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Evaluation of Pathologic Staging using Number of Nodes in p16-Negative Head and Neck Cancer

Douglas R. Farquhar, MD[1], **Andrew J. Coniglio, MD**[1], **Maheer M. Masood, MD**[1,2], **Nicholas Lenze, BS**[1], **Paul Brennan, PhD MSc**[3], **Devasena Anantharaman, PhD MSc**[3], **Behnoush Abedi-Ardekani, MD**[4], **Adam M. Zanation, MD**[1], **Mark C. Weissler, MD**[1], **Andrew F. Olshan, PhD**[5,1], **Siddharth Sheth, MD**[6,1,*], **Trevor G. Hackman, MD**[1,*]

[1.]Department of Otolaryngology/Head and Neck Surgery, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC

[2.]Department of Otolaryngology/Head and Neck Surgery, University of Kansas Medical Center, Kansas City, KS

[3.]International Agency for Research on Cancer (IARC/WHO), Genetic Epidemiology Group, Lyon, France

[4.]International Agency for Research on Cancer (IARC/WHO), Genetic Cancer Susceptibility Group, Lyon, France

[5.]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC

[6.]Division of Hematology/Oncology, Department of Medicine, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC

Abstract

Objectives: The 8th edition AJCC staging guidelines for head and neck squamous cell carcinoma (HNSCC) recently introduced pathologic staging criteria for nodal disease among p16-positive patients. In this study we evaluate pathologic staging in p16-negative HNSCC.

Materials and Methods: We compared pathologic staging to the 7th and 8th edition AJCC staging systems using a statewide population-based cohort. All M0 p16-negative surgical patients were included. The outcome was five-year overall survival.

Results: Of 304 patients identified, 113 were NO, 157 had 1-4 positive nodes, and 34 had ≥4 nodes. Survival was 71% (95% CI 61–78%) with no nodes, 48% (36% - 60%) for 1-4 nodes, and 24% (11 – 39%) for >4 nodes. When compared to the AJCC systems, the pathologic staging

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Corresponding Author: Douglas R. Farquhar MD, University of North Carolina at Chapel Hill School of Medicine, Department of Otolaryngology/Head and Neck Surgery, 170 Manning Drive, Campus Box# 7070, Chapel Hill, NC 27599, Phone: 984-974-6484, Fax: 919-966-7941, Douglas.Farquhar@unchealth.unc.edu.

*Connotes that authors contributed equally to the manuscript

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yielded a larger total survival gradient, more montonic survival, better consistency across primary sites, and a slightly lower Bayesian information criterion (1510 vs 1538). After adjusting for disease characteristics, demographics, and tobacco use, hazard ratios for survival were similar using pathologic and AJCC criteria.

Conclusion: In this cohort, pathological staging was more prognostic than AJCC staging. This is the first study to evaluate pathologic staging in p16-negative cancer; if these findings are verified, a universal nodal staging system could be introduced.

Keywords

Head and Neck Cancer; Head and Neck Squamous Cell Carcinoma; Nodal Staging; AJCC Staging; Pathologic Staging; Survival; HPV-negative; Nodal Disease; p16-negative

Introduction:

The epidemiology of head and neck squamous cell carcinoma (HNSCC) has changed dramatically over the past 20 years with the discovery of human papillomavirus (HPV) associated oropharyngeal squamous cell carcinoma (OPSCC).[1–4] HPV-associated OPSCCs have superior outcomes compared to traditional non-HPV-related HNSCC even in the setting of extensive nodal disease.[5–10] In light of this, randomized controlled trials have demonstrated promising results for de-intensified treatment pathways.[5–10] One of the mainstays of the American Joint Committee on Cancer (AJCC) staging system is the stratification of prognosis for patients based on initial presentation to optimize treatment selection. With proven excellent outcomes for HPV-associated disease despite advanced presentation, the hazard discrimination and predictive ability of the current AJCC 7th edition was rendered obsolete.[11–13] The AJCC released the 8th edition in January 2017 with separate criteria for p16-positive disease to address this limitation.

One major change in the AJCC 8th edition is the new categorization of distinct clinical and pathological nodal (N) staging schemes for p16-positive OPSCC. While the clinical nodal staging system relies on the laterality and size of nodes, the pathological staging guidelines now emphasize the number of pathologically-positive lymph nodes (LN) (N0 = 0 LNs, N1 = 1-4 LNs, and N2 = >4 LNs).[14] In p16-negative HNSCC, there is no separate pathologic staging scheme and the traditional scheme of nodal size and laterality found in the 7th edition manual continues to be used. The only change to nodal staging was the inclusion of extranodal extension (ENE), which results in automatic upstaging to N3b. While there is supporting data that HNSCC driven by HPV is biologically distinct from tobacco and alcohol related HSNCC, it is unclear why AJCC did not include pathologic N stage criteria for p16 negative HNSCC.[1–4]

In this study, we evaluated whether the pathologic number of positive of lymph nodes, as classified by AJCC 8th edition for p16-positive HNSCC (0 vs. 1-4 vs. 4+), is associated with overall survival in p16-negative HSNCC. Additionally, we hoped to determine whether pathologic staging may have more prognostic accuracy for p16-negative HNSCC than the AJCC 7th and 8th edition systems. If successful, this model could lead to a simplified universal pathologic staging system for the two diseases.

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Materials and Methods:

Population:

Data was obtained from the Carolina Head and Neck Cancer Epidemiology Study (CHANCE); a population-based case-control study in North Carolina (NC).[15,16] Cases were identified through rapid case ascertainment with the NC Central Cancer Registry. Patients were eligible if they had been diagnosed with a first primary squamous cell carcinoma of the oral cavity, pharynx, or larynx between January 1, 2002, and February 28, 2006, were ages 20 to 80 years at diagnosis, and resided in a 46-county region in central NC. The Institutional Review Board (IRB) of the University of North Carolina approved this study.

Clinical Assessment and Patient Characteristics:

Demographic characteristics, carcinogenic behaviors, income, insurance, and other indicators of socioeconomic status were assessed by trained nurse-interviewers using a structured questionnaire during an in-home visit. Cases were interviewed soon after cancer diagnosis (the average time between diagnosis and interview was 5.3 months). Clinical information such as stage and cancer treatments were abstracted from the cases' medical records and reviewed independently by a head and neck surgeon and a pathologist. Extracapsular extension (ECE) was able to be extracted from pathology reports for only 128 of patients with nodal disease (67% of population with nodal disease). A secondary analysis was also conducted to compare patients with and without ECE captured. Patients with higher N stage disease were more likely to have ECE reported (52% for N1 disease, vs. 72% and 60% for N2 and N3 disease respectively; $p = 0.002$). There were no significant differences in the patient demographics, health behaviors, or indicators of socioeconomic status (Supplemental Table).

Inclusion Criteria:

Within the CHANCE dataset, only patients who had received primary surgery with neck dissection and had pathology reports available were included for review (N = 337). One patient with distant metastases (N = 1) was excluded. An additional 32 patients with p16-positive oropharyngeal cancer were excluded, as p16 positivity is the recognized biomarker for HPV-driven disease in the 8th edition AJCC staging system. Of note, 8 HPV-positive and p16 negative oropharyngeal cancer patients were identified. These were incorporated into the dataset; however, the oropharyngeal dataset was subsequently re-analyzed with these patients excluded for comparison.

Outcome:

The primary outcome was 5-year overall survival. Deaths were determined through the National Death Index, linking on name, social security number, date of birth, sex, race, and state of residence. Deaths were identified through December 31, 2013. More than 75% of the CHANCE cases were perfect or near-perfect NDI matches on social security number, date of birth, and sex. The remaining near-matches were confirmed by examining the United States Social Security Death Index and obituaries on newspaper websites.

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Analysis

Overall survival was calculated from the date of diagnosis to either the date of death due to any cause or censored at 5 years. The CHANCE database has complete follow-up information for every patient for 5+ years. Differences in covariate distributions by stage were tested by Pearson chi-square tests or by Fisher exact tests with < 5 patients in a cell.

Hazard ratios for the effect of stage classifications on overall survival were estimated using Cox proportional hazard models. These models were also calculated with an adjustment set to determine the independent effects of nodal classification after controlling for other patient and tumor characteristics. The adjustment set included T stage (1-4), site (laryngeal/ hypopharyngeal, oral cavity, and oropharyngeal), age, sex, race (white vs. nonwhite), income (dichotomized at $20,000), insurance (private vs. non-private), tobacco use (dichotomized at 10 pack years), and treatment. Treatment was characterized as one modality (surgery), two modalities (surgery with adjuvant chemotherapy or radiation), or three modalities (surgery with adjuvant chemoradiation). Kaplan-Meier plots were created for overall survival both with and without adjustment.

A Harrell's C-index was also calculated to compare the discrimination ability of each classification scheme. With this measure, a C-index of 1 represents perfect predictability while 0.5 represents the prediction equivalent to chance.[17] Bayesian information criterion (BIC) was also used to compare the two models; a lower BIC statistic indicates a preferable model.[18,19] Significance was set at $p < 0.05$. All statistical analysis was performed using STATA/IC 15.0 software (Stata Corporation, College Station, TX).

Results:

Population Characteristics:

As summarized in Table 1a, the age breakdown of the cohort by thirds was 27% under 50 (n=82), 49% between 50 and 65 (n=149), and 24% 65+ (n=73). By sex, 72% of patients were male (n=218) and 28% female (n=86). The primary cancers were located in the oral cavity (n = 144; 47%), larynx (n = 93; 31%), oropharynx (n = 54; 18%) and hypopharynx (n = 13; 4%). Patients were treated with surgery alone (n=118; 39%), surgery with adjuvant radiation (n=122; 40%), surgery with adjuvant chemotherapy (n=2; 1%), and surgery with adjuvant chemoradiation (n = 62; 20%).

Reclassification Based on Number of Nodes

*P*16 negative patients were reclassified for pathologic staging using the number of positive lymph nodes instead of N stage (based on 7th or 8th edition AJCC criteria). The categories were 0 nodes (N0), 1-4 nodes, and 4+ nodes, based on the 8th edition pathologic staging criteria for HPV-associated patients. In the 1-4 nodes category, 66 (42%) had been N1, 84 (53%) had been N2, and 7 (4%) had been N3 based on 7th edition AJCC criteria. In the 4+ nodes category, none had been N1, 31 (91%) had been N2, and 3 (8%) had been N3 (**Table a;** for reference, Tables 1b and 1c show the nodal staging system as reclassified by each category of the 7th and 8th edition AJCC systems respectively).

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Overall Survival:

Five-year overall survival by nodal status according to AJCC 7th edition criteria was 71% for NO disease (95% CI 61–78%), 48% for N1 (95% CI 36-60%), 42% for N2 (95% CI 33-51%) and 30% for N3 (95% CI 7-58%) (Figure 1). When classifying N2 disease into sub-categories for patients with available information, survival was 25% for N2a, 39% for N2b, and 33% for N2c. Survival results incorporating ENE positivity (8th edition) were similar with 46% (33% - 58%) for N1, 42% (32% - 51%) for N2, 43% (10% - 73%) for N3, and 31% (11% - 53%) for N3b respectively (Figure 2).

