JAMA Oncology | Brief Report

Association of Quantitative Metastatic Lymph Node Burden With Survival in Hypopharyngeal and Laryngeal Cancer

Allen S. Ho, MD; Sungjin Kim, MS; Mourad Tighiouart, PhD; Cynthia Gudino, MPH; Alain Mita, MD; Kevin S. Scher, MD; Anna Laury, MD; Ravi Prasad, MD; Stephen L. Shiao, MD, PhD; Nabilah Ali, PA-C; Chrysanta Patio, PA-C; Jon Mallen-St. Clair, MD, PhD; Jennifer E. Van Eyk, PhD; Zachary S. Zumsteg, MD

IMPORTANCE Nodal staging for laryngohypopharyngeal cancers is based primarily on size and laterality, with less value placed on absolute number of metastatic lymph nodes (LNs). We are aware of no studies to date that have specifically addressed the prognostic effect of quantitative nodal burden in larynx or hypopharynx malignancies.

OBJECTIVE To assess the independent impact of quantitative metastatic LN burden on mortality risk.

DESIGN, SETTING, AND PARTICIPANTS Univariate and multivariable models were constructed to evaluate the association between patients' number of metastatic LNs and their survival, adjusting for factors such as nodal size, laterality, extranodal extension, margin status, and adjuvant treatment. Participants were patients with squamous cell carcinoma of the larynx or hypopharynx undergoing upfront surgical resection for curative intent at a US hospital between 2004 and 2013, as identified in the National Cancer Database. A neck dissection of a minimum of 10 LNs was required.

MAIN OUTCOMES AND MEASURES Overall survival.

RESULTS Overall, 8351 cases were included (mean [SD] age, 61 [10.1] years; 6499 men [77.8%]; 4710 patients with metastatic LNs and 3641 with no metastatic LNs). Mortality risk escalated continuously without plateau as number of metastatic nodes increased, with the hazard per node (hazard ratio [HR], 1.19; 95% CI, 1.16-1.23; $P < .001$) most pronounced up to 5 positive LNs. Extranodal extension was also associated with increased mortality (HR, 1.34; 95% CI, 1.13-1.59; $P < .001$). Increasing number of nodes examined was associated with improved survival, albeit to a lesser degree (per 10 LNs: HR, 0.97; 95% CI, 0.96-0.98; $P < .001$) and without a detectable change point. Other nodal factors, including nodal size, contralateral LN involvement (TNM stage N2c), and lower LN involvement (levels 4-5), were not associated with mortality in multivariable models when accounting for number of positive LNs. A novel, parsimonious nodal staging system derived by recursive partitioning analysis exhibited greater concordance with survival than the TNM staging system outlined in the American Joint Committee on Cancer's *AJCC Staging Manual*, 8th edition.

CONCLUSIONS AND RELEVANCE The number of metastatic nodes is a predominant independent factor associated with mortality in hypopharyngeal and laryngeal cancers. Moreover, standard nodal staging factors like LN size and contralaterality have no independent prognostic value when accounting for positive LN number. Deeper integration of quantitative metastatic nodal disease may simplify staging and better triage the need for adjuvant therapy.

Invited Commentary
page 989

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Allen S. Ho, MD, Department of Surgery, Cedars-Sinai Medical Center, 8635 W Third St, Ste 590W, Los Angeles, CA 90048 (allen.ho@cshs.org).

JAMA Oncol. 2018;4(7):985-989. doi:10.1001/jamaoncol.2017.3852
Published online November 30, 2017.

The management of laryngohypopharyngeal cancers remains daunting, owing to functional morbidity and poor prognosis. Though organ preservation trials have shown efficacy with chemoradiation,[1-6] surgery remains the standard of care for resectable disease, especially with extralaryngeal extension or pretreatment laryngeal dysfunction.[7]

The American Joint Committee on Cancer's *AJCC Staging Manual*, 8th edition[8] (AJCC 8E) TNM staging system considers a combination of lymph node (LN) factors, including number, size, laterality, and extranodal extension. However, the independent impact of each factor remains poorly defined. Current staging may underestimate the cumulative effect of escalating metastatic nodal burden; for example, patients with 2 positive LNs may be staged the same as those with 10, despite the likelihood that the latter will do much worse clinically. We therefore investigated quantitative metastatic nodal burden in a large hypopharyngeal and laryngeal cancer cohort.

