Editorial Commentary

American Joint Committee on Cancer 8th edition staging—an improvement in prognostication in HPV-associated oropharyngeal cancer?

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Updates to the TNM staging system are needed in instances when clinical outcomes improve or patient demographics change. Since 1990, the incidence of HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) has increased at a rate of 5% per year (1,2). These patients are distinct from HPV negative OPSCC counterparts as the demographic is younger, healthier, with less exposure to tobacco (1). Furthermore, patients with HPV-associated OPSCC have a disease that is highly responsive to treatment and portends a favorable prognosis (3). Given the dramatically improved survival of patients with HPV-associated OPSCC, it became clear that the seventh edition of the American Joint Committee on Cancer (AJCC 7th ed) staging system was no longer accurate in predicting outcomes in this patient population (4).

Particularly problematic in the AJCC 7th ed were issues related to the N classification or the lymph node metastasis status in HPV-associated OPSCC. The vast majority of these patients were initially staged with N2a or N2b disease making them stage IVa on diagnosis. With overall 3-year survival approaching 85% for these patients, it was clear that AJCC 7th ed nodal staging system was flawed (3,4). To address these problems, the recently released eighth edition (AJCC 8th ed) incorporated a new staging system to distinguish HPV-associated OPSCC. While the T classification system remained very similar, N classification was changed significantly. In AJCC 8th ed, pathologic N1 (pN1) is defined as cervical metastasis in four or fewer lymph nodes and pN2 is defined as metastasis in greater than four lymph nodes. All emphasis on lymph node size, laterality, or extranodal extension (ENