The Laryngoscope

Mucosal Melanoma of the Oral Cavity: What is the Role of Elective Neck Dissection?

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Objectives: Mucosal melanoma (MM) is a rare malignancy that can present in the head and neck (H&N). The Oral cavity is the second most common primary site in the H&N after sinonasal mucosa. This study investigates the impact of demographic and clinical factors on survival in oral cavity MM. Further, it investigates the outcomes and utility of elective neck dissections (END) in the management of oral MM.

Methods: The National Cancer Database was used to evaluate 432 patients with oral cavity MM from 2004 to 2016. Kaplan-Meir and Cox regression analyses were used to determine variables associated with survival.

Results: The mean age was 64.0 ± 16.0 years. Most patients were white (85.1%) and male (60.0%). Gingiva (37.6%) and hard palate (36.1%) were the most common primary subsites in the oral cavity. Five-year overall survival was 31.0%. Age (Hazards Ratio [95% Confidence Interval], 1.03 [1.01–1.06]), N-stage (1.94 [1.10–3.42]), M-stage (10.13 [3.33–30.86]), male sex (1.79 [1.06–3.03]), and African-American race (2.63 [1.14–6.11]) were significantly associated with worse survival. 199 patients (46.9%) underwent neck dissection including 118 with lymph node yield (LNY) ≥ 18. The rate of occult nodal positivity was 45.4% for LNY ≥ 18 and 28.3% for LNY ≥ 1. ENDs were not associated with improved outcomes. However, occult lymph node involvement was associated with worse overall survival ($p = 0.004$).

Conclusions: Oral cavity MM has a poor prognosis. Lymph node involvement, distant metastasis, age, race, and male sex are associated with worse outcomes. Performing an END did not improve survival. However, END may have a prognostic role and help select patients for treatment intensification.

Key Words: mucosal melanoma, oral cavity, national cancer database, neck dissection.

Level of Evidence: 4

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INTRODUCTION

Mucosal melanoma (MM) is a rare subtype of melanoma, accounting for less than 1.3% of all melanomas, with the majority occurring in the head and neck.[1] Primary mucosal melanomas are believed to arise from non-cutaneous melanocytes.[1] While most cutaneous melanomas are diagnosed in the radial growth phase, mucosal melanomas are more likely to be found in the invasive, vertical growth phase, and are thus associated with worse outcomes.[2,3] Among head and neck melanomas, the nasal cavity and paranasal sinuses are the most common primary site (70%) followed by the oral cavity (25%).[4]

Mucosal melanomas make up less than 1% of all oral cavity malignancies.[5] Early diagnosis and treatment are essential due to the associated poor survival. Five-year overall survival (OS) for head and neck mucosal melanomas is approximately 25%. Oral and nasal cavity primary sites are associated with higher 5-year OS at approximately 35%, compared to the nasopharynx, oropharynx, and paranasal sinuses.[6] Despite the low prevalence of MM, a trend of increasing incidence during the last several decades is remarkable, highlighting the increasing clinical relevance of this disease.[5]

Oral MM often presents as a painless, rapidly growing mass; though, ulceration, bleeding, swelling, loose teeth, and ill-fitting dentures may also occur in the early stages.[4,7] Compared to sinonasal MM, oral cavity MMs are more likely to have evidence of nodal metastasis on presentation.[4,8] Because of the higher likelihood of nodal metastasis, the National Comprehensive Cancer Network (NCCN) recommends elective neck dissections for mucosal melanomas of the oral cavity, though not of other primary sites.[9] However, a study of 74 patients in South Korea found there to be no survival benefit in patients undergoing neck dissection.[10] To our knowledge, there are no published data on the rate of positive nodal

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metastasis in elective neck dissections for this malignancy.

Prior studies have used national multicenter databases to investigate factors associated with survival among head and neck MMs. The primary site, age, tumor size, and nodal and distant metastases were associated with OS, while treatment modality was not.[6] When considering sinonasal mucosal melanoma specifically, age, T-stage, M-stage, and margin status were associated with survival outcomes.[11] However, there have been no prior population-based studies of mucosal melanoma-specific to the oral cavity. This study utilizes the national cancer database (NCDB) to describe demographics, clinicopathologic factors, and treatment modalities in oral cavity mucosal melanoma, and their associations with overall survival. Further, it investigates the outcomes and utility of elective neck dissections in this cohort.

METHODS

This study is a retrospective, population-based analysis of the NCDB—a national clinical oncology registry sponsored by the Commission on Cancer of the American Academy of Surgeons, and the American Cancer Society.[12] The NCDB contains data from over 1500 Commission on Cancer accredited programs. Because the data is de-identified, the study was exempt from our institution's Institutional Review Board.

