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ORIGINAL REPORT

Metastatic Lymph Node Burden and Survival in Oral Cavity Cancer

Allen S. Ho, Sungjin Kim, Mourad Tighiouart, Cynthia Gudino, Alain Mita, Kevin S. Scher, Anna Laury, Ravi Prasad, Stephen L. Shiao, Jennifer E. Van Eyk, and Zachary S. Zumsteg

Author affiliations and support information (if applicable) appear at the end of this article.

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Corresponding author: Allen S. Ho, MD, Department of Surgery, Cedars-Sinai Medical Center, 8635 West Third St, Suite 590W, Los Angeles, CA 90048; e-mail: allen.ho@cshs.org.

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ABSTRACT

Purpose
Current staging systems for oral cavity cancers incorporate lymph node (LN) size and laterality, but place less weight on the total number of positive metastatic nodes. We investigated the independent impact of numerical metastatic LN burden on survival.

Methods
Adult patients with oral cavity squamous cell carcinoma undergoing upfront surgical resection for curative intent were identified in the National Cancer Data Base between 2004 and 2013. A neck dissection of a minimum of 10 LNs was required. Multivariable models were constructed to assess the association between the number of metastatic LNs and survival, adjusting for factors such as nodal size, laterality, extranodal extension, margin status, and adjuvant treatment.

Results
Overall, 14,554 patients met inclusion criteria (7,906 N0 patients; 6,648 node-positive patients). Mortality risk escalated continuously with increasing number of metastatic nodes without plateau, with the effect most pronounced with up to four LNs (HR, 1.34; 95% CI, 1.29 to 1.39; $P < .001$). Extranodal extension (HR, 1.41; 95% CI, 1.20 to 1.65; $P < .001$) and lower neck involvement (HR, 1.16; 95% CI, 1.06 to 1.27; $P < .001$) also predicted increased mortality. Increasing number of nodes examined was associated with improved survival, plateauing at 35 LNs (HR, 0.98; 95% CI, 0.98 to 0.99; $P < .001$). In multivariable models accounting for the number of metastatic nodes, contralateral LN involvement (N2c status) and LN size were not associated with mortality. A novel nodal staging system derived by recursive partitioning analysis exhibited greater concordance than the American Joint Committee on Cancer (8th edition) system.

Conclusion
The number of metastatic nodes is a critical predictor of oral cavity cancer mortality, eclipsing other features such as LN size and contralaterality in prognostic value. More robust incorporation of numerical metastatic LN burden may augment staging and better inform adjuvant treatment decisions.

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INTRODUCTION

Regional neck metastasis represents an ominous prognostic factor in head and neck squamous cell carcinoma (HNSCC). The presence of just one metastatic lymph node (LN) commits patients to an advanced-stage disease category and has been shown to confer up to a 50% decrease in overall survival (OS).[1] The American Joint Committee on Cancer (AJCC) staging system classically incorporates numerous factors to account for nodal disease, including size, laterality, and number of malignant nodes. Recent changes also factor in extranodal extension (ENE), also known as extracapsular spread.[2]

The influence of biologic heterogeneity is increasingly recognized, with head and neck staging systems evolving to better approximate the clinical behavior of unique subsites. Both nasopharyngeal and human papillomavirus–positive oropharyngeal carcinoma staging systems highlight changes that reflect their distinct pathogenic underpinnings. By comparison, nodal staging for HNSCC sites more associated with tobacco- and alcohol-mediated carcinogenesis remains broad in scope: N2b status encompasses any number of ipsilateral nodes greater than one, whereas N3 status includes all nodes greater than 6 cm. This area deserves further study, given that it may underperform in certain aspects. For instance, patients with 10 ipsilateral metastatic nodes

ASSOCIATED CONTENT

Appendix
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empirically fare much worse than those with two, yet remarkably, they are staged the same. Nodal staging also remains generalized for oral cavity, larynx, and hypopharynx cancers, which arguably involve disparate prognoses and management.

Recent studies in mucosal head and neck cancers have suggested that the number of positive nodes or the number of nodes examined may convey a better measure of prognosis.[3-6] Given the need for more precise staging metrics and treatment stratification, we investigated the impact of quantitative metastatic nodal burden in a large population of patients with oral cavity cancer. We focused on oral cavity cancers because of their surgical treatment paradigm with more complete pathologic nodal data.

METHODS

Data Source

Data were abstracted from the National Cancer Data Base (NCDB), a tumor registry maintained by the American Cancer Society and the Commission on Cancer of the American College of Surgeons. The NCDB captures data from more than 1,500 hospitals for approximately 70% of all patients with cancer treated in the United States. All current NCDB head and neck participant user files were investigated, covering patients treated from 2004 to 2013. This study was deemed exempt by the Cedars-Sinai Medical Center institutional review board.

Patients

All adult patients $\geq$ 18 years old undergoing upfront surgical resection that included neck dissection for primary oral cavity squamous cell carcinoma (International Classification of Diseases, 9th revision, clinical modification, 0-3 codes 8050-8084) for curative intent were eligible. Specific subsites included oral tongue (C02.0-C02.3), upper/lower gum (C03.0-C03.9), floor of mouth (C04.0-C04.9), hard palate (C05.0), and other parts of the mouth (eg, buccal mucosa, retromolar trigone; C06.0-C06.9). Ambiguous or overlapping sites that could potentially be oropharyngeal in origin (ie, C02.8-C02.9 for tongue/base of tongue, C05.8-C05.9 for hard palate/soft palate) were excluded.

Patients with incomplete staging, treatment, or follow-up data were excluded. Patients with clinical or pathologic distant metastasis were eliminated. Patients with fewer than 10 LNs examined were also omitted to filter out excisional LN biopsies and censure substandard neck dissections that might have artificially undermined survival.

Statistical Analysis

Missing data patterns for the variables with missing values (ie, race, insurance, income, AJCC (7th edition) N classification, LN size, lower LN involvement, ENE, margins, and contralateral LN involvement) were examined using the method proposed by Little.[7] Missing rates were 24.2% for ENE, 11.2% for LN size, and 1.2% to 5.5% for other variables. The data were found to be not missing completely at random. To reduce the chance of bias from missing data, missing values were imputed using fully conditional specification implemented by the multivariable imputation by chained equations algorithm under the missing at random assumption.[8,9] We generated 15 complete data sets, which were analyzed separately with results combined using the formula given in Rubin.[10]

The primary outcome was OS calculated from diagnosis to the date of death or censored at last follow-up. Baseline characteristics in patients with AJCC N0 classification versus N-positive classification were compared with Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables. Median follow-up was calculated using the reverse Kaplan-Meier method.[11] Survival functions were estimated by the Kaplan-Meier method and compared using a log-rank test.[12] Univariable and multivariable survival analyses were carried out using a Cox proportional hazards model.[13] Multivariable analyses were performed using a stepwise variable selection procedure on the basis of Akaike information criterion (AIC).[14] Final multivariable models were returned by the lowest AIC value. The proportional hazards assumption was assessed graphically and analytically with scaled Schoenfeld residuals.[15] Violation of the proportional hazards assumption was addressed by use of a stratified Cox regression model.

The number of positive metastatic LNs and number of LNs examined were modeled using a restricted cubic spline function allowing for their nonlinear association with OS. The optimal number of knots was chosen based on the lowest AIC. For positive metastatic LNs, three knots were placed at one, two, and seven positive metastatic LNs corresponding to the 55th, 75th, and 95th percentiles, respectively, because of their right-skewed distribution. For the number of LNs examined, three knots were placed at 14, 28, and 57 LNs corresponding to default quantiles for three knots, 10th, 50th, and 90th percentiles, respectively.[16] Estimated associations were illustrated with smoothed restricted cubic spline plots of the natural logarithm of adjusted hazard ratios (HRs) versus the number of positive metastatic LNs and number of LNs examined, with 0 and 10 as the reference levels, respectively. HRs were estimated with Cox proportional hazards models stratified on postoperative radiation after adjusting for age, gender, race, insurance status, income, Charlson-Deyo comorbidity index, T classification, number of positive LNs with three knots, number of LNs examined with three knots, lower neck (level 4-5) LN involvement, ENE, margins, and postoperative chemotherapy. Change points in the number of positive metastatic LNs and number of LNs examined were further estimated with a piecewise linear regression model.[17]

A new N classification system was devised via recursive partitioning analysis (RPA)[18,19] using independent nodal predictors of mortality (ie, number of positive LNs [continuous], ENE, and lower LN involvement) in patients with a determinable AJCC (8th edition) stage. A conditional inference tree was estimated by the optimized binary recursive partitioning on the basis of a permutation test with a quadratic form of the standardized log-rank statistic with Bonferroni-adjusted P values for multiple comparisons. The performance of the multivariable models with the proposed N classification system derived from RPA and AJCC (8th edition) N classification were assessed with c-indices.[16] Internal validation was performed by estimating and correcting possible optimism in c-indices using the bootstrap method with 1,000 replicates.[16,20]

Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) and R package (Version 3.3.2; *mice*, *rms*, *survival*, *SiZer, party* libraries),[21] with two-sided tests and a significance level of .05.

RESULTS

Patient Cohort

Of 85,786 eligible patients with oral cavity cancer, 14,554 met inclusion criteria (Appendix Fig A1; Appendix Table A1, online only). Median OS was 68.3 months (95% CI, 64.4 to 71.7), with a median follow-up of 46.5 months (95% CI, 45.7 to 47.3). The mean number of LNs examined was 32.1 (standard deviation $\pm$ 17.4). Among patients with node-positive disease with known data, the mean number of identified positive metastatic nodes was 3.3 (standard deviation $\pm$ 4.3), 17.2% had lower neck (level 4-5) involvement, 45.2% demonstrated ENE, and 13.3% harbored contralateral nodal involvement.

Number of Positive Metastatic LNs

In univariable analysis, the number of metastatic LNs strongly predicted for worsening OS; $P < .001$; Table 1). The estimated 5-year OS rates were 65.3%, 49.9%, 41.1%, 29.7%, 27.5%, 18.5%, and 9.7% for those with zero, one, two, three, four to six, seven to

Table 1. Univariable and Multivariable Analyses of Overall Survival in Oral Cavity Cancer

Variable	Univariable			Multivariable	
	No.	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
No. of positive metastatic LNs*	14,554	—	< .001	—	< .001
Age	14,554	1.02 (1.02 to 1.03)	< .001	1.02 (1.02 to 1.02)	< .001
Gender					
Male	8,992	1 (reference)		1 (reference)	
Female	5,562	0.96 (0.91 to 1.02)	.176	0.94 (0.89 to 0.99)	.034
Race†			< .001‡		.081‡
White	12,958	1 (reference)		1 (reference)	
Black	1,005	1.25 (1.14 to 1.38)	< .001	1.04 (0.95 to 1.15)	.380
Other	591	0.81 (0.70 to 0.94)	.006	0.87 (0.75 to 1.00)	.057
Facility type					
Nonacademic	4,888	1 (reference)			
Academic	9,666	0.96 (0.91 to 1.01)	.152	§	
Facility volume					
Low, ≤ 75th percentile	11,346	1 (reference)			
High, > 75th percentile	3,208	0.98 (0.92 to 1.04)	.535	§	
Region			.085‡		
East	2,673	1 (reference)			
South	5,480	1.05 (0.97 to 1.13)	.211	§	
Midwest	4,213	0.97 (0.89 to 1.04)	.385		
West	2,188	0.92 (0.84 to 1.00)	.062		
Insurance status†			< .001‡		< .001‡
Private	5,848	1 (reference)		1 (reference)	
Uninsured	822	1.29 (1.14 to 1.46)	< .001	1.17 (1.03 to 1.32)	.016
Medicaid	1,472	1.71 (1.56 to 1.87)	< .001	1.45 (1.32 to 1.59)	< .001
Medicare	6,166	1.83 (1.72 to 1.94)	< .001	1.25 (1.16 to 1.35)	< .001
Other government	246	1.55 (1.27 to 1.91)	< .001	1.19 (0.97 to 1.46)	.102
Income ($)†					
≤ 46,000	9,138	1 (reference)		1 (reference)	
> 46,000	5,416	0.83 (0.78 to 0.88)	< .001	0.92 (0.87 to 0.98)	.006
Charlson-Deyo comorbidity index			< .001‡		< .001‡
0	10,943	1 (reference)		1 (reference)	
1	2,824	1.26 (1.18 to 1.34)	< .001	1.15 (1.08 to 1.22)	< .001
≥ 2	787	1.75 (1.59 to 1.93)	< .001	1.56 (1.41 to 1.73)	< .001
AJCC (7th edition) T classification			< .001‡		< .001‡
T1	4,316	1 (reference)		1 (reference)	
T2	4,176	1.69 (1.57 to 1.82)	< .001	1.50 (1.39 to 1.62)	< .001
T3	1,255	2.66 (2.41 to 2.93)	< .001	2.21 (2.00 to 2.45)	< .001
T4	4,807	2.75 (2.56 to 2.95)	< .001	2.14 (1.98 to 2.31)	< .001
No. of LNs examined†	14,554	—	.004	—	< .001
LN size (cm)†			< .001‡		
0.0-1.0	9,659	1 (reference)			
1.1-2.0	2,230	2.18 (2.03 to 2.34)	< .001	§	
2.1-3.0	1,385	2.14 (1.96 to 2.34)	< .001		
3.1-4.0	508	2.55 (2.25 to 2.89)	< .001		
4.1-5.0	213	2.33 (1.91 to 2.85)	< .001		
5.1-6.0	411	2.72 (2.38 to 3.11)	< .001		
> 6.0	148	2.35 (1.84 to 3.01)	< .001		
Lower LN (level 4-5) involvement†					
No	13,401	1 (reference)		1 (reference)	
Yes	1,153	2.50 (2.31 to 2.70)	< .001	1.16 (1.06 to 1.27)	< .001
Contralateral (N2c) LN involvement†					
No	13,666	1 (reference)			
Yes	888	2.42 (2.22 to 2.64)	< .001	§	
ENE†					
ENE−	11,552	1 (reference)		1 (reference)	
ENE+	3,002	2.62 (2.37 to 2.90)	< .001	1.41 (1.20 to 1.65)	< .001
Margins†					
Negative	12,643	1 (reference)		1 (reference)	
Positive	1,911	1.80 (1.68 to 1.92)	< .001	1.38 (1.28 to 1.48)	< .001
Postoperative radiation‖					
No	7,003	1 (reference)			
Yes	7,551	1.37 (1.30 to 1.44)	< .001	‖	

(continued on following page)

Table 1. Univariable and Multivariable Analyses of Overall Survival in Oral Cavity Cancer (continued)

Variable	No.	Univariable Hazard Ratio (95% CI)	Univariable *P*	Multivariable Hazard Ratio (95% CI)	Multivariable *P*
Postoperative chemotherapy					
No	10,937	1 (reference)		1 (reference)	
Yes	3,617	1.45 (1.37 to 1.53)	< .001	0.80 (0.74 to 0.86)	< .001
Year of diagnosis	14,554	0.99 (0.98 to 1.01)	.255	§	

Abbreviations: AJCC, American Joint Committee on Cancer; ENE, extranodal extension; LN, lymph node.
*No. of positive metastatic LNs and No. of LNs examined were modeled using restricted cubic spline functions with three knots at one, two, and seven, and 14, 28, and 57, respectively.
†Missing data were imputed by multiple imputation.
‡Overall *P* value for categorical variables with more than two levels.
§Variables dropped out of the model.
||Multivariable model was stratified on postoperative radiation because of nonproportional hazards.

nine, and 10 or more metastatic LNs, respectively (Fig 1A). A similar impact of the number of metastatic LNs was seen in N2b (Fig 1B) and N2c (Fig 1C) subgroups. After adjustment for potential confounders in a multivariable model, the number of positive metastatic LNs remained strongly associated with OS ($P < .001$). Using a three-knot restricted cubic spline function, mortality risk escalated continuously with increasing number of metastatic nodes without plateau (Fig 2A). Given the nonlinear relationship between mortality and the number of metastatic LNs, a change point at four metastatic LNs was identified. The HR per metastatic LN increased steeply up to four metastatic LNs (HR, 1.34; 95% CI, 1.29 to 1.39; $P < .001$). Beyond this, the risk of death continued to increase with each additional metastatic LN, albeit more slowly (HR, 1.03; 95% CI, 1.02 to 1.04; $P < .001$; Table 2).

Number of LNs Examined

An increasing number of LNs examined was associated with improved OS in multivariable analyses ($P < .001$). As with the number of metastatic LNs, number of LNs examined exhibited a nonlinear relationship with mortality. A multivariable model with a three-knot restricted cubic spline function showed that the risk of death decreased continuously with each additional node harvested (with a baseline of 10 LNs examined) up to a change point of 35 LNs (HR, 0.98; 95% CI, 0.98 to 0.99; $P < .001$; Fig 2B). However, no significant improvement in survival was appreciated beyond 35 LNs (HR, 1.00; 95% CI, 0.99 to 1.00; $P = .126$; Table 2). Because stage I to II patients (T1-2N0) are often treated with surgery alone, they were separately compared with stage III to IV patients (T1-2N1-3/T3-4N0-3), who are often treated with surgery and adjuvant therapy. Subset analysis found similar change points for number of LNs dissected and magnitude of benefit on survival (Appendix Fig A2).

Metastatic LN Features

After adjustment for covariables, including positive metastatic LNs and number of total nodes examined, both ENE (HR, 1.41; 95% CI, 1.20 to 1.65; $P < .001$) and lower neck (level 4-5) involvement (HR, 1.16; 95% CI, 1.06 to 1.27; $P < .001$) were independently associated with mortality risk. However, LN size and contralateral LN involvement (N2c disease) had no significant impact on survival (Table 1).

Proposed Nodal Staging System

RPA using nodal covariables independently associated with survival generated a novel schema comprising metastatic nodal number and ENE (Fig 3). Kaplan-Meier estimates of the schema and AJCC (8th edition) system are illustrated in Figure 4. Lower neck (level 4-5) involvement dropped out of the model relative to other covariables. Patients with one positive LN who were ENE positive and patients with two positive LNs clustered separately in the RPA analysis, but were grouped together because of similar survival rates (Appendix Table A2, online only). The most advanced nodal category (N3b) showed HRs of 6.54 (95% CI, 5.43 to 7.89) and 3.68 (95% CI, 3.25 to 4.16) for the proposed system and AJCC (8th edition) system, respectively (Appendix Table A3, online only). The optimism-corrected c-index for the proposed system showed improvement in predictive ability (0.706; 95% CI, 0.694 to 0.718) over the AJCC (8th edition) system (0.703; 95% CI, 0.691 to 0.715).

DISCUSSION

In this study, we demonstrated that the absolute number of metastatic LNs is a critical predictor of oral cavity cancer mortality, surpassing other nodal covariables, including size, contralaterality, ENE, and lower neck involvement. Using a continuous multivariable regression model, we found that successive positive nodes increased the risk of death without plateau. Each positive LN conferred an added 34% increased risk of death through four positive nodes, whereas each successive positive node beyond this increased relative mortality by 3% (Table 2). In addition, we found that the number of positive LNs significantly affected prognosis among N2b and N2c cohorts (Fig 1B and 1C), suggesting that such conventional subgroups themselves comprise a wide spectrum of outcomes.

These results build on previous studies assessing metastatic LN number on head and neck cancer outcome.[3,22] However, our study design contains several meaningful differences, including adjustment for covariables that are both nodal (eg, LN size, ENE, lower neck involvement) and non-nodal (eg, adjuvant chemoradiation, margin status). In contrast to prior reports, we excluded oropharyngeal malignancies because of their