Key Points

Question What is the independent impact of quantitative metastatic nodal burden in hypopharyngeal and laryngeal malignancies?

Findings This study of 8351 cases identified continuously escalating mortality risk with increasing number of metastatic lymph nodes, eclipsing conventional nodal staging factors such as node size and contralaterality. A simplified nodal staging system based on metastatic node number exhibited improved prognostic value and discrimination compared with the TNM staging system outlined in the American Joint Committee on Cancer's *AJCC Staging Manual*, 8th edition.

Meaning Greater incorporation of numerical metastatic nodal burden into nodal classification for hypopharyngeal and laryngeal cancers may streamline staging, refine patient prognosis, and triage patients who may benefit from adjuvant treatment.

Methods

Patients

This study was deemed exempt by the Cedars-Sinai institutional review board, and the requirement for patient consent was waived. Data from the National Cancer Database between 2004 and 2013 were evaluated. All patients 18 years or older undergoing surgery and neck dissection for hypopharyngeal or laryngeal squamous cell carcinoma for curative intent were assessed. Cases with fewer than 10 LNs examined were eliminated to remove excisional biopsies and substandard neck dissections.

Statistical Analysis

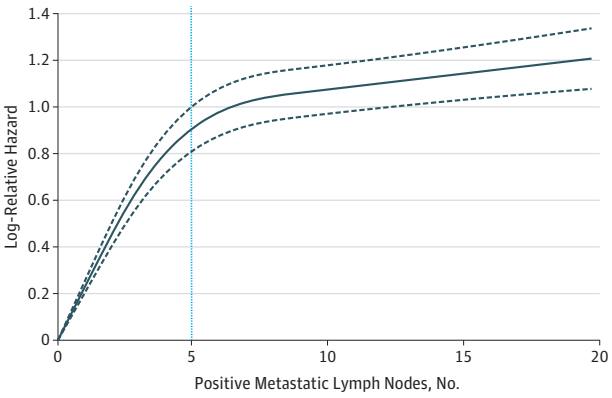
Detailed methods are listed in the Supplement. Missing values were imputed using the multivariate imputation by chained equations algorithm.[9,10] Univariate and multivariable survival analyses were performed with Cox proportional hazards models. Restricted cubic spline functions were used to model relationships between positive LN number and overall survival (OS). Optimal numbers of knots were chosen based on the lowest Akaike information criterion. Three knots were placed at 1, 3, and 9 positive LNs corresponding to 55th, 75th, and 95th percentiles, respectively. Change points were estimated with piecewise linear regression modeling.[11] Recursive partitioning analysis was used to create a nodal classification system, with performance assessed via the C statistic using the bootstrap method.

Results

Number of Positive Metastatic LNs

Overall, 8351 patients (mean [SD] age, 61 [10.1] years; 6499 men [77.8%]) met inclusion criteria (eFigure 1 and eTable 1 in the Supplement). Increased number of metastatic LNs correlated with worse OS (eTable 2 and eFigure 2 in the Supplement). Mortality risk continually increased with increasing number of positive LNs without plateau (**Figure 1**) even after adjustment for nodal and nonnodal covariates. The relationship between OS and the number of positive LNs was nonlinear: the hazard of death per positive LN increased to a change point of 5 metastatic LNs (hazard ratio [HR], 1.19; 95% CI, 1.16-1.23; $P < .001$). Beyond this, the risk of death increased modestly (HR, 1.01; 95% CI, 1.01-1.02; $P = .001$) (eTable 3 in the Supplement). Because significant interactions between anatomic site and number of positive LNs on survival were detected, patients with larynx and hypopharynx cancers were analyzed separately (eTable 4 in the Supplement). The results were similar for both larynx and hypopharynx cancers, although the hazard per LN was greater for larynx cancers vs hypopharynx cancers for each positive LN up to 5. The reverse was true for more than 5 positive LNs.