The NCDB was investigated to collect patients with mucosal melanoma of the oral cavity between 2004 and 2016. Malignant MM was selected using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology codes 8720–8780. Patients with primary malignant oral cavity MM were selected based on ICD-O-3 topography codes. The oral cavity subsite was categorized into the following: lip mucosa, tongue, gingiva, floor of mouth, hard palate, buccal mucosa, vestibule of mouth, retromolar trigone, and other/unspecified (Table S1).

Demographic data included in the analysis were patient age, sex, insurance status, household median income, facility type, and degree of urbanization. The race was classified as White, African American, Asian, and other. Insurance status was classified as uninsured, Medicaid, Medicare, private insurance, and other government insurance. Household median income was categorized into quartiles based on the median income in the patient's zip code. Facility type was grouped as community cancer programs, academic/research programs, and integrated network cancer programs. The degree of urbanization was categorized as metropolitan, urban, and rural-based on population.

Clinicopathological variables were defined based on the American Joint Committee on Cancer (AJCC) T stage (T3 or T4), N Stage (N0 or N1), M stage (M0 or M1), and clinical stage (III or IV). Charlson-Deyo comorbidity index was used to categorize the severity of patients' comorbidities and was reported as 0, 1, 2, or 3+. Treatment variables analyzed included surgery and surgical margin status, radiation, chemotherapy, immunotherapy, and neck dissection.

Patients were considered to have undergone a neck dissection if at least 18 lymph nodes were examined—a validated indicator of an adequate lymph node dissection in head and neck cancers.[13] Because lymph node yield (LNY) of 18 nodes was validated on cases of squamous cell carcinoma of the head and neck and not MM, we also performed analyses when any number of lymph nodes were sampled, excluding lymph node aspirations (LNY ≥ 1). Elective neck dissections (END) were defined as neck dissections performed in patients who had no clinical evidence of nodal (N0) or distant (M0) metastases. Occult lymph node positivity was defined as the percentage of these patients who had lymph nodes examined and were found to have positive pathologic lymph node involvement.

Overall survival was calculated for the cohort and stratified by the above variables. Patients lost to follow up or alive at the end of the study period in 2016 were coded as right-censored data. Statistical analyses were performed using SPSS statistical software version 25 (IBM Corporation, Armonk, NY). Kaplan–Meier (KM) univariate analysis was used to determine variables associated with OS. Multivariable analysis was completed using Cox regression to determine factors independently associated with OS. To avoid overfitting, only age, sex, and variables with $p < 0.10$ on univariate analysis were included in the model. Hazards ratios (HR) with 95% confidence intervals (CI) were reported for Cox regression. We then repeated the above analyses in the cohort of patients with N0 M0 disease to determine factors associated with survival in patients without clinical nodal or distant metastases. Statistical significance was established as $p < 0.05$ for univariate and multivariable analyses.

RESULTS

Study Population and Demographics

There were 432 identified cases of primary oral cavity MM. Demographics, clinicopathologic characteristics, and treatment in the cohort are shown in Table I. The most common primary subsite within the oral cavity was the gingiva (37.6%) followed by the hard palate (36.1%). On presentation, most oral cavity MMs had a T stage of 3 (57.3%). Clinical nodal metastasis was present in 36.9% of cases and distant metastasis was present in 13.4% of cases. The majority of patients received surgery (83.8%) with negative surgical margins (83.0%). Radiation (44.7%) was the second most common treatment provided, followed by immunotherapy (15.1%) and chemotherapy (13.5%). Neck dissection with a lymph node yield (LNY) of at least 18 nodes was performed in 28.2% of patients. Neck dissection with an LNY of at least one node was performed in 46.9% of patients. Mean ± SD LNY was 11.9 ± 18.7 nodes and the mean number of pathologically positive nodes was 2.2 ± 3.6.

Univariate Survival Analysis

Median survival time was 32.9 months and five-year overall survival was 31.0% (Fig. 1). On Kaplan–Meier univariate analysis, age ($p < 0.001$), race ($p = 0.002$), clinical T stage ($p = 0.009$), clinical N stage ($p < 0.001$), clinical M stage ($p < 0.001$), and AJCC clinical stage ($p < 0.001$) were associated with OS (Table II). Figure 2 demonstrates overall survival by T, N, and M stages. No surgery ($p < 0.001$), positive margin status ($p = 0.01$), undergoing chemotherapy ($p = 0.002$), and undergoing neck dissections ($p = 0.02$) were associated with worse OS on unmatched KM analysis (Table II). Radiotherapy ($p = 0.07$) and immunotherapy ($p = 0.46$) were not associated with survival.

TABLE I.
Demographic and Clinicopathologic Factors of Oral Cavity Mucosal Melanoma.