Patients with 1-4 positive nodes and 4+ positive nodes had survival rates of 48% (36% - 60%) and 24% (11 – 39%) respectively (Figure 1). When +ENE was added to the criteria, these became 53% (44% - 61%), and 9% (1% - 33%) respectively, with 31% (20% - 43%) survival for +ENE patients (Figure 2).

Survival Gradients:

Two key measures of a prognostic system are the survival gradient between each category and the total survival gradient between the highest and lowest categories. A good system has the most consistent (monotonic) gradient between each category, and the largest total survival gradient.

The survival gradients between N0, N1, N2 and N3 disease were 22%, 7%, and 12% using 7th edition criteria (Figure 1), and 25%, 3.6%, −1%, and 12% (between N3 and N3b) using 8th edition (Figure 2). The pathologic staging system was more monotonic; the differences between no nodes and 1-4 nodes, and 1-4 and 4+ nodes, were 23% and 24% respectively.

The 7th and 8th edition AJCC systems had total survival gradients of 40 and 41% respectively between N0 and N3 categories. The pathologic staging system had a 47% total gradient between no nodes and 4+ nodes categories (Figures 1 **and** 2).

Hazard Ratios

In order to further explore the pathologic staging system, we determined overall hazard ratios for survival, hazard ratios by tumor site, and adjusted hazard ratios using Cox regressions. Hazard ratios for 1-4 and 4+ nodes were 2.2 (95% CI 1.5 – 3.3) and 4.9 (95% CI 2.9 – 8.2) respectively in comparison to patients with no nodes (Table 2a). Hazard ratios based on AJCC 7th and 8th edition criteria, as well as incorporating ECE into nodal staging, are presented for comparison in Tables 2a **and** 2b. These were relatively consistent across sites; patients with 1-4 nodes had hazard ratios of 2.6 (95% CI 1.4 – 4.9) for laryngeal and hypopharyngeal cancer, 2.5 (1.4 – 4.5) for oral cavity cancer, and 2.3 (0.3 – 17.8) for p16 and HPV negative oropharyngeal cancer (Table 3, Figures 3a **and** 3b). Of note, the hazard ratio was lower when using only p16 as criteria (Table 3).

We also examined hazard ratios after adjusting for T stage, site, demographics, income, insurance, tobacco use, and treatment. In comparison to patients with no positive nodes, there were hazard ratios of 2.4 (1.5 – 3.7) and 5.7 (2.9 – 11.1) for 1-4 nodes and 4+ nodes respectively (Table 4,). N stage based on 7th edition AJCC criteria had relatively similar

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hazard ratios, of 2.1 (1.2 – 3.4) 3.1 (1.8 – 5.2) and 5.5 (2.0 – 15.6) for N1, N2 and N3 disease respectively.

Harrell's C-Index:

The discriminative ability of the nodal classification systems was compared using a Harrell's C-index. A C-index value close to 1 indicates the optimal predictability, while a value of 0.5 indicates predictability similar to chance. The C-index for nodal positivity was 0.63 (95% CI 0.59 – 0.67); the C-index for N stage was 0.622 (95% CI 0.58 – 6.7) and 0.62 (95% CI 0.58 – 0.66) for the 7th and 8th edition AJCC classifications respectively.

Bayesian Information Criteria

The discriminative ability was also compared using Bayesian information criteria (BIC). For this statistic, a smaller BIC indicates a better fit for the model. The BIC for staging by number of nodes was 1510; the BIC for the 7th and 8th edition AJCC classification systems were 1538 and 1545 respectively.

Discussion:

The AJCC Staging Manual 8th edition for HNSCC arose due to limitations of the 7th edition in hazard discrimination and predictive ability for HPV-positive OPSCC.[11,12,20,21] Huang et al proposed a new staging system for HPV-positive OPSCC which was refined and validated by O'Sullivan et al. and the International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S).[12,22] The most significant update to the 8th edition AJCC system thus involved a separate staging algorithm for p16-positive OPSCC. This relied heavily upon changes in nodal classification, both clinically and pathologically, with a new importance in the number of nodes in the pathologic staging.[12] With the exception of including extranodal extension as a poor prognostic indicator, the p16-negative HNSCC nodal classification remained largely unchanged.

The aim of our study was to evaluate the 8th edition AJCC pathological nodal staging model in p16-negative HNSCC. Patients in the CHANCE cohort who underwent primary neck dissection for their p16-negative disease were redistributed into three groups: 0 positive nodes, 1-4 positive nodes, and >4 positive nodes. Survival based on this prognostic system was then compared with the 7th and 8th edition AJCC nodal classification systems.

The 7th edition AJCC system had poor hazard discrimination in our population, particularly in N2 disease, which was consistent with O'Sullivan and others.[12] Survival discrimination was only marginally better when using the 8th edition staging system with ENE, although information on ENE was limited in our dataset.

In contrast, the pathologic nodal system showed somewhat improved prognostic discrimination. There was a larger total survival gradient, and more monotonic survival between groups (Figures 1 **and** 2). Additionally, overall hazard ratios for 1-4 and 4+ nodes compared to zero nodes remained relatively constant across various head and neck cancer sites (Figure 3a). The survival curve for patients with 1-4 positive LN's was similar to combined N1 and N2 curves, and hazard ratios after adjusting for several confounders

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including T stage, site, and tobacco use, were relatively similar to those of the AJCC 7th and 8th edition (Table 4).

Based on these results, the pathologic nodal staging criteria could be applied to staging criteria for p16-negative HNSCC. This change could lead to more accurate staging, and a universal pathological staging system for HNSCC would help prevent confusion from separate systems for p16-positive and p16-negative disease. However, further efforts will need to independently validate these findings in separate cohorts before any changes to the AJCC criteria can be recommended.

Our study is the first to investigate overall survival based on number of pathologic cervical lymph nodes in p16-negative HNSCC using the AJCC 8th edition pathologic nodal criteria. Several other studies have explored the predictive outcome of number or density of lymph nodes in lung, colon, and, more recently, head and neck salivary gland cancer.[23–25] These studies, have demonstrated the prognostic importance of lymph node metastasis but focus mainly on size, laterality, extranodal extension, and postsurgical lymph node density.[26]

This also is the first study to apply the new staging system for HNSCC to a population-based case cohort; other studies on the 8th edition AJCC system have focused solely on patients treated at academic institutions.[21,27,28] The CHANCE cohort consists of a socioeconomically and geographically diverse population treated by a mixture of academic and community-based providers. Thus the associations are likely more generalizable than those of cohorts from academic institutions alone. Our data is further strengthened by complete follow up at our 5 year survival endpoint.

The chief weakness of our study is that clinical or pathologic ENE was only available for a subset of patients. Reporting extranodal extension in pathology reports was not standard practice across North Carolina during the study time period. We conducted a secondary analysis to compare patient characteristics by ECE reporting; the only significant difference was that patients with high N-stage disease were more likely to have ECE reported. Referral patterns may have contributed to this discrepancy; patients were larger neck disease may have been more likely to be treated at academic medical centers, who were more likely to report ECE at the time.” Additionally, tumor thickness, rather than depth of invasion (DOI), was routinely used in pathological reports at the time, and so we were not able to retrospectively apply DOI, another component of the 8th edition AJCC criteria, to the T-staging staging criteria for oral cavity patients.

Furthermore, it is important to note that only surgically treated patients were included. This criteria is consistent with the 8th edition AJCC pathological staging system for p16-positive oropharyngeal carcinoma.[14] A future pathological staging system suggested by these results would apply only to surgically treated patients. Finally, this study utilized a population-based database including academic and community hospitals, and treatment according to guidelines may have been inconsistent across sites. For example, two patients with 4+ lymph nodes were treated with surgery alone (table 1). Nonetheless, the population bases for this study likely makes the results more generalizable to the overall population of head and neck cancer patients in the United States.

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Conclusion

The 8th edition AJCC staging system for HPV-associated oropharyngeal cancer includes a new nodal staging system with pathological criteria. When this system was applied to p16-negative HNSCC cancers at all sites, it demonstrated slightly more accurate prognostication than the 7th and 8th edition AJCC systems. This is the first study to evaluate the nodal prognostic system in p16-negative HNSCC patients, and if these findings are verified, a simplified universal pathologic staging system for nodal disease among HNSCC patients could be introduced.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research Highlights:

- A pathologic nodal staging system now exists for p16+ head and neck cancer patients
- We evaluated pathologic staging in p16− patients in a population-based cohort
- In this study, pathological nodal staging was more prognostic than AJCC staging
- If these findings are verified, a universal nodal staging system could be introduced

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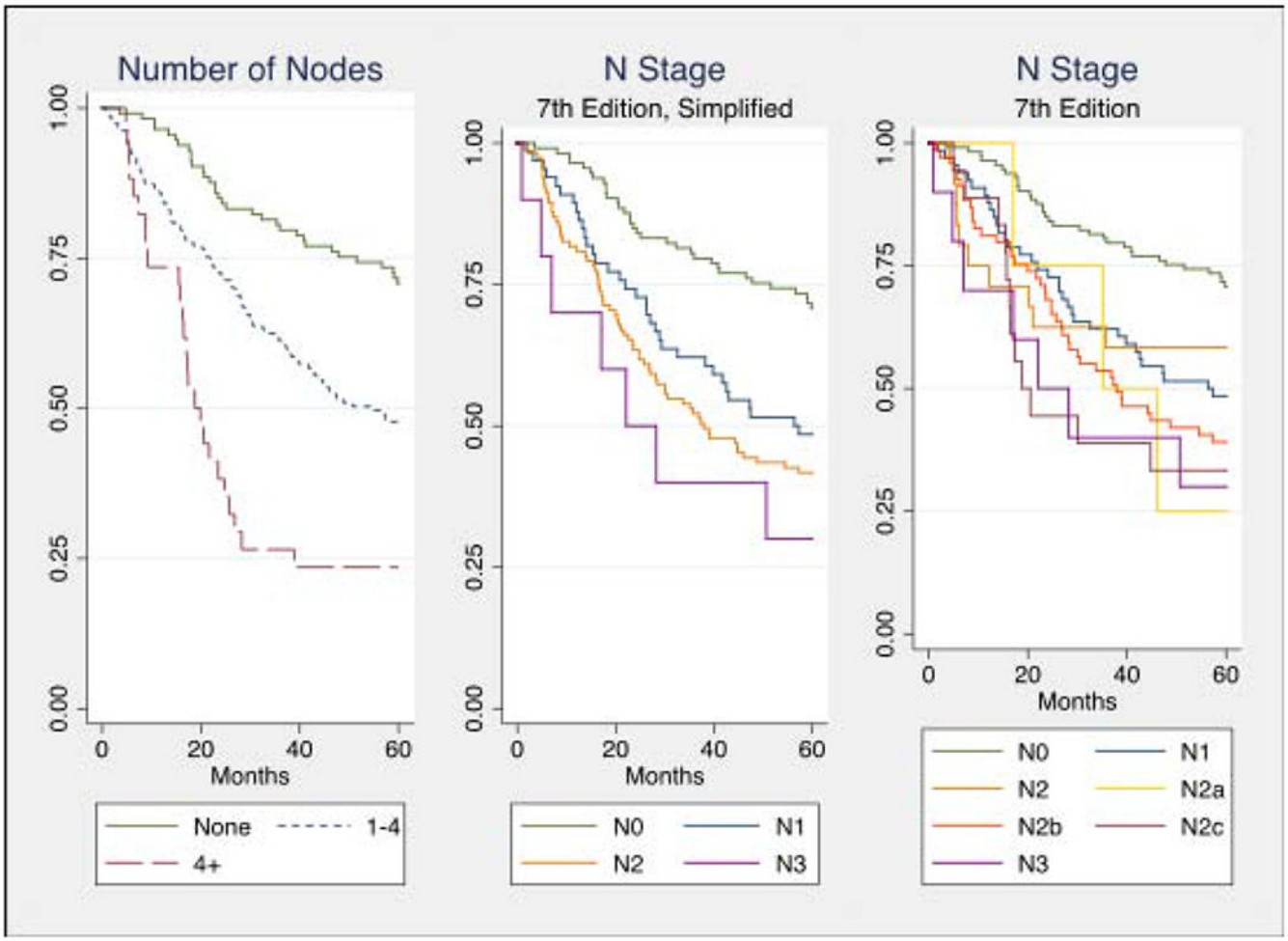

Figure 1:
Kaplan Meier curves for 5-year overall survival by nodal staging system.

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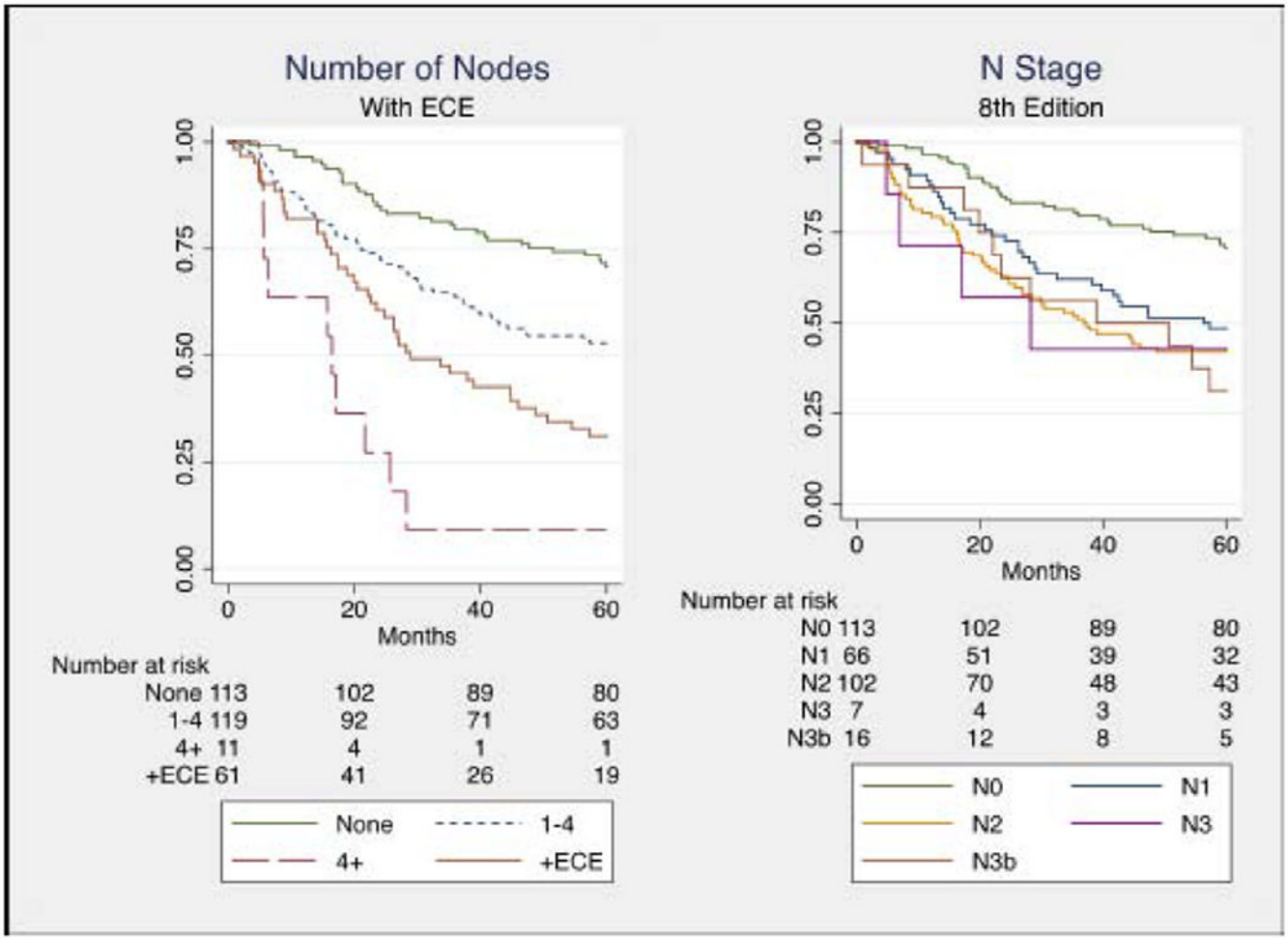

Figure 2:

Kaplan Meier curves for 5-year overal survival comparing 8th edition AJCC criteria to the number of nodes including ECE. The 8th edition AJCC criteria uses ECE to upstage oropharyngeal cancer with ECE to stage 3b.

