lip cancers (N = 8589) and salivary primaries (N = 28,206) were excluded given that these are not mucosal sites. For other head and neck sites, International Classification of Diseases for Oncology 3rd edition morphologic codes 8720–8790 were used to extract 2009 patients diagnosed with invasive mucosal melanoma of all non-cutaneous, mucosal head and neck

sites between the years 2004 and 2012. Patients were staged according to the American Joint Committee on Cancer 7th edition. We excluded patients with unknown details regarding follow up (N = 233), chemotherapy (N = 60), or the timing of radiotherapy with respect to surgery (N = 11). Patients who received non-external beam radiotherapy (N = 6), intraoperative radiotherapy (N = 1), or underwent a non-excisional surgical procedure were excluded (N = 2). Patients that presented with distant metastases (N = 214) or patients without any definitive local therapy (N = 114) were also excluded from this study. The remaining 1368 patients were included in our analysis. Tumor and nodal clinical staging information was only available for patients diagnosed in 2010 or later. Patients with full clinical staging information were analyzed in a separate subgroup analysis.

Kaplan-Meier calculations were used to estimate survival. Survival curves were compared using log-rank tests. Median follow-up was calculated with the reverse Kaplan-Meier method. Univariate and multivariate Cox regression analysis was used to calculate hazards ratios (HR) and 95% confidence intervals (CI).

**Table 1**

Baseline demographic and clinical characteristics of patients with head and neck mucosal melanomas, stratified by anatomic site. RT, radiotherapy. N/A, not applicable.

Patient demographics					
Variable	Nasal cavity	Paranasal Sinuses		Other Sites	Total
Total patients (N)	749	293		326	1368
Age [Median (range)]	73 (29–90)	71 (24–90)		66 (21–90)	71 (21–90)
	N (%)	N (%)	p*	N (%)	p**
Sex			0.6		<b>0.002</b>
Male	335 (44.7)	136 (46.4)		180 (55.2)	651 (47.6)
Female	414 (55.3)	157 (53.6)		146 (44.8)	717 (52.4)
Race			<b>0.04</b>		<b>0.02</b>
White	681 (90.9)	280 (95.6)		279 (85.6)	1240 (90.6)
Black	30 (4.0)	7 (2.4)		26 (8.0)	63 (4.6)
Other	38 (5.1)	6 (2.0)		21 (6.4)	65 (4.8)
Year of diagnosis			0.8		<b>0.04</b>
2004–2006	226 (30.2)	93 (31.7)		93 (28.5)	412 (30.1)
2007–2009	264 (35.2)	104 (35.5)		95 (29.1)	463 (33.8)
2010–2012	259 (34.6)	96 (32.8)		138 (42.3)	493 (36.0)
Academic center			0.3		<b>0.02</b>
No	285 (38.1)	100 (34.1)		95 (29.1)	482 (35.2)
Yes	455 (60.7)	186 (63.5)		213 (65.3)	855 (62.5)
Unknown	9 (1.2)	7 (2.4)		18 (5.5)	34 (2.4)
Charlson/Deyo Score			0.1		0.3
0	637 (85.0)	255 (87.0)		271 (83.1)	1163 (85.0)
1	97 (13.0)	28 (9.6)		43 (13.2)	168 (12.3)
2	15 (2.0)	10 (3.4)		12 (3.7)	37 (2.7)
Clinical T stage			<b>0.001</b>		<b>0.01</b>
cT3	136 (18.2)	24 (8.2)		73 (22.4)	233 (17.0)
cT4a	50 (6.7)	27 (9.2)		35 (10.7)	112 (8.2)
cT4b	24 (3.2)	11 (3.8)		5 (1.5)	40 (2.9)
cTX	539 (72.0)	231 (78.8)		213 (65.3)	983 (71.9)
Clinical N Stage			0.8		<b>&lt;0.001</b>
cN0	215 (28.7)	59 (20.1)		74 (22.7)	348 (25.4)
cN1	13 (1.7)	3 (1.0)		43 (13.1)	59 (4.3)
cNX	521 (69.6)	231 (78.8)		209 (64.1)	961 (70.2)
Neck dissection			0.3		<b>&lt;0.001</b>
No	668 (89.2)	268 (91.5)		200 (61.3)	1136 (83.0)
Yes	81 (10.8)	25 (8.5)		126 (38.6)	232 (17.0)
Chemotherapy			<b>&lt;0.001</b>		<b>0.05</b>
No	695 (92.8)	249 (85.0)		291 (89.2)	1235 (90.3)
Yes	54 (7.2)	44 (15.0)		35 (10.7)	133 (9.7)
Definitive treatment			<b>&lt;0.001</b>		<b>&lt;0.001</b>
Surgery Alone	320 (42.7)	90 (30.7)		172 (52.8)	566 (41.4)
RT Alone	40 (5.3)	37 (12.6)		24 (7.4)	98 (7.2)
Surgery and RT	389 (51.9)	166 (56.7)		130 (39.9)	704 (51.5)

Bold values identify statistically significant covariates (P ≤ 0.05).

\* Difference between frequencies in nasal cavity and paranasal sinuses, Chi-Squared analysis.

\*\* Difference between frequencies in nasal cavity and other anatomic sites, Chi-Squared analysis.

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