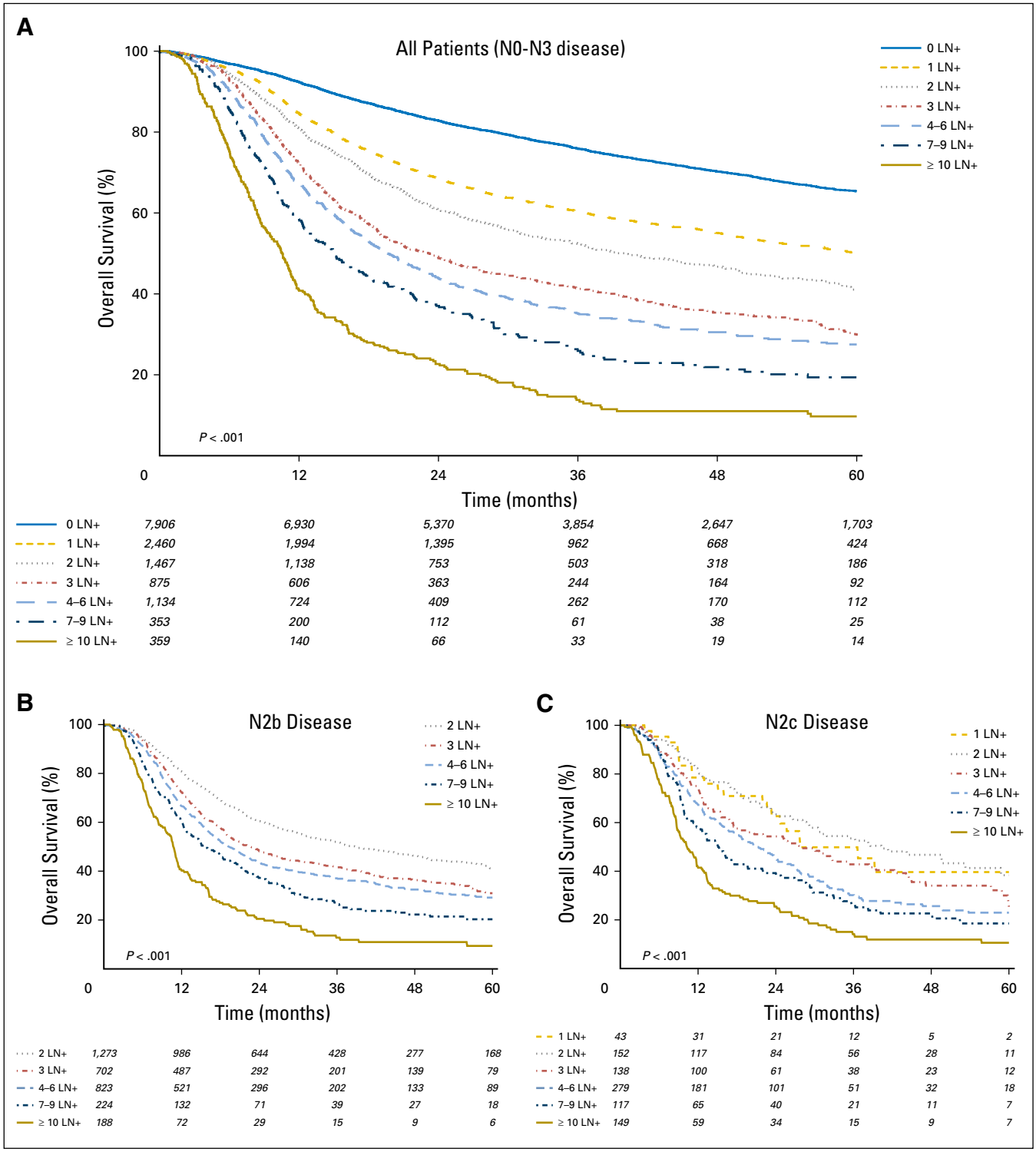

Fig 1. Kaplan-Meier estimates of overall survival in oral cavity cancer, stratified by number of positive metastatic lymph nodes in (A) all patients, (B) patients with N2b disease, and (C) patients with N2c disease. LN+, lymph node–positive;

fundamentally different relationship between nodal burden and prognosis,[23,24] now reflected in a separate AJCC nodal staging system for human papillomavirus–positive oropharyngeal cancer.[2] Our analysis focused on the HNSCC sites (eg, tongue, buccal mucosa, hard palate), for which surgery, and specifically neck dissection, is the predominant treatment modality and depicts a granular representation of each metastatic node's added impact on survival.

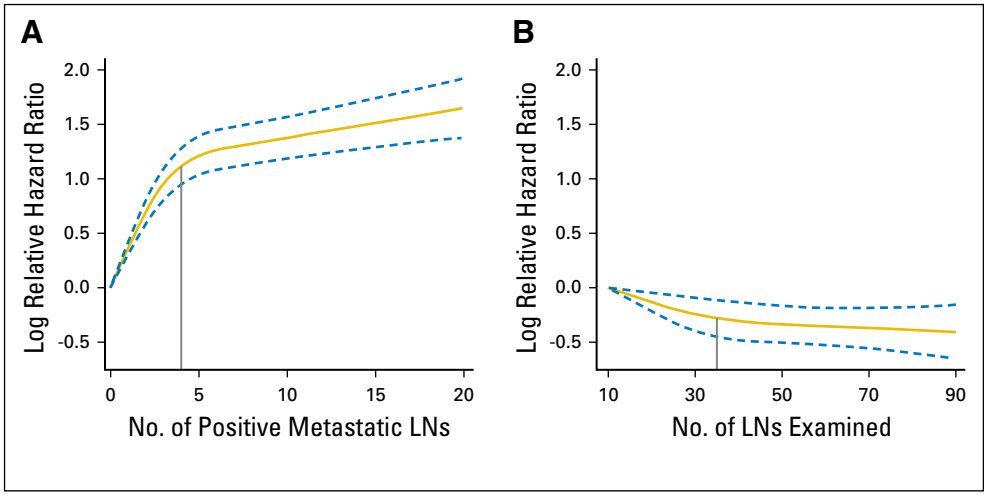

Fig 2. Adjusted hazard ratio (HR) with increasing number of positive metastatic lymph nodes (LNs) and LNs examined in oral cavity cancer. Blue dashed lines represent estimated 95% CIs of the predicted HRs. (A) Gold solid line represents smoothed restricted cubic spline plot of the natural logarithm of predicted adjusted HR versus the number of positive metastatic LNs, with a reference value of 0. Gray vertical line represents the estimated change point at four positive LNs. (B). Gold solid line represents smoothed restricted cubic spline plot of the natural logarithm of predicted adjusted HR versus the number of LNs examined, with a reference value of 10. Gray vertical line represents the estimated change point at 35 examined LNs.

A related finding is that when accounting for the number of cancerous LNs, classic prognostic factors used by AJCC staging (ie, LN size and contralaterality) were no longer independent predictors of survival, suggesting that they may be surrogates for overall nodal burden. This result supports a prior multicenter study demonstrating similar outcomes in patients with N2b and N2c disease, when accounting for the fact that patients with N2c disease tend to have more metastatic nodes than do patients with N2b disease.[25] Conversely, in our analysis, ENE and lower neck involvement were independently associated with worse survival. Both elements have been linked to distant metastasis in head and neck cancer[26-29] and are incorporated into HNSCC and nasopharyngeal cancer staging systems, respectively.

We proposed a novel nodal staging schema (Appendix Table A2) using an agnostic recursive partitioning analysis algorithm, illustrating the importance of pure metastatic LN number in prognosis and management. ENE was retained in this schema, but only for patients with a single positive LN (Fig 3). The predictive power of the proposed system was improved over that of the AJCC (8th edition) staging system, although the absolute difference in c-indices was relatively modest. This may be because conventional nodal factors in the AJCC (8th edition) system (ie, LN size and contralaterality) serve as proxies for absolute metastatic LN number.

There are several advantages of the proposed schema beyond mildly improved prediction of survival. First, it is based on factors that independently drive outcomes, rather than surrogates. It also represents a concise stratification, relying almost entirely on a single variable. All the N categories in the proposed system identify patient groups with distinct, nonoverlapping prognoses (Fig 4). The proposed system furthermore partitions risk over a greater spectrum: patients classified as N3b ($\geq$ 8 LN+) in the proposed system have 6.5 times the risk of death as patients classified as N0 (Appendix Table A3), with 3-year OS of 14.5%. In comparison, the HR and 3-year OS for AJCC (8th edition) N3b patients is 3.7 and 35.3%, respectively. Given the poor outcomes in patients with a high metastatic LN burden ($\geq$ 8 positive LNs), these patients may derive greater benefit from intensification of adjuvant therapy such as concomitant chemoradiation. They may also be excellent candidates for novel therapeutic regimens, such as the addition of immunologic checkpoint inhibitors to standard chemoradiation. Collectively, the proposed system encapsulates a parsimonious model that exhibits greater discrimination at the high end of patient risk.