Figure 1. Escalating Mortality Risk With Increase in Metastatic Lymph Node Number



Escalating adjusted hazard ratio (HR) with increasing number of positive metastatic lymph nodes (LNs) in hypopharyngeal and laryngeal cancers. Gray dashed lines represent estimated 95% CIs of the predicted HRs. Black solid line represents multivariable smoothed restricted cubic spline plot of the natural logarithm of adjusted HR vs the number of positive metastatic LNs. Blue vertical line represents the estimated change point at 5 positive LNs.

Table. Overall Survival for Proposed and AJCC 8th Edition TNM Nodal Staging Systems for Hypopharyngeal and Laryngeal Cancers

N Category	Criteria	3-Year OS, %
Proposed Nodal Staging System		
N0	0 LN+	73.2
N1	1 LN+ without ENE	62.3
N2	2-3 LN+ or 1 LN+ with ENE	51.7
N3a	4-6 LN+	43.2
N3b	≥7 LN+	27.9
AJCC 8th Edition TNM Nodal Staging System		
N0	0 LN+	73.2
N1	1 Ipsilateral LN+, ≤3 cm, without ENE	61.6
N2a	1 Ipsilateral or contralateral LN+, ≤3 cm, with ENE; or 1 ipsilateral LN+ 3-6 cm, without ENE	52.8
N2b	>1 Ipsilateral LN+, ≤6 cm, without ENE	55.1
N2c	>1 Bilateral or contralateral LN+, ≤6 cm, without ENE	48.7
N3a	≥1 LN+, >6 cm, without ENE	NA
N3b	1 Ipsilateral LN+, >3 cm, with ENE; or >1 ipsilateral, contralateral, or bilateral LN+, with ENE	38.8

Abbreviations: AJCC, American Joint Committee on Cancer; ENE, extranodal extension; LN+, metastatic lymph node; NA, not applicable; OS, overall survival.

Number of LNs Examined

Number of LNs examined exhibited a linear association with mortality, with no change point observed. The risk of death decreased continuously with each additional node harvested (per 10 LNs examined: HR, 0.97; 95% CI, 0.96-0.98; $P < .001$) (eFigure 3 and eTable 3 in the Supplement). An interaction between margin status and number of LNs examined was identified (eTable 5 in the Supplement).

Metastatic LN Features

Extranodal extension remained independently associated with decreased OS in multivariable models (HR, 1.34; 95% CI, 1.13-1.59; $P = .001$). Node size, lower LN involvement (level 4-5), and contralateral LN involvement (TNM stage N2c) had no independent impact on survival (eTable 2 in the Supplement).

Proposed Nodal Staging System

Recursive partitioning analysis was used to generate a novel nodal staging system (eFigure 4 in the Supplement). One positive LN with extranodal extension and 2 to 3 positive LNs clustered separately but were grouped as N2 owing to similar survival rates (**Table**). The proposed system showed improvement in predictive ability (optimism-corrected C statistic, 0.674; 95% CI, 0.661-0.687) over the AJCC 8E TNM system (C statistic, 0.671; 95% CI, 0.658-0.684) (eTable 6 in the Supplement).

Discussion

This study systematically addressed quantitative metastatic nodal disease burden in larynx and hypopharynx cancers. In continuous multivariable regression models, we observed that successive positive LNs were associated with increased risk of death without plateau. Notably, each metastatic node up to 5 was associated with an additional 19% mortality risk, while each positive node beyond 5 was associated with continually escalating cumulative hazard. The results were similar for larynx and hypopharynx cancers individually, although risk of death per LN increased more rapidly for larynx cancers than hypopharynx cancers with each positive LN up to 5, while the opposite trend was observed with each positive LN beyond 5. It is intuitive that increasing number of metastatic nodes might increase risk of death; it is moreover provocative that factors used by TNM staging, including size and laterality, had no prognostic significance. As these covariates influenced survival in univariate analysis, they likely act as surrogates for metastatic nodal number. Consistent with this theme, divergent outcomes were observed within TNM N2b and N2c subgroups (eFigure 2B and C in the Supplement).