Variable	No.	%
Total	432	100
Age, mean (±SD), years	64 (SD ± 16)	
Sex		
Male	259	60.0
Female	173	40.0
Race		
White	365	85.1
Black	34	7.9
Asian/Pacific Islander	21	4.9
Other	9	2.1
Unknown	3	
Insurance status		
Not insured	19	4.6
Private Insurance	160	39.0
Medicaid	25	6.1
Medicare	202	49.3
Other Government Insurance	4	1.0
Unknown	22	—
Median Household Income		
<$40,227	72	16.8
$40,227–50,353	89	20.8
$50,354–63,332	103	24.1
> = $63,333	164	38.3
Unknown	4	—
Degree of Urbanization		
Metropolitan	335	80.5
Urban	71	17.1
Rural	10	2.4
Unknown	16	—
Facility Type		
Community	108	27.1
Academic/Research	253	63.6
Integrated Network	37	9.3
Unknown	34	
Charlson-Deyo Score		
0	351	81.3
1	65	15
2	11	2.5
3+	5	1.2
Primary Site		
Lip Mucosa	31	7.9
Tongue	13	3.3
Gingiva	147	37.6
Floor of Mouth	13	3.3
Hard Palate	141	36.1
Buccal Mucosa	30	7.7
Vestibule	7	1.8
Retromolar Trigone	9	2.3
Other/Unknown	41	—
T Stage		
T3	133	57.3
T4	99	42.7
Unknown	200	—
N Stage		
N0	154	63.1
N1	90	36.9
Unknown	188	—
M Stage		
M0	226	86.6
M1	35	13.4
Unknown	171	—
AJCC Stage		
3	88	37.4
4	147	62.6
Unknown	197	—
Surgery		
Yes	361	83.8
No	70	16.2
Unknown	1	—
Surgical Margins		
Negative	278	83.0
Positive	57	17.0
Unknown	26	—
Radiation		
Yes	193	44.7
No	239	55.3
Chemotherapy		
Yes	56	13.5
No	359	86.5
Unknown	17	—
Immunotherapy		
Yes	65	15.1
No	366	84.9
Unknown	1	—
Lymph Node Dissection (LNY ≥ 18)		
Yes	118	28.2
No	300	71.8
Unknown	14	—
Lymph Node Dissection (LNY ≥ 1)		
Yes	199	46.9
No	225	53.1
Unknown	8	—

LNY = lymph node yield; SD = standard deviation.

Multivariable Survival Analysis

Cox regression analysis was performed with age, sex, race, T-stage, N-stage, M-stage, treatment modality, margin status, and neck dissection (LNY ≥ 18) included as covariates. Advanced age (HR: 1.03, 95% CI: [1.01–1.06]), African American race (2.63 [1.14–6.11]), nodal

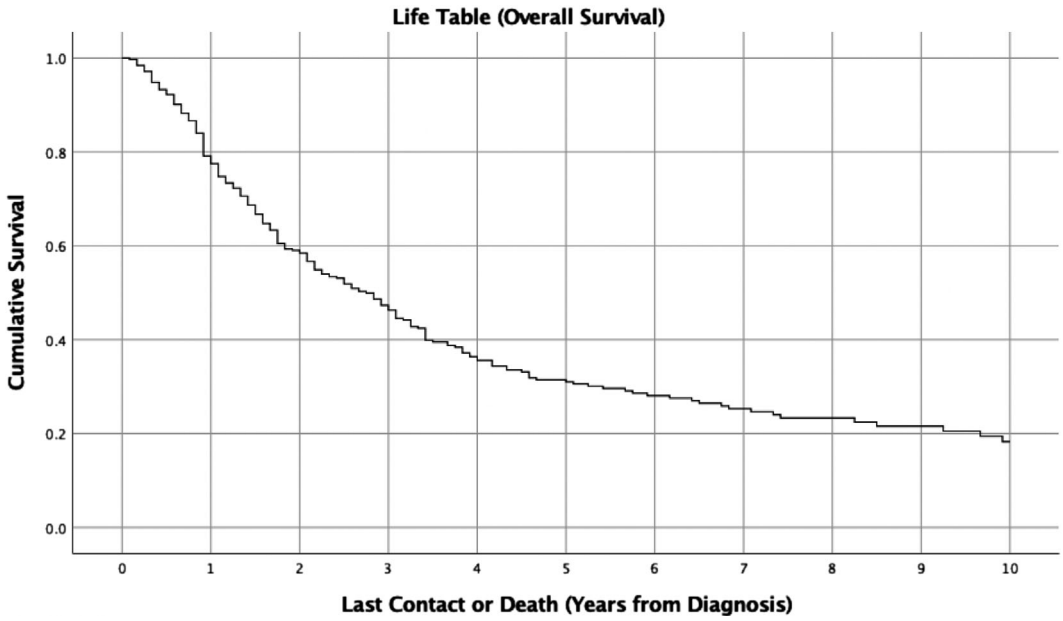

Fig. 1. Kaplan–Meier survival curve of overall survival in oral cavity mucosal melanoma. Five-year overall survival is 31.0% and median survival time is 32.9 months.

metastasis (1.94 [1.10–3.42]), distant metastasis (10.13 [3.33–30.86]), and neck dissections with LNY ≥ 18 (2.23 [1.17–4.24]) were independently associated with worse survival (Table III). Female sex (0.56 [0.33–0.94]) was associated with improved survival outcomes. T-stage, treatment modality and margin status were not associated with OS.