Table 2. Summary of Hazard Ratios for No. of Positive Metastatic LNs and No. of LNs Examined in Oral Cavity Cancer, Stratified by Change Point

	Univariable		Multivariable	
Variable	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
No. of positive metastatic LNs*				
> 4	1.03 (1.02 to 1.04)	< .001	1.03 (1.02 to 1.04)	< .001
≤ 4	1.41 (1.38 to 1.44)	< .001	1.34 (1.29 to 1.39)	< .001
No. of LN examined†				
> 35	1.00 (1.00 to 1.01)	.145	1.00 (0.99 to 1.00)	.126
≤ 35	0.99 (0.99 to 1.00)	.004	0.98 (0.98 to 0.99)	< .001

NOTE. Hazard ratio is expressed as 1-unit increment. Missing data were imputed by multiple imputation.
Abbreviation: LN, lymph node.
*Multivariable models were stratified on postoperative radiation and adjusted for age, gender, tumor site, facility volume, insurance status, income, Charlson-Deyo comorbidity index, American Joint Committee on Cancer T classification, No. of LNs examined with three knots at 14, 28, and 57 LNs corresponding to 10th, 50th, and 90th percentiles, respectively; lower LN (Level 4-5) involvement; extranodal extension; margins; and postoperative chemotherapy.
†Multivariable models were stratified on postoperative radiation and adjusted for age, gender, tumor site, facility volume, insurance status, income, Charlson-Deyo comorbidity index, American Joint Committee on Cancer T classification, No. of positive LNs with three knots at 1, 2, and 7 LNs corresponding to 55th, 75th and 95th percentiles, respectively; lower LN (Level 4-5) involvement; extranodal extension; margins; and postoperative chemotherapy.

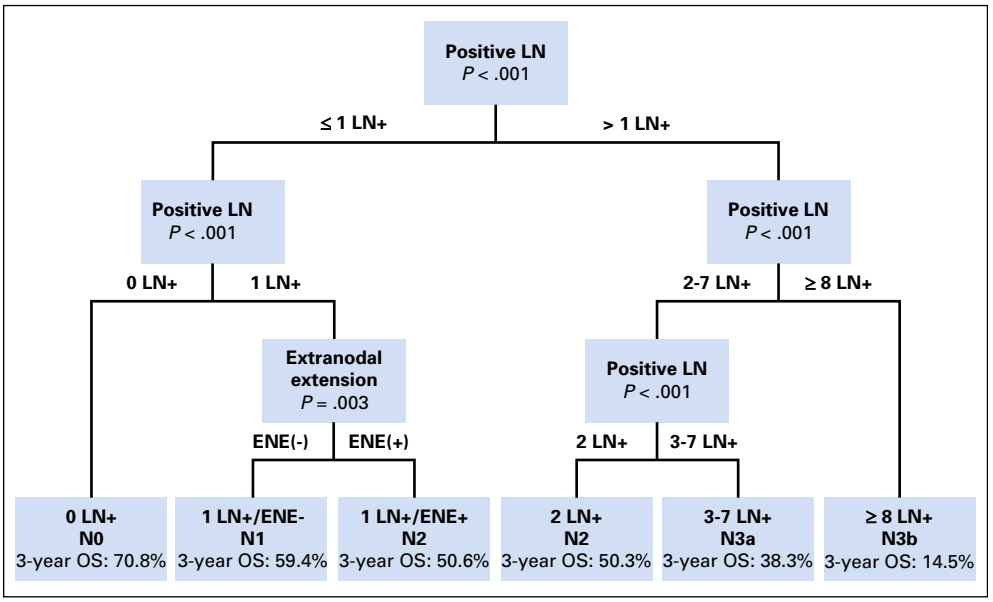

Fig 3. Novel proposed nodal staging system developed by recursive partitioning analysis in patients with oral cavity cancer with determinable American Joint Committee on Cancer (8th edition) stage. Bonferroni-adjusted *P* values are given in the inner nodes, and Kaplan-Meier estimates for 3-year overall survival (OS) are displayed in the terminal nodes. Given similar OS rates, one LN+/ENE+ and two LN+ categories were merged to N2 status. ENE–, extranodal extension–negative; ENE+, extranodal extension–positive; LN+, lymph node–positive; OS, overall survival.

A final key finding is that the number of LNs examined (benign or malignant) is associated with improved survival and that this effect is much less pronounced than the impact of number of cancerous LNs. Specifically, the relative risk of death was reduced by 2% for each additional LN examined, up to 35 LNs, with no significant improvement in survival beyond this number (Fig 2B). A growing body of literature supports the number of LNs examined as an important physician-modifiable determinant of outcome in head and neck cancer,[4-6,30,31] with most investigators choosing 18 nodes examined as a threshold. There are several factors that likely contribute to these different cut points, including our focus on oral cavity cancer and the requirement of at least 10 LN examined, which excludes biopsies and minor neck procedures. Our results suggest that although examining 18 LNs is associated with decreased mortality risk, survival continues to improve with more extensive neck dissections that yield nearly twice this number.

Although the exact reason why an increasing number of LNs examined improves survival is unclear, plausible hypotheses exist. First, a more thorough neck dissection may be therapeutic, increasing the probability of eliminating micrometastatic nodal deposits. Second, higher nodal yield may be a measure of surgeon acumen. Finally, the number of LNs reported in part depends on

