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Authors

Orosco, Ryan K
Cohen, Ezra E

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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

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 comorbidity index was actually a stronger prognosticator (HR, 1.42; 95% CI, 1.28-1.58; $P < .001$ in multivariable analysis) than metastatic LN burden, emphasizing the need for more salient oncologic data (recurrence and cancer-specific survival) and more cancer-specific markers. To date, the quest for better prognostication and staging has been heavily weighted with clinical phenotypic markers of disease severity. We look forward to the day when our understanding of the molecular basis of cancer development and progression becomes refined enough to incorporate robust genetic and proteomic markers into our risk-stratification models.

The greatest impact of this study by Ho and colleagues[1] is not in the subtle reclassification of lower and middle nodal categories, but in the characterization of a subgroup of patients with the worst survival. Importantly, the authors' novel nodal staging schema more accurately characterizes patients with advanced nodal disease (N3 category). Based on National Comprehensive Cancer Network guidelines,[4] these patients already receive multimodality adjuvant therapy, but further stratifying their risk based on the number of positive nodes defines an ultrahigh-risk population that may benefit from intensified adjuvant protocols and clinical trials.

Targeted therapies are a promising avenue for research, particularly in patients at ultrahigh risk. A recent study[5] in patients with resected, human papillomavirus–negative, high-risk SCCHN reported promising results with adjuvant intensification through the addition of panitumumab to standard cisplatin concurrent chemoradiation. Growing success with adjuvant immunotherapies like durvalumab,[6] an anti-programmed cell death ligand-1 antibody, is ushering in an exciting new era in cancer care. There are currently 16 studies using checkpoint inhibition as neoadjuvant or adjuvant modality for treatment of SCCHN with curative intent.[7]

For now, we will continue to stage patients based on AJCC criteria and use the National Comprehensive Cancer Network guidelines[4] and others for treatment guidance. Characterizing the disease of patients with ultrahigh-risk head and neck cancer based on LN burden may translate into meaningful clini-

cal trial selection criteria. In the future, cancer staging may change based on work like that of Ho and colleagues,[1] streamlining tumor and nodal categories based on fewer independently prognostic characteristics.

ARTICLE INFORMATION

Author Affiliations: Division of Otolaryngology–Head & Neck Surgery, Department of Surgery, University of California, San Diego, Moores Cancer Center, La Jolla (Orosco); Division of Hematology-Oncology, Department of Internal Medicine, University of California, San Diego, Moores Cancer Center, La Jolla (Cohen).

Corresponding Author: Ezra E. Cohen, MD, Division of Hematology-Oncology, Department of Internal Medicine, University of California San Diego Moores Cancer Center, 3855 Health Sciences Dr, MC# 0658, La Jolla, CA 92093 (ecohen@ucsd.edu).

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