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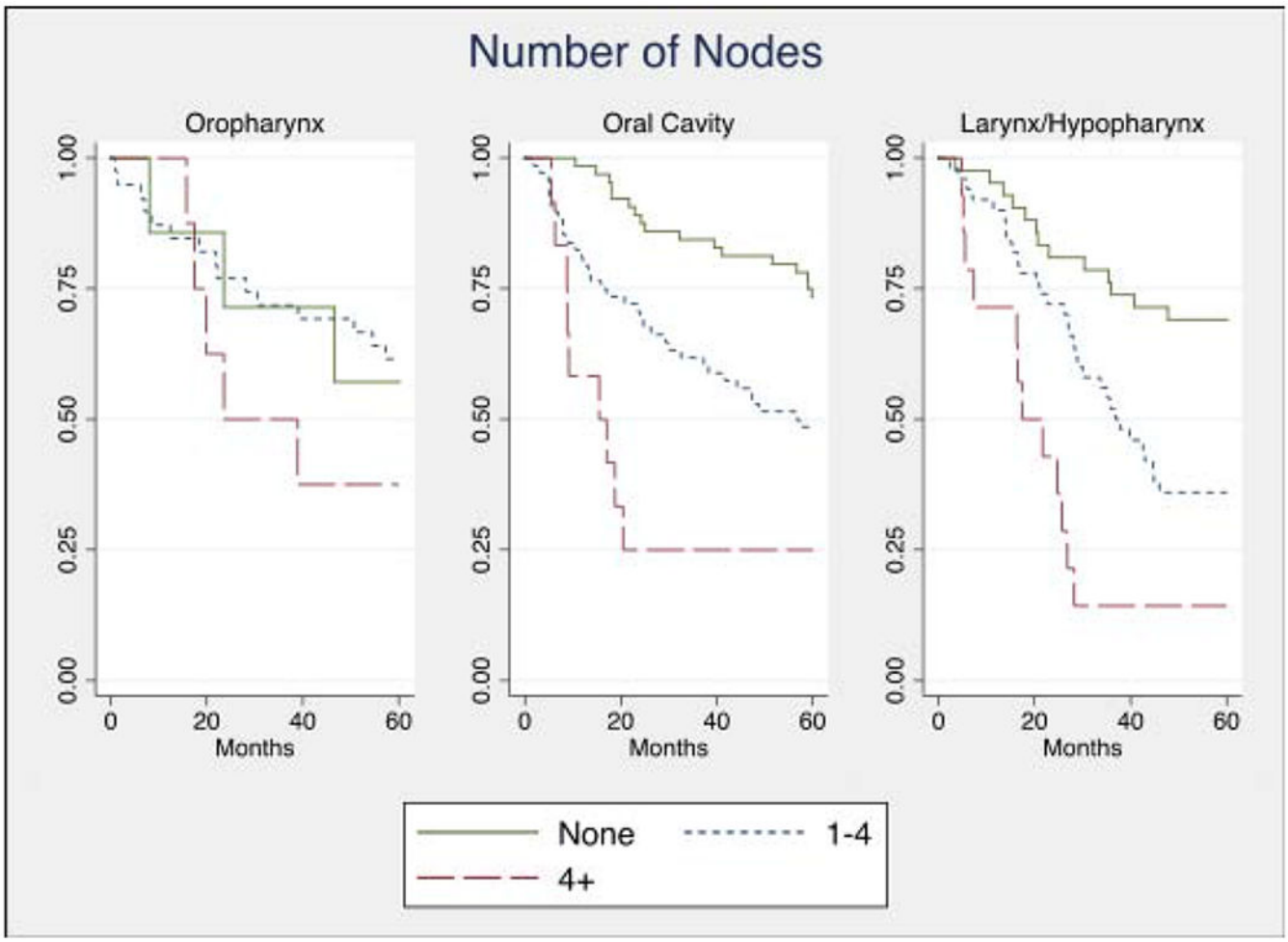