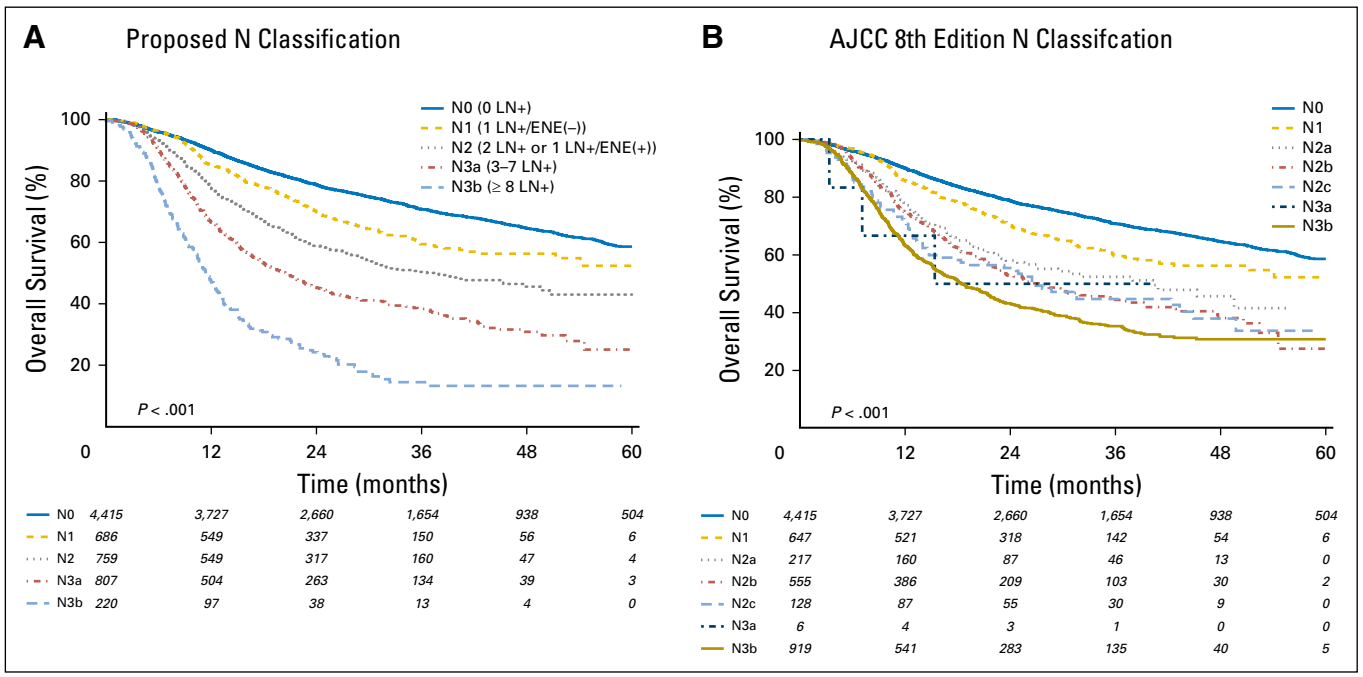

Fig 4. Kaplan-Meier estimates for (A) proposed and (B) AJCC (8th edition) N classification systems in oral cavity cancer. AJCC, American Joint Committee on Cancer; ENE–, extranodal extension–negative; ENE+, extranodal extension–positive; LN+, lymph node–positive.

the diligence of the pathology department and may be an indirect gauge of institutional expertise.[32,33] Together with work from other solid malignancy sites (eg, colorectal, breast, gastric, bladder),[34-37] our data support the notion that surgeons and pathologists should strive for thorough compartmental dissection and pathologic evaluation. Neck dissection may deserve a larger role for diagnostic, therapeutic, and staging purposes.[38,39]

Several caveats to this analysis require mention, including its retrospective nature and absence of disease-specific survival metrics. Although the data are broad in scope, there is a lack of information on certain prognostic features, including smoking status, alcohol consumption, and perineural invasion. Factors such as chemotherapy regimen, bilateral versus ipsilateral neck dissection, and radiation quality are also not assessable in the NCDB. Our results should be validated in independent data sets to determine whether the survival detriment is due to locoregional or distant relapse, which would have implications for when to use adjuvant therapy. Finally, it is unclear whether our results can be translated to clinically staged patients, given that clinical and radiographic identification of positive LN number is often less exact than pathologic LN assessment.[40,41] Nevertheless, our results represent the most compelling evidence to date of the importance of metastatic LN number in oral cavity squamous cell carcinoma.

In summary, we established that metastatic nodal burden is a central predictor of mortality in patients with oral cavity cancer, with each additional metastatic LN conferring escalated risk of mortality. Classic factors such as LN size and contralateral nodal metastasis lack independent prognostic value when accounting for number of metastatic nodes. Our data suggest that deeper integration of quantitative nodal burden could better calibrate the wide spectrum of risk that staging systems presently capture. Such adjustments would be a promising means to more effectively articulate patient prognosis, tailor clinical trial design, and ultimately advance clinical decision making.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Allen S. Ho, Zachary S. Zumsteg
Collection and assembly of data: Allen S. Ho, Zachary S. Zumsteg
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Affiliations

All authors: Cedars-Sinai Medical Center, Los Angeles, CA.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Metastatic Lymph Node Burden and Survival in Oral Cavity Cancer

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Allen S. Ho
No relationship to disclose

Sungjin Kim
No relationship to disclose

Mourad Tighiouart
No relationship to disclose

Cynthia Gudino
No relationship to disclose

Alain Mita
Speakers' Bureau: Genentech

Kevin S. Scher
No relationship to disclose

Anna Laury
No relationship to disclose

Ravi Prasad
No relationship to disclose

Stephen L. Shiao
No relationship to disclose

Jennifer E. Van Eyk
No relationship to disclose

Zachary S. Zumsteg
Leadership: Scripps Proton Therapy Center
Consulting or Advisory Role: EMD Serono

Appendix

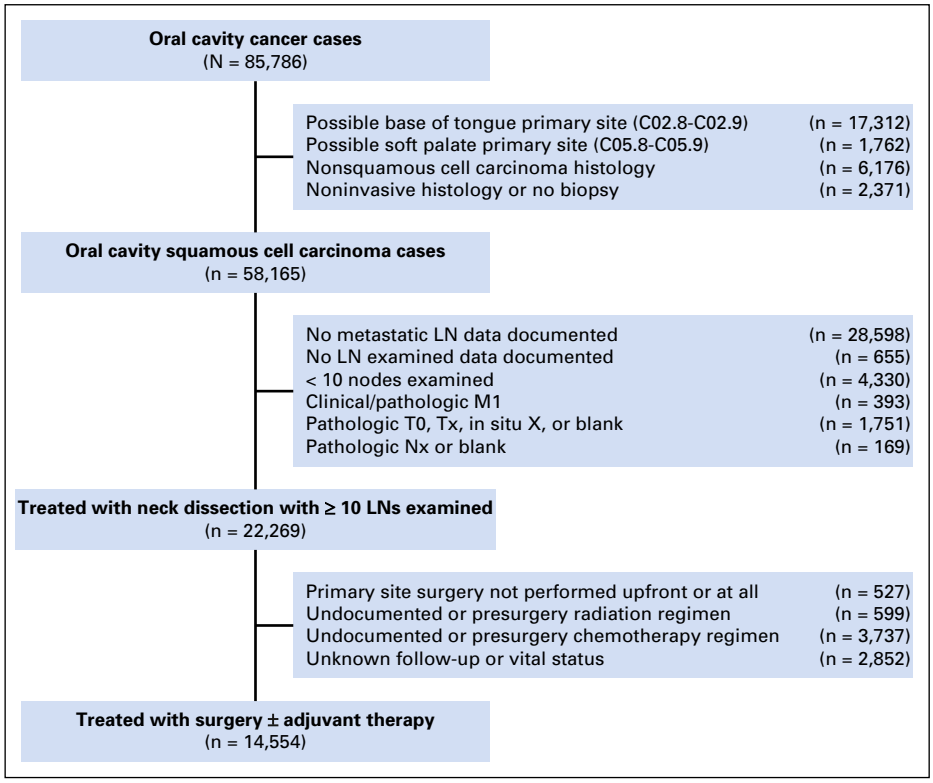

Fig A1. CONSORT diagram. LN, lymph node.