The above analysis was repeated with neck dissections defined as LNY ≥ 1, as neck dissections with LNY ≥ 18 were validated on cases of squamous cell carcinoma of the head and neck and not MM. There was no association between neck dissection with LNY ≥ 1 and OS (1.54 [0.81–2.93]).

Clinical N0 and M0 Disease

There were 138 cases identified without clinical nodal or distant metastatic disease. Median survival was 43.2 months and five-year overall survival was 34.2%. On Kaplan–Meier univariate analysis, advanced age ($p = 0.002$), male sex ($p = 0.03$), T-stage ($p = 0.004$), AJCC stage ($p = 0.003$), and postoperative radiation ($p = 0.03$) were associated with worse OS (Table II). On multivariable Cox regression, older age (HR 1.07 [1.01–1.11]), T4 tumors (3.38 [1.37–8.32]), and undergoing neck dissection with LNY ≥ 18 (2.92 [1.04–8.19]) were associated with worse OS (Table IV). There was no difference in survival between patients undergoing surgery with radiation versus surgery alone. Margin status, race, and sex did not impact OS. When repeating the analysis of neck dissection with LNY ≥ 1, neck dissections were marginally associated with worse outcomes (1.95 [0.99–4.30]).

Elective Neck Dissections (END)

Of patients with clinical N0 M0 disease, 24.4% underwent END with an LNY ≥ 18, and 44.9% underwent a neck dissection of at least 1 node (Table V). On Kaplan–Meier analysis, there was no difference in survival between patients who did and did not undergo END, regardless of LNY (Table II). Of the 62 patients identified as having ENDs of at least 1 node, 17 (28.3%) yielded positive pathologic lymph node involvement. Among these patients, 7 had T3 tumors, 7 had T4 tumors, and the tumor stage was unknown for 3 patients. The rate of occult node positivity in patients undergoing neck dissection with LNY ≥ 18 was 45.4%. Positive lymph node involvement was associated with worse survival outcomes ($p = 0.004$; Table II).

DISCUSSION

To our knowledge, this is the largest study to systematically examine the associations of patient demographics, tumor characteristics, and treatment modality with overall survival in patients with primary MM of the oral cavity. Mucosal melanoma is a rare malignancy with a poor prognosis, and the oral cavity is the second most common subsite in the head and neck.[4] Our findings suggest that the 5-year OS rate is 31.0%, which is consistent with some of the largest published retrospective and epidemiological studies that have proposed 5-year survival rates ranging from 15 to 35%.[4,14,15]

Patient Demographics

The average age of patients in this cohort was 64 years, consistent with previous studies of patients

TABLE II.
Patient Characteristics and Univariate Kaplan–Meier Analysis of Overall Survival.

Total Cohort				Local Disease Only (Clinical N0 M0)			
Total	389			Total	118		
Overall Survival (OS)	%			Overall Survival (OS)	%		
1-Yr	77.5			1-Yr	90.3		
3-Yr	46.3			3-Yr	63.5		
5-Yr	31.0			5-Yr	34.2		
10-Yr	18.2			10-Yr	—		
Median	32.9 Months			Median	43.2 Months		
Variable	*N*	5-Yr OS (%)	*p* value	Variable	*N*	5-YR OS (%)	*p* value
Total	389	31.0		Total	118	34.2	
Age			<0.001	Age			0.002
18–59	140	34.7		18–59	36	38.8	
60–69	90	32.9		60–69	32	47.5	
70–79	89	30.3		70–79	32	25.9	
80+	67	17.1		80+	17	23.1	
Sex			0.13	Sex			**0.03**
Male	226	27.5		Male	69	28.8	
Female	163	35.8		Female	49	35.4	
Race			**0.002**	Race			0.15
White	327	32.5		White	104	36.3	
African American	31	14.5		African American	8	31.3	
Asian-Pacific Islander	21	43.9		Asian-Pacific Islander	3	33.3	
Other	7	14.3		Other	1	0	
Primary Payer			0.11	Primary Payer			0.31
Not insured	18	0		Not insured	2	0	
Private Insurance	143	37.2		Private Insurance	46	46.5	
Medicaid	23	42.9		Medicaid	8	62.5	
Medicare	181	26.4		Medicare	56	24.5	
Other Government Insurance	3	0		Other Government Insurance	1	0	
Median Income Quartile			0.14	Median Income Quartile			0.92
<$40,227	61	23.48		<$40,227	18	33.3	
$40,227–50,353	81	39.24		$40,227–50,353	27	37.9	
$50,354–63,332	97	30.33		$50,354–63,332	29	46.2	
>= $63,333	146	30.4		>= $63,333	43	29.2	
Facility Type			0.80	Facility Type			0.12
Community	96	28.3		Community	29	28.2	
Academic/Research	228	31.2		Academic/Research	67	38.6	
Integrated Network	35	22.9		Integrated Network	12	13.9	
Degree of Urbanization			0.22	Degree of Urbanization			0.54
Metropolitan	303	31.7		Metropolitan	87	33.1	
Urban	62	26.6		Urban	25	27.5	
Rural	8	66.7		Rural	4	66.7	
Primary Site			0.57	Primary Site			0.22
Lip Mucosa	25	54		Lip Mucosa	12	65.6	
Tongue	12	32.1		Tongue	2	0	
Gingiva	129	28.1		Gingiva	32	27	
Floor of Mouth	12	25		Floor of Mouth	4	33.3	
Hard Palate	133	31.2		Hard Palate	44	32	
Buccal Mucosa	29	45.1		Buccal Mucosa	12	53.6	
Vestibule	6	25		Vestibule	1	—	