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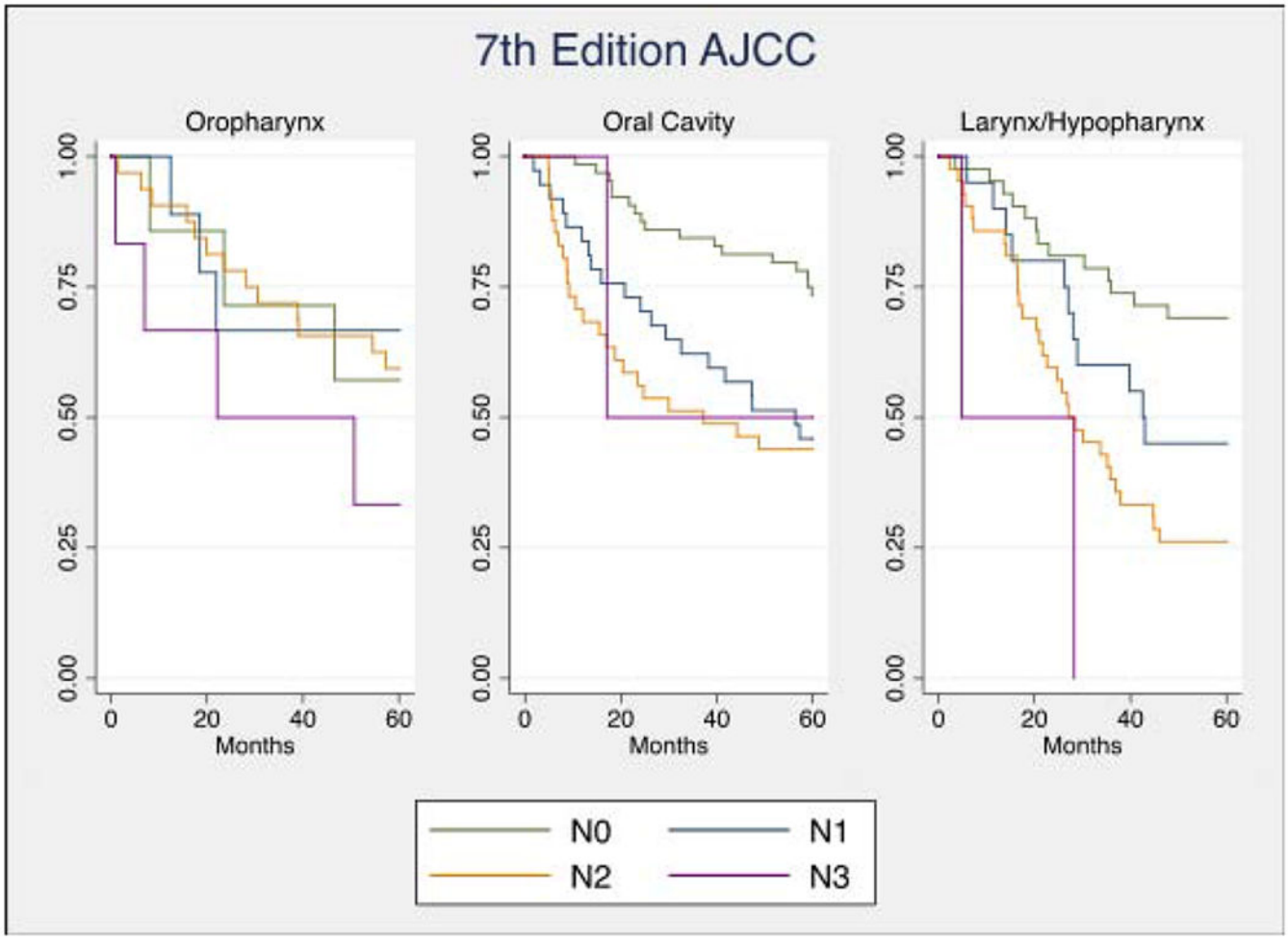

Figure 3.

a: Kaplan Meier curves for 5-year overall survival by site, using the number of nodes.

b: Kaplan Meier curves for 5-year overall survival by site, using 7th edition AJCC criteria.

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Table 1a:

Characteristics of CHANCE cohort by number of nodes; total n = 304

	No Nodes (n=113)		1-4 Nodes (n=157)		4+ Nodes (n=34)		P-Value
	No.	%	No.	%	No.	%	
Age Category							
< 50 (n=82; 27%)	35	31%	40	25%	7	21%	0.727
50-65 (n=149; 49%)	51	45%	79	50%	19	56%	
65+ (n=73; 24%)	27	24%	38	24%	8	24%	
Sex							
Male (n=218; 72%)	77	68%	116	74%	25	74%	0.568
Female (n=86; 28%)	36	32%	41	26%	9	26%	
Race							
White (n=201; 66%)	78	69%	104	66%	19	56%	0.535
Black (n=98; 32%)	33	29%	50	32%	15	44%	
Other (n=5; 2%)	2	2%	3	2%	0	0%	
Smoking History							
< 10 Years (n=62; 21%)	25	22%	34	22%	3	9%	0.22
> 10 Years (n=238; 79%)	88	78%	120	78%	30	91%	
Drinking History							
< 1 Drink / Week (n=40; 14%)	17	15%	18	12%	5	15%	0.713
> 1 Drink / Week (n=256; 86%)	94	85%	133	88%	29	85%	
Primary Site							
Hypopharynx (n=13; 4%)	1	1%	8	5%	4	12%	0.025 *
Larynx (n=93; 31%)	41	36%	42	27%	10	29%	0.098 *
Oral cavity (n=144; 47%)	64	57%	68	43%	12	35%	0.013 *
Oropharynx (n=54; 18%)	7	6%	39	25%	8	24%	< 0.001 *
T Stage							
T1 (n=64; 21%)	29	26%	28	18%	7	21%	** 0.045
T2 (n=98; 32%)	40	35%	52	33%	6	18%	
T3 (n=67; 22%)	20	18%	35	22%	12	35%	
T4 (n=75; 25%)	24	21%	42	27%	9	26%	
N Stage							
N0 (n=113; 37%)	113	100%	0	0%	0	0%	
N1 (n=66; 22%)	0	0%	66	42%	0	0%	
N2 (unspecified laterality) (n=24; 8%)	0	0%	18	11%	6	18%	
N2a (n=4; 1%)	0	0%	4	3%	0	0%	
N2b (n=69; 23%)	0	0%	54	34%	15	44%	
N2c (n=18; 6%)	0	0%	8	5%	10	29%	
N3 (n=10; 3%)	0	0%	7	4%	3	9%	
ECE							
No (n=70; 23%)	0	0%	66	42%	4	12%	< 0.001

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	No Nodes (n=113)		1-4 Nodes (n=157)		4+ Nodes (n=34)		P-Value
	No.	%	No.	%	No.	%	
Yes (n=63; 21%)	0	0%	40	25%	23	68%	
Not available (n=171; 56%)	113	100%	51	32%	7	21%	
Treatment Category							
Surgery Only (n=118; 39%)	80	71%	36	23%	2	6%	< 0.001
Surgery + Chemotherapy (n=2; 1%)	0	0%	1	1%	1	3%	
Surgery + Radiation (n=122; 40%)	28	25%	81	52%	13	38%	
Surgery + Chemoradiation (n=62; 20%)	5	4%	39	25%	18	53%	