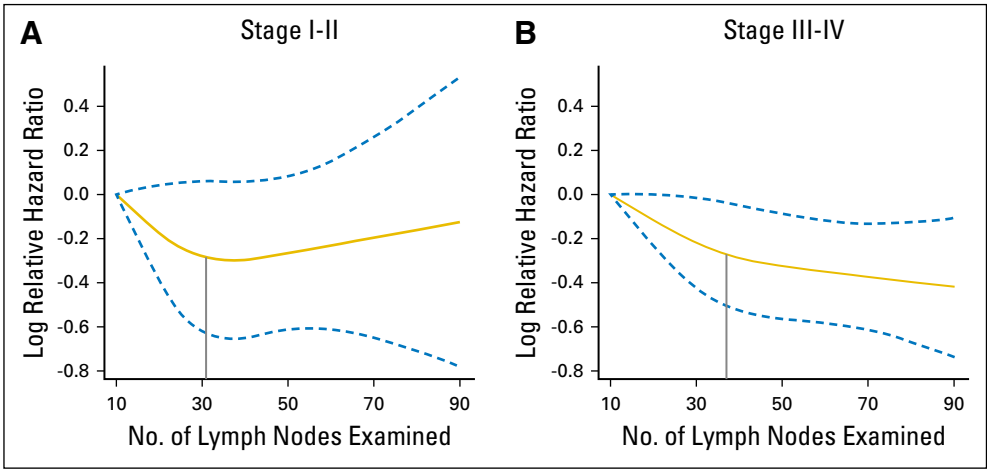

Fig A2. Adjusted hazard ratio (HR) with increasing number of lymph nodes (LNs) examined in (A) stage I to II (T1-2N0) compared with (B) stage III to IV (T1-2N1-3/T3-4N0-3) oral cavity cancer. Gold solid lines represent smoothed restricted cubic spline plots of the natural logarithm of predicted adjusted HR versus the number of LNs examined, with a reference value of 10. Gray vertical lines represent the estimated change point of (A) 31 LNs examined and (B) 37 LNs examined. Three knots for the number of LNs examined were placed at (A) 13, 25, and 49 and (B) 14, 30, and 60, each corresponding to 10th, 50th, and 90th percentiles, respectively. Blue dashed lines represent estimated 95% CIs of the predicted HRs.

Table A1. Baseline Patient Demographics Stratified by Nodal Status

Variable	All Patients (N = 14,554)	N0 (n = 7,906)	N+ (n = 6,648)	*P*
Age (years)				< .001
Median (IQR)	62 (53-71)	62 (53-71)	61 (53-71)	
Mean (± SD)	62.0 (± 12.8)	62.5 (± 13.0)	61.5 (± 12.6)	
Gender				
Male	8992 (61.8)	4767 (60.3)	4225 (63.6)	< .001
Female	5562 (38.2)	3139 (39.7)	2423 (36.5)	
Race*				
Other	591 (4.1)	311 (3.9)	280 (4.2)	< .001
White	12958 (89.0)	7155 (90.5)	5803 (87.3)	
Black	1005 (6.9)	440 (5.6)	565 (8.5)	
Facility type				
Nonacademic	4888 (33.6)	2551 (32.3)	2337 (35.2)	< .001
Academic	9666 (66.4)	5355 (67.7)	4311 (64.9)	
Facility volume				
Low ≤ 75th percentile	12626 (86.8)	6809 (86.1)	5817 (87.5)	.015
High > 75th percentile	1928 (13.3)	1097 (13.9)	831 (12.5)	
Region				
East	2673 (18.4)	1439 (18.2)	1234 (18.6)	.590
Midwest	4213 (29.0)	2296 (29.0)	1917 (28.8)	
South	5480 (37.7)	2956 (37.4)	2524 (38.0)	
West	2188 (15.0)	1215 (15.4)	973 (14.6)	
Insurance status*				
Private	5848 (40.2)	3274 (41.4)	2574 (38.7)	< .001
Medicaid	1472 (10.1)	649 (8.2)	823 (12.4)	
Medicare	6166 (42.3)	3450 (43.6)	2716 (40.8)	
Other government	246 (1.7)	113 (1.4)	134 (2.0)	
Uninsured	822 (5.7)	421 (5.3)	401 (6.0)	
Income ($)*				
≤ 46,000	9138 (62.8)	4831 (61.1)	4307 (64.8)	< .001
> 46,000	5416 (37.2)	3075 (38.9)	2341 (35.2)	
Charlson-Deyo comorbidity index				
0	10943 (75.2)	5891 (74.5)	5052 (76.0)	.041
1	2824 (19.4)	1594 (20.2)	1230 (18.5)	
≥ 2	787 (5.4)	421 (5.3)	366 (5.5)	
AJCC T classification (7th edition)				
T1	4316 (29.7)	3003 (38.0)	1313 (19.8)	< .001
T2	4176 (28.7)	2213 (28.0)	1963 (29.5)	
T3	1255 (8.6)	499 (6.3)	756 (11.4)	
T4	4807 (33.0)	2191 (27.7)	2616 (39.4)	
No. of positive metastatic LNs				< .001
Median (IQR)	0 (0-2)	0 (0-0)	2 (0-2)	
Mean (± SD)	1.5 (± 3.3)	0 (± 0)	3.3 (± 4.3)	
No, of LNs examined				< .001
Median (IQR)	28 (19-41)	26 (19-41)	30 (19-41)	
Mean (± SD)	32.1 (± 17.4)	29.9 (± 16.3)	34.7 (± 18.4)	
LN size (cm)*				
0.0-1.0	9659 (66.4)	7822 (98.9)	1837 (27.6)	< .001
1.1-2.0	2230 (15.3)	34 (0.4)	2196 (33.0)	
2.1-3.0	1385 (9.5)	21 (0.3)	1364 (20.5)	
3.1-4.0	508 (3.5)	7 (0.1)	501 (7.5)	
4.1-5.0	213 (1.5)	6 (0.1)	207 (3.1)	
5.1-6.0	411 (2.8)	1 (0.0)	409 (6.2)	
> 6.0	148 (1.0)	16 (0.2)	133 (2.0)	
Lower LN (level 4-5) involvement*				
No	13401 (92.1)	7897 (99.9)	5504 (82.8)	< .001
Yes	1153 (7.9)	9 (0.1)	1144 (17.2)	
ENE*				
ENE−	11552 (79.4)	7906 (100.0)	3646 (54.8)	< .001
ENE+	3002 (20.6)	0 (0.0)	3002 (45.2)	
Margins*				
Negative	12643 (86.9)	7167 (90.7)	5476 (82.4)	< .001
Positive	1911 (13.1)	739 (9.3)	1172 (17.6)	
Depth of invasion (mm)				
≤ 5	2956 (70.5)	1713 (72.9)	1243 (67.4)	< .001
5.1-10	549 (13.1)	313 (13.3)	236 (12.8)	
> 10	688 (16.4)	324 (13.8)	364 (19.8)	

(continued on following page)

Table A1. Baseline Patient Demographics Stratified by Nodal Status (continued)

Variable	All Patients (N = 14,554)	N0 (n = 7,906)	N+ (n = 6,648)	*P*
Postoperative radiation				
No	7003 (48.1)	5229 (66.1)	1774 (26.7)	< .001
Yes	7551 (51.9)	2677 (33.9)	4874 (73.3)	
Postoperative chemotherapy				
No	10937 (75.2)	7244 (91.6)	3693 (55.6)	< .001
Yes	3617 (24.9)	662 (8.4)	2955 (44.5)	
Contralateral (N2c) LN involvement*				
No	13666 (93.9)	7906 (100.0)	5760 (86.7)	< .001
Yes	888 (6.1)	0 (0.0)	888 (13.3)	
Year of diagnosis				.613
Median (IQR)	2010 (2008-2011)	2010 (2008-2011)	2010 (2008-2011)	
Mean (± SD)	2009.3 (± 2)	2009.3 (± 2)	2009.3 (± 2.0)	

Abbreviations: AJCC, American Joint Committee on Cancer; ENE, extranodal extension; IQR, interquartile ratio; LN, lymph node; N+, node-positive; SD, standard deviation.
*Missing data were imputed by multiple imputation.