(Continues)

TABLE II.
Continued

Variable	N	5-Yr OS (%)	p value	Variable	N	5-YR OS (%)	p value
Retromolar Trigone	8	37.5		Retromolar Trigone	3	66.7	
Charlson-Deyo Score			0.50	Charlson-Deyo Score			0.84
0	315	30.9		0	94	32.6	
1	60	32.6		1	21	43.1	
2	10	13.3		2	2	0	
3+	4	50		3+	1	—	
T Stage			**0.009**	T Stage			**0.004**
T3	108	32.9		T3	68	44.8	
T4	86	13.4		T4	36	10.2	
N Stage			**<0.001**				
N0	131	33					
N1	74	15.3					
M Stage			**<0.001**				
M0	194	29.9					
M1	27	0					
AJCC Stage			**<0.001**	AJCC Stage			**0.003**
III	73	44.7		III	68	44.8	
IV	124	11		IV	35	9.9	
Surgery			**<0.001**	Surgery			0.42
No	62	15.2		No	7	42.9	
Yes	326	34.2		Yes	111	33.7	
Radiation			0.07	Radiation			0.11
No	211	36.1		No	68	43.5	
Yes	178	25.2		Yes	50	23.7	
Chemotherapy			**0.002**	Chemotherapy			0.80
No	325	32.4		No	108	31.9	
Yes	51	23.1		Yes	5	40.0	
Immunotherapy			0.46	Immunotherapy			0.73
No	339	31.2		No	107	32.8	
Yes	49	30.7		Yes	11	51.9	
Surgical Margins			**0.01**	Surgical Margins			0.10
Negative	253	36.6		Negative	94	33.6	
Positive	49	23		Positive	15	30.5	
Lymph Node Dissection (LNY ≥ 18)			**0.02**	Lymph Node Dissection (LNY ≥ 18) (Elective)			0.24
No	272	33.9		No	85	37.5	
Yes	103	24.2		Yes	30	21.1	
Lymph Node Dissection (LNY ≥ 1)			0.79	Lymph Node Dissection (LNY ≥ 1) (Elective)			0.80
No	206	29.7		No	65	32.7	
Yes	175	32.7		Yes	53	36.6	
				Occult LN involvement			**0.004**
				No	38	45.1	
				Yes	15	0	
				Treatment Regimen			**0.03**
				Surgery Alone	54	42.8	
				Surgery + RT	37	11.5	

Note: Bold indicates *P*-value < 0.05.
LNY = lymph node yield.

with oral cavity MM.[4,5,16,17] Most patients were male and White. As demonstrated in previous studies, the most common anatomical subsites were the gingiva and hard palate.[4,5,15] Advanced age, male sex, and African American race were each associated with poorer survival on multivariable analysis (Table III). In the United States, the incidence of MM has been found to be lower in African American than White populations.[18]