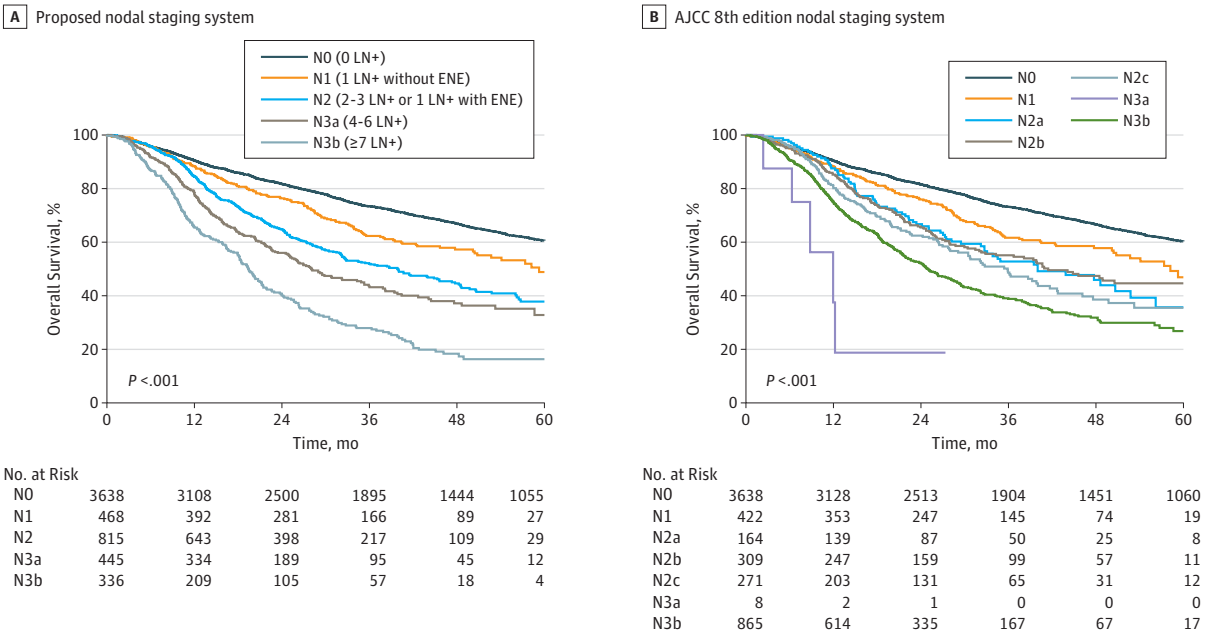
The predictive capability of this system was mildly improved in comparison to AJCC 8E. This may be because contralaterality and LN size associate tightly with number of positive LNs. Nonetheless, the proposed nodal staging system derived by recursive partitioning analysis confers several advantages considered qualitatively desirable by AJCC, beyond what can be measured by the C statistic.[12] It is concise, consisting of fewer substratifications and based largely on a single variable. The distribution of patients across stages is relatively even (**Figure 2**). In contrast, AJCC 8E TNM staging for N2a through N2c classifications exhibits overlapping survival curves, with very few patients (n = 8) classified as N3a. The proposed system also partitions patients across a wider spectrum of outcomes. The patients at highest risk in the proposed system (those with 7 or more positive LNs) have 4.7 times the risk of death as patients with no LN metastases (eTable 6 in the Supplement). In comparison, the patients at highest risk in the AJCC 8E TNM system have 2.9 times higher risk of death than patients with no LN metastases. Altogether, the proposed system is simpler, is more discriminating, eliminates nonprognostic factors, and captures a greater range of mortality risk (Table).

These results are remarkably consistent with what we have observed in oral cavity cancer,[13] suggesting unifying relationships among human papillomavirus–negative head and neck cancers that differ from virally driven oropharyngeal or nasopharyngeal carcinomas.[14] As such, the influential role of positive LN number warrants additional investigation for adjuvant therapy. For example, treatment intensification with adjuvant chemoradiation may augment survival in those with 7 or more positive LN, given their poor prognosis.