Table A2. Comparison of New Proposed Nodal Staging System With AJCC (8th edition) System in Patients With Oral Cavity Cancer With Determinable AJCC (8th edition) Stage

Proposed N Classification System			AJCC (8th edition) N Classification System		
Category	Criteria	3-Year OS (%)	Category	Criteria	3-Year OS (%)
N0	0 LN+	70.8	N0	0 LN+	70.8
N1	1 LN+/ENE−	59.4	N1	1 ipsilateral LN+, ≤ 3 cm, and ENE−	59.6
N2	2 LN+ or 1 LN+/ENE+	50.4	N2a	1 ipsilateral or contralateral LN+, ≤ 3 cm, and ENE+; or 1 ipsilateral LN+ that is 3-6 cm and ENE−	52.4
			N2b	> 1 ipsilateral LN+, ≤ 6 cm, and ENE−	44.4
			N2c	> 1 bilateral or contralateral LN+, ≤ 6 cm, and ENE−	44.7
N3a	3-7 LN+	38.3	N3a	≥ 1 LN+, > 6 cm, and ENE−	50.0
N3b	≥ 8 LN+	14.5	N3b	1 ipsilateral LN+, > 3 cm, and ENE+; or > 1 ipsilateral, contralateral, or bilateral LN+, any with ENE+	35.3

Abbreviations: AJCC, American Joint Committee on Cancer; ENE, extranodal extension; LN, lymph node; OS, overall survival.

Table A3. Multivariable Analyses With Proposed N Classification System and AJCC (8th edition) N Classification System in Oral Cavity Cancer

Variable	Proposed N Classification		AJCC (8th edition) N Classification	
	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Proposed N classification		< .001*		
N0 (0 LN+)	1 (reference)		Not included	
N1 (1 LN+/ENE−	1.61 (1.39 to 1.85)	< .001		
N2 (2 LN+ or 1 LN+/ENE+)	2.43 (2.14 to 2.76)	< .001		
N3a (3-7 LN+)	3.51 (3.09 to 3.98)	< .001		
N3b (≥ 8 LN+)	6.54 (5.43 to 7.89)	< .001		
AJCC (8th edition) N classification				< .001*
N0	Not included		1 (reference)	
N1			1.59 (1.37 to 1.84)	< .001
N2a			2.27 (1.84 to 2.81)	< .001
N2b			2.70 (2.35 to 3.10)	< .001
N2c			2.91 (2.25 to 3.75)	< .001
N3a			2.04 (0.65 to 6.36)	.219
N3b			3.68 (3.25 to 4.16)	< .001
Age	1.02 (1.01 to 1.02)	< .001	1.02 (1.01 to 1.02)	< .001
Gender				
Male	1 (reference)			
Female	0.93 (0.86 to 1.01)	.090	†	
Race‡				
White				
Black	†		†	
Other				
Facility type				
Nonacademic				
Academic	†		†	
Facility volume				
Low, ≤ 75th percentile				
High, > 75th percentile	†		†	
Region				
East				
South	†		†	
Midwest				
West				
Insurance status‡		< .001*		< .001*
Private	1 (reference)		1 (reference)	
Uninsured	1.37 (1.14 to 1.65)	.001	1.35 (1.12 to 1.62)	.001
Medicaid	1.47 (1.28 to 1.69)	< .001	1.47 (1.28 to 1.69)	< .001
Medicare	1.27 (1.14 to 1.42)	< .001	1.30 (1.16 to 1.45)	< .001
Other government	1.05 (0.75 to 1.45)	.791	1.06 (0.76 to 1.48)	724
Income ($)‡				
≤ 46,000	1 (reference)		1 (reference)	
> 46,000	0.90 (0.82 to 0.98)	.012	0.90 (0.82 to 0.98)	.014
Charlson-Deyo comorbidity index		.001*		.001*
0	1 (reference)		1 (reference)	
1	1.07 (0.97 to 1.18)	.189	1.08 (0.98 to 1.19)	.131
≥ 2	1.59 (1.37 to 1.84)	< .001	1.58 (1.36 to 1.83)	< .001
AJCC (8th edition) T classification		< .001*		< .001*
T1	1 (reference)		1 (reference)	
T2	1.50 (1.09 to 2.06)	.013	1.54 (1.12 to 2.11)	.008
T3	2.06 (1.55 to 2.74)	< .001	2.12 (1.59 to 2.81)	< .001
T4	2.84 (2.14 to 3.77)	< .001	2.96 (2.23 to 3.92)	< .001
No. of LNs examined§	—	< .001	—	< .001
LN size (cm)‡				
0.0-1.0	†		Not included	
1.1-2.0				
2.1-3.0				
3.1-4.0				
4.1-5.0				
5.1-6.0				
> 6.0				
Lower LN (level 4-5) involvement‡				
No	1 (reference)		1 (reference)	
Yes	1.25 (1.08 to 1.46)	.004	1.46 (1.26 to 1.69)	< .001
Contralateral (N2c) LN involvement				
No				
Yes	†		Not included	

(continued on following page)

Table A3. Multivariable Analyses With Proposed N Classification System and AJCC (8th edition) N Classification System in Oral Cavity Cancer (continued)

Variable	Proposed N Classification		AJCC (8th edition) N Classification	
	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Margins‡				
Negative	1 (reference)		1 (reference)	
Positive	1.47 (1.32 to 1.62)	< .001	1.50 (1.35 to 1.66)	< .001
Postoperative radiation‖				
No				
Yes	‖		‖	
Postoperative chemotherapy				
No	1 (reference)		1 (reference)	
Yes	0.89 (0.79 to 0.99)	.028	0.89 (0.79 to 0.99)	.033
Year of diagnosis	†		†	
C-index (95% CI)	0.709 (0.697 to 0.721)		0.706 (0.694 to 0.718)	
Optimism-corrected c-index (95% CI)	0.706 (0.694 to 0.718)		0.703 (0.691 to 0.715)	

Abbreviations: LN, lymph node.
*Overall *P* value for categorical variables with more than two levels.
†Variables dropped out of the model.
‡Missing data were imputed by multiple imputation.
§No. of LNs examined was modeled using a restricted cubic spline function with three knots at 14, 29, and 59 LNs.
‖Multivariable models were stratified on postoperative radiation due to nonproportional hazards.