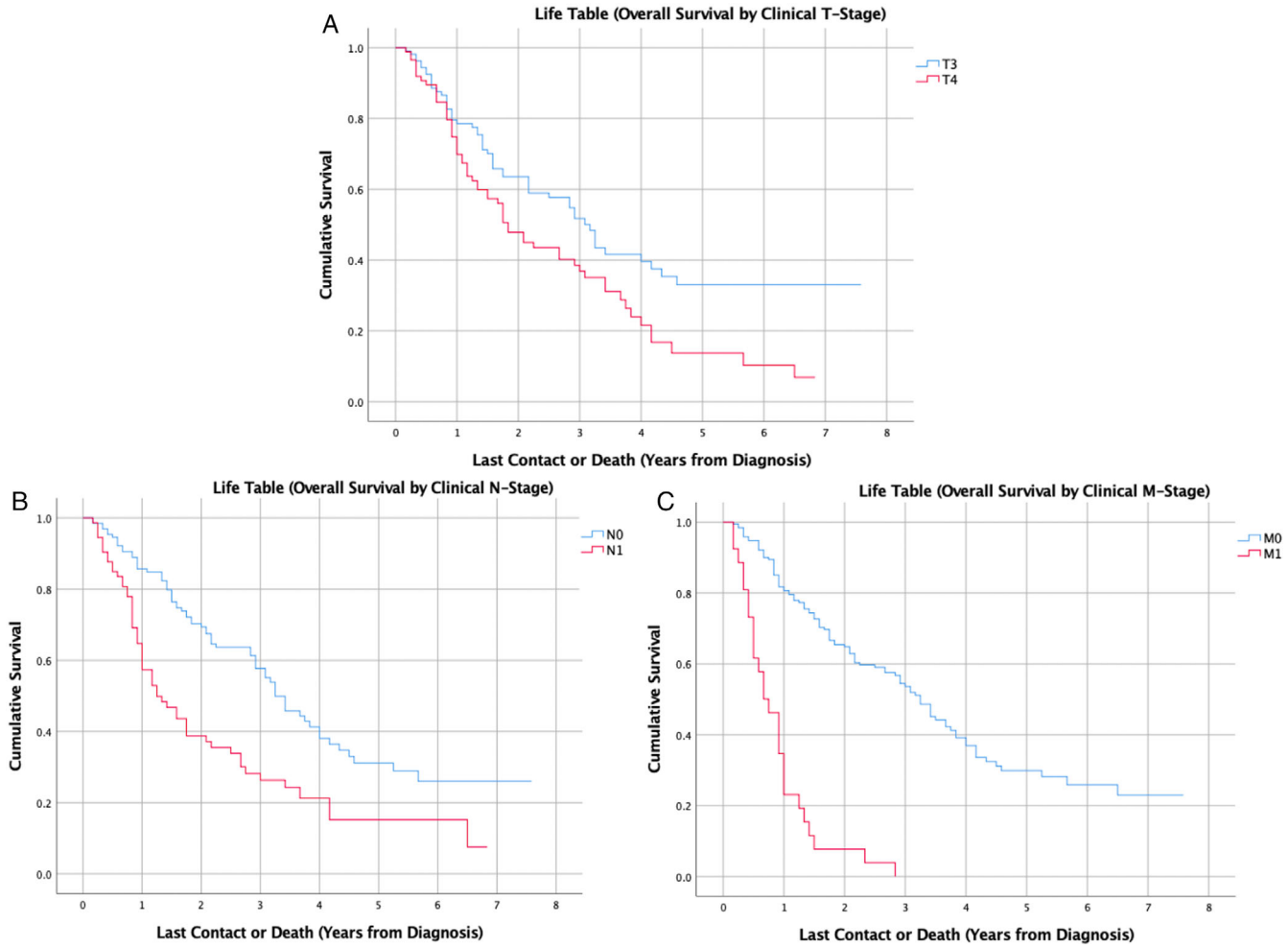

Fig. 2. Kaplan–Meier survival curve of overall survival in oral cavity mucosal melanoma stratified by (A) Clinical T-Stage (B) Clinical N-Stage and (C) Clinical M-stage. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

However, prior studies of head and neck MMs overall and specific to the oral cavity have not found discrepancies in survival by race.[6,11,19] Further research is warranted to determine the reason for worse survival outcomes among African American patients with oral cavity MM. Possible contributing factors may include different tumor biology, later presentation, and healthcare disparities.

Treatment Modalities

Wide surgical resection with negative margins is the primary treatment for mucosal melanoma stage III through IVA, as it has been shown to optimize local control and survival.[20–22] Most patients (83.8%) in our study received surgery as part of their treatment. Surgery and negative margins were associated with improved survival on univariate analysis (Table II). However, on multivariable analysis, there was no difference in overall survival between treatment regimens or margin status (Tables III and IV). Jethanamest et al. demonstrated similar results, showing no difference in survival by treatment modality.[6]

Surgical resection is considered the mainstay treatment for oral MM, with adjuvant radiotherapy recommended in selected cases to improve locoregional control.[9,23] Postoperative radiation for head and neck MM is recommended in cases of extracapsular nodal disease, involvement of at least 2 cervical or intraparotid lymph nodes, any node 3 cm or greater, nodal excision without neck dissection, or locoregional recurrence.[9] The T staging for mucosal melanoma omits the early T stage, so by definition, every MM is either T3 or T4. Therefore, all MM is considered an advanced T stage, which can be another justification for adjuvant RT. For oral cavity melanomas, adjuvant radiation may be used more often due to the higher likelihood of nodal metastasis.[9]

Overall, 44.7% of patients underwent radiotherapy as part of their treatment. Among N0 and M0 patients, 51.2% of patients underwent surgery alone and 33.1% underwent surgery with radiotherapy. Our results demonstrated that in N0 M0 disease, adjuvant radiation therapy was not associated with improved survival outcomes (Tables III and IV). This is similar to prior studies on head and neck MM. Although radiotherapy was associated with longer local disease-free survival and improved locoregional control, there was no significant impact of

TABLE III.
Cox Proportional Hazards Multivariable Regression of Overall Survival in Oral Cavity Mucosal Melanoma.

Covariate	Total ($N = 120$)	Hazard Ratio (95% CI)	p value
Age		1.03 (1.01–1.06)	**0.003**
Sex			
Male	70	1.00 (reference)	
Female	50	0.56 (0.33–0.94)	**0.03**
Race			
White	103	1.00 (reference)	
Black	11	2.63 (1.14–6.11)	**0.02**
Asian/Pacific Islander	6	1.55 (0.45–5.22)	0.48
T Stage			
T3	70	1.00 (reference)	
T4	50	0.95 (0.57–1.82)	0.95
N Stage			
N0	82	1.00 (reference)	
N1	38	1.94 (1.10–3.42)	**0.02**
M Stage			
M0	115	1.00 (reference)	
M1	5	10.13 (3.33–30.86)	**<0.001**
Treatment		—	
Surgery	56	1.00 (reference)	
Surgery + RT	48	1.57 (0.88–2.78)	0.12
Surgery + Chemotherapy	4	1.94 (0.54–6.94)	0.31
Surgery + Immunotherapy	5	2.24 (0.48–10.41)	0.31
Surgery + CRT	7	1.09 (0.38–3.19)	0.87
Margins			
Negative	98	1.00 (reference)	
Positive	22	1.07 (0.56–2.03)	0.85
Neck Dissection (LNY ≥ 18)			
No	76	1.00 (reference)	
Yes	44	2.23 (1.17–4.24)	**0.02**
Neck Dissection (LNY ≥ 1)*			
No	50	1.00 (reference)	
Yes	73	1.54 (0.81–2.93)	0.19

Note: Bold indicates *P*-value <0.05.
CI = confidence interval; CRT = chemoradiotherapy; LNY = lymph node yield; RT = radiation therapy.
*For regression with Neck Dissection (LNY ≥ 1), $N = 123$;

postoperative radiotherapy on the likelihood of developing distant metastases or overall survival.[14,24,25]

In our analysis, 15.1% of patients received immunotherapy. Immunotherapy did not demonstrate any significant difference in overall survival on univariate analysis. Immunotherapy has a clearly established role in cutaneous melanoma, however, the benefit of immunotherapy in mucosal melanoma is less clear.[11,26,27] Current immunotherapy options for melanoma include cytokine treatment (INF-a and IL-2), as well as treatments targeting immune checkpoints including CTLA-4, PD-1, and PDL-1.[10] In a pooled analysis that included 86 mucosal melanoma patients with unresectable disease receiving immunotherapy, the median progression-free survival, was only 3 months and the objective response rate was only 23.3%.[28]

Oral cavity mucosal melanomas have been found to have a higher proportion of c-Kit aberrations compared to cutaneous melanomas.[29] Therapies targeting KIT such as Imatinib have been found to have a response rate of 30% in oral mucosal melanoma.[29] Immunotherapy with the combination of monoclonal antibodies nivolumab and ipilimumab have been shown to improve progression-free survival over either agent alone in late-stage MM. Though these regimens are more effective in cutaneous melanoma, results in clinical trials for MM are promising and further studies are warranted.[28] Given the poor prognosis for these patients, treatment intensification with novel agents should continue to be investigated.

Lymph Node Metastasis and Management of the Neck

The risk of cervical lymph node involvement is 50%–60% higher in oral cavity MM than in other MM of the

head and neck.[5,9,26,27] Nodal metastasis has been found to be associated with a worse survival outcomes in oral cavity MM, and this was confirmed in our study.[30] Elective neck dissection (END) in N0 M0 oral cavity mucosal melanoma and radical, modified, or selective neck dissection in N1 M0 cases are typically recommended to maximize locoregional control.[9,31] A lymph node yield of at least 18 has been defined as a quality metric of adequate neck dissection in head and neck malignancies.[13] We found that 28.2% of patients underwent a neck dissection with LNY ≥ 18. This demonstrates that the majority of surgeons treating oral cavity MM are not following NCCN guidelines as they are omitting neck dissection. However, undergoing neck dissection with LNY ≥ 18 was associated with worse prognosis on univariate and multivariable analyses. Given that a minority of patients underwent neck dissection with LNY ≥ 18, it is probable that these neck dissections were performed in cases of more advanced local disease. This was likely a significant confounding factor that influenced these results. We found that the rate of occult node positivity in oral cavity mucosal melanoma in patients with LNY ≥ 18 was 45.4%, which is well above the threshold of 20% typically discussed for assessing the utility of neck dissection.