*P-value for proportion with nodes, relative to other cancer sites

**P-value for high vs. low T-stage

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Table 1b:

Reclassification of 7th edition AJCC categories into nodal staging categories

	7th Edition AJCC Stage Category							
	N0	**N1**	**N2**	**N2a**	**N2b**	**N2c**	**N3**	**Total**
7th Edition AJCC (total n)	113	66	24	4	69	18	10	304
No Nodes (total n, % of AJCC category)	113 (100%)	0	0	0	0	0	0	113 (37%)
1-4 Nodes (total n, % of AJCC category)	0	66 (100%)	18 (75%)	4 (100%)	54 (78%)	8 (44%)	7 (70%)	157 (52%)
4+ Nodes (total n, % of AJCC category)	0	0	6 (25%)	0	15 (22%)	10 (56%)	3 (30%)	34 (11%)

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Table 1c:

Reclassification of 8th edition AJCC categories into nodal staging categories

	8th Edition AJCC Stage Category								
	N0	**N1**	**N2**	**N2a**	**N2b**	**N2c**	**N3**	**N3b**	**Total**
8th Edition AJCC (total n)	113	66	23	4	57	18	7	16	304
No Nodes (total n, % of AJCC category)	113 (100%)	0	0	0	0	0	0	0	113 (37%)
1-4 Nodes (total n, % of AJCC category)	0	66 (100%)	17 (74%)	4 (100%)	48 (84%)	8 (44%)	4 (57%)	10 (63%)	157 (52%)
4+ Nodes (total n, % of AJCC category)	0	0	6 (26%)	0	9 (16%)	10 (56%)	3 (43%)	6 (37%)	34 (11%)

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Table 2a:

Hazard ratios for 5-year overall survival by nodal staging classification.

	Hazard Ratio	95% CI	P-Value
Number of Nodes (relative to N0)			
1-4	2.2	1.5 - 3.3	< 0.001
4+	4.9	2.9 - 8.2	< 0.001
N Stage - 7th Edition AJCC (relative to N0)			
N1	2.1	1.3 - 3.4	0.002
N2 (all subsites)	2.7	1.8 - 4.0	< 0.001
N2a (if available)	*3.1*	*1.0 - 10.2*	*0.057*
N2b (if available)	*2.7*	*1.7 - 4.3*	*< 0.001*
N2c (if available)	*3.5*	*1.8 - 6.8*	*< 0.001*
N3	3.8	1.7 – 8.7	0.001

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Table 2b:

Hazard ratios for 5-year overall survival by nodal staging classification, incorporating ECE and using the 8th edition AJCC classification for nodal stage.

	Hazard Ratio	95% CI	P-Value
Number of Nodes (relative to N0)			
1-4	1.9	1.2 - 3.0	0.003
4+	8.2	4.0 - 16.9	< 0.001
+ECE	3.4	2.1 - 5.3	< 0.001
N Stage - 8th Edition AJCC (relative to N0)			
N1	2.1	1.3 - 3.4	0.002
N2 (all subsites)	2.7	1.8 - 4.1	< 0.001
N2a (if available)	*3.1*	*1.0 - 10.2*	*0.057*
N2b (if available)	*2.7*	*1.7 - 4.4*	*< 0.001*
N2c (if available)	*3.5*	*1.8 - 6.8*	*< 0.001*
N3	2.9	1.0 - 8.2	0.042
N3b	3.0	1.5 - 5.9	0.002

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Table 3:

Hazard ratios 5-year overall survival by site. Hazard ratios presented for P-16 negative and HPV-negative oropharyngeal cancer patients, in addition to P-16 negative patients, for comparison.

	Larynx/Hypopharynx (n=106)			Oral Cavity (n=144)			P16-neg Oropharynx (n=54)			P16-neg HPV-neg Oropharynx (n=46)		
	HR	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**
Number of Nodes (relative to N0)												
1-4	2.6	1.4 - 4.9	0.004	2.5	1.4 - 4.5	0.002	0.9	0.3 - 3.1	0.868	2.3	0.3 - 17.8	0.410
4+	6.2	2.8 - 13.9	0.000	5.8	2.6 - 13.2	< 0.001	1.8	0.4 - 7.4	0.436	3.3	0.3 - 32.2	0.297
N Stage (relative to N0)												
N1	2.1	0.9 - 4.6	0.075	2.6	1.3 - 4.9	0.004	0.8	0.2 - 3.9	0.774	1.9	0.2 - 18.6	0.569
N2 (all subsites)	3.5	1.8 - 6.7	0.000	3.1	1.6 - 5.8	< 0.001	0.9	0.3 - 3.3	0.926	2.1	0.3 - 16.6	0.474
N3	9.2	2.0 - 41.6	0.004	2.5	0.3 - 18.7	0.376	2.1	0.5 - 9.4	0.331	6.8	0.8 - 61.2	0.087

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Table 4:

Hazard ratios for 5-year overall survival, adjusting for T stage, site, demographics, income, insurance, tobacco use, and treatment. N = 279 patients with complete data.

	Hazard Ratio	95% CI	P-Value
Number of Nodes (relative to N0)			
1-4	2.4	1.5 - 3.7	< 0.001
4+	5.7	2.9 - 11.1	< 0.001
N Stage - 7th edition AJCC (relative to N0)			
N1	2.1	1.2 - 3.4	0.005
N2 (all subsites)	3.1	1.8 - 5.2	< 0.001
N3	5.5	2.0 - 15.6	0.001