Limitations

Several caveats deserve mention, including the study's retrospective analysis and the focus on laryngeal and hypopharyngeal cancers undergoing surgery. Certain factors correlating with outcome, including smoking status,

Figure 2. Overall Survival for Proposed and AJCC 8th Edition TNM Nodal Staging Systems



No. at Risk

N0	3638	3108	2500	1895	1444	1055
N1	468	392	281	166	89	27
N2	815	643	398	217	109	29
N3a	445	334	189	95	45	12
N3b	336	209	105	57	18	4

No. at Risk

N0	3638	3128	2513	1904	1451	1060
N1	422	353	247	145	74	19
N2a	164	139	87	50	25	8
N2b	309	247	159	99	57	11
N2c	271	203	131	65	31	12
N3a	8	2	1	0	0	0
N3b	865	614	335	167	67	17

A, Kaplan-Meier estimate for proposed nodal staging system. B, Kaplan-Meier estimate for AJCC 8th edition TNM staging system. ENE indicates extranodal extension; LN+, metastatic lymph node.

chemotherapy type, and perineural invasion, were not available. Our analysis is specific to pathologic staging and may not fully translate to clinical staging, given that imaging and physical examinations are less precise for determining metastatic LN number. Our proposed system may thus be more helpful in determining adjuvant, rather than definitive, treatment decision making. This distinction is relevant for laryngohypopharyngeal cancers, for which definitive chemoradiation can be equally considered for treatment. Nevertheless, this study provides strong empirical evidence to guide pathologic nodal staging.

Conclusions

Our data underscore the principal importance of metastatic LN number in delineating larynx and hypopharynx cancer prognosis. Each additional positive LN is associated with an escalation in mortality risk without plateau, with conventional nodal factors like size and contralaterality eclipsed in prognostic value. We advocate metastatic LN number as a prime component in nodal classification for larynx and hypopharynx cancers to refine staging and drive adjuvant treatment recommendations.

ARTICLE INFORMATION

Accepted for Publication: August 28, 2017.

Published Online: November 30, 2017. doi:10.1001/jamaoncol.2017.3852

Author Affiliations: Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California (Ho, Kim, Tighiouart, Gudino, Mita, Scher, Laury, Prasad, Shiao, Ali, Patio, Mallen-St. Clair, Van Eyk, Zumsteg); Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, California (Ho, Ali, Patio, Mallen-St. Clair); Biostatistics and Bioinformatics Research Center, Cedars-Sinai Medical Center, Los Angeles, California (Kim, Tighiouart); Division of Medical Oncology, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California (Mita, Scher); Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, California (Laury); Department of Radiology, Cedars-Sinai Medical Center, Los Angeles, California (Prasad); Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, California (Shiao, Zumsteg); Advanced Clinical Biosystems Research Institute, Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, California (Van Eyk).

Author Contributions: Drs Ho and Zumsteg had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
Administrative, technical, or material support: All authors.
Study supervision: Ho, Zumsteg.

Conflict of Interest Disclosure: Zachary Zumsteg serves on the external advisory board of the Scripps Proton Therapy Center and has been a paid consultant for EMD Serono.

Funding/Support: This study was supported in part by the National Institutes of Health (grant No. R01 CA188480-01A1), National Center for Advancing Translational Sciences (grants No. UL1TR000124 and UL1TR001881-01), the Donna and Jesse Garber Award for Cancer Research, and the Health Network Foundation Service Excellence Award.

Role of the Funder/Sponsor: The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T; EORTC Head and Neck Cancer Cooperative Group. Larynx preservation in

pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. *J Natl Cancer Inst*. 1996;88(13):890-899.

2. Lefebvre JL, Andry G, Chevalier D, et al; EORTC Head and Neck Cancer Group. Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. *Ann Oncol*. 2012;23(10):2708-2714.

3. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. *J Natl Cancer Inst*. 2009;101(7):498-506.

4. Janoray G, Pointreau Y, Garaud P, et al. Long-term results of a multicenter randomized phase III trial of induction chemotherapy with cisplatin, 5-fluorouracil, ± docetaxel for larynx preservation. *J Natl Cancer Inst*. 2015;108(4):djv368.

5. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003;349(22):2091-2098.

6. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol*. 2013;31(7):845-852.

7. Adelstein D, Gillison ML, Pfister DG, et al. NCCN guidelines insights: head and neck cancers, version 2.2017. *J Natl Compr Canc Netw*. 2017;15(6):761-770.

8. American Joint Committee on Cancer. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer International Publishing; 2017.

9. van Buuren S, Groothuis-Oudshoorn K. MICE: multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45(3):1-67.

10. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res*. 2007;16(3):219-242.

11. Toms JD, Lesperance ML. Piecewise regression: a tool for identifying ecological thresholds. *Ecology*. 2003;84:2034-2041.

12. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and neck cancers—major changes in the American Joint Committee on Cancer eighth edition Cancer Staging Manual. *CA Cancer J Clin*. 2017;67(2):122-137.

13. Ho AS, Kim S, Tighiouart M, et al. Metastatic lymph node burden and survival in oral cavity cancer. *J Clin Oncol*. 2017;JCO2016711176. doi:10.1200/JCO.2016.71.1176.

14. O'Sullivan B, Huang SH, Su J, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. *Lancet Oncol*. 2016;17(4):440-451.

Invited Commentary

Characterizing an Ultra–High-Risk Subset of Patients With Hypopharynx and Larynx Cancer

The Power of Lymph Node Burden

Ryan K. Orosco, MD; Ezra E. Cohen, MD

Staging systems for squamous cell carcinoma of the head and neck (SCCHN) vary by anatomic subsite. Nodal classifications across subsites are similar and are based on the size, number, and laterality of positive regional lymph nodes (LNs). In clinical practice, it is commonly held that contralateral nodal metastases are a poor prognosticator, and the same logic is generally applied to cases with large positive nodes. The American Joint Committee on Cancer's *AJCC Staging Manual*, 8th edition, to be implemented in 2018, continues using the traditional nodal characteristics and adds extranodal extension as an important feature.

Related article page 985

In this issue of *JAMA Oncology*, Ho and colleagues[1] evaluate the relationship between quantitative metastatic lymph node burden and overall survival in patients with squamous cell carcinoma of the hypopharynx and larynx. These authors recently published a similar analysis[2] in patients with oral cavity cancer and now expand their work by evaluating other subsites. In patients from the National Cancer Database treated with primary surgery, the authors found LN burden (number of positive nodes) to be a strong prognosticator—overall mortality increased continuously with greater nodal burden. Surprisingly, the prognostic value of traditional node characteristics (size and laterality) was less than that of nodal burden, although extranodal extension continued to be an important prognosticator.

At 5 positive LNs, Ho and colleagues[1] identified a key change point. For each positive LN from 1 to 5, the risk of mortality rose rapidly (hazard ratio [HR], 1.19; 95% CI, 1.16-1.23; $P < .001$). Although patients with more than 5 positive nodes continued to experience increasing mortality risk, it was to a lesser degree (HR, 1.01; 95% CI, 1.01-1.02; $P = .001$). Another study[3] evaluating a broad group of patients with SCCHN in the SEER (Surveillance, Epidemiology, and End Results) database used this same cutoff of 5 positive LNs to characterize patients with the worst survival. Ho and colleagues[1] propose an alternative nodal classification system based on LN burden and extranodal extension, which they found to outperform the AJCC 8th edition TNM staging system.

The limitations of this analysis, and any national database study, primarily arise from a paucity of detail, such as chemotherapy, radiation, and surgery information; comorbidity details; and factors influencing decision making leading to surgical vs nonsurgical treatment. Perhaps the most glaring weakness of such studies is the absence of recurrence and cancer-specific mortality data. Despite these inherent shortcomings, Ho and colleagues correctly assert the importance of their findings as the strongest empirical evidence to guide pathological nodal staging. Their novel nodal classification schema was built on data from patients treated with surgery, so we should be cautious of extrapolating this to patients treated with primary radiation and chemoradiation. Additional work should be done to correlate and validate the nodal burden findings in nonsurgical cohorts.

It should not be surprising that nononcologic prognosticators also arise from studies like this.[1] The Charlson/Deyo