The NCCN advocates for considering elective neck dissection (END) for any case of oral cavity mucosal melanoma.[9] END with LNY ≥ 18 was performed in 24.4% of patients with clinical N0 M0 disease, and END with LNY ≥ 1 was performed in 44.9% of patients (Table V). Pathological nodes were found in 28.3% of ENDs overall and in 45.4% with LNY ≥ 18. This demonstrates that a comprehensive neck dissection allows for adequate and accurate staging, which offers important prognostic information to the patient. While there was no survival benefit of END on univariate or multivariable analyses, cases where pathological nodes were found were associated with worse survival (Table II). This suggests that while the therapeutic benefit of END is uncertain, it may serve a prognostic role. Prior studies showed no direct mortality benefit of END in oral cavity MM.[10,32] Wu et al. found that while there was no overall survival benefit of END in oral cavity MM, patients with nodular-subtype tumors

TABLE IV.
Cox Proportional Hazards Multivariable Regression of Overall Survival in Clinical N0 M0 Oral Cavity Mucosal Melanoma.

Covariate	Total ($N = 71$)	Hazard Ratio (95% CI)	p value
Age		1.07 (1.03–1.11)	**<0.001**
Sex			
Male	46	1.00 (reference)	
Female	25	0.52 (0.23–1.16)	0.11
Race			
White	66	1.00 (reference)	
Black	5	1.51 (0.40–5.78)	0.55
T Stage			
T3	45	1.00 (reference)	
T4	26	3.38 (1.37–8.32)	**0.008**
Treatment		—	
Surgery	40	1.00 (reference)	
Surgery + RT	31	0.93 (0.38–2.26)	0.88
Margins			
Negative	59	1.00 (reference)	
Positive	12	0.93 (0.35–2.52)	0.89
Elective Neck Dissection (LNY ≥ 18)			
No	54	1.00 (reference)	
Yes	17	2.92 (1.04–8.19)	**0.04**
Elective Neck Dissection (LNY ≥ 1)*			
No	42	1.00 (reference)	
Yes	31	1.95 (0.88–4.30)	0.10

Note: Bold indicates P-value <0.05.
CI = confidence interval; LNY = lymph node yield; RT = radiation therapy.
*For the regression including LNY ≥ 1, $N = 73$.

TABLE V.
Elective Neck Dissections and Occult Nodal Involvement in Oral Cavity Mucosal Melanoma.

	LNY ≥ 18			LNY ≥ 1		
	Number	%	5-Yr OS (%)	Number	%	5-Yr OS (%)
Lymph Node Dissection						
Yes	118	28.2	24.1	199	46.9	32.7
No	300	71.8	33.9	225	53.1	29.7
Unknown	14	—		8	—	
Elective Neck Dissection						
Yes	33	24.4	21.1	62	44.9	36.6
No	102	75.6	37.5	76	55.1	32.7
Unknown	3	—	—	0	—	
Elective Neck Dissection Result						
No Positive LN	18	54.5	44.4	43	71.7	45.1
Positive LN	15	45.4	0.0	17	28.3	0.0
Missing	0	—		2	—	

LNY = lymph node yield; OS = overall survival.

experienced a survival benefit.[30] Despite the uncertain survival benefit of END in oral cavity MM, it may be useful for staging and identifying candidates for treatment intensification in the form of adjuvant therapies.

Limitations

There are several limitations to this study. The accuracy of data in the NCDB is dependent on the integrity of data entry from the many contributing centers, and there are some missing or incomplete data fields. The NCDB includes overall survival data but does not have information on disease-specific survival or locoregional control. Although to our knowledge, this is the largest analysis of oral mucosal melanoma, it is nevertheless a rare disease and the sample size is limited. The NCDB does not report specific data regarding chemotherapy and immunotherapy agents used during treatment. As new agents are being approved for the treatment of melanoma, their effect on MM will need to be elucidated in the setting of clinical trials. While neck dissection was a reported variable, the timing of neck dissection and relation to additional therapy was not reported.

CONCLUSIONS

This study analyzed the largest cohort of patients with mucosal melanoma of the oral cavity. Advanced age, male sex, and African American race were independently associated with worse survival outcomes. Treatment modality did not impact survival. For oral cavity mucosal melanoma, the rate of occult nodal positivity is 45.4%. While elective neck dissection did not improve survival, the finding of pathologically positive lymph nodes was associated with worse survival outcomes. Elective lymph node dissections may serve a prognostic role and help select patients for additional adjuvant treatments, despite the lack of mortality benefit at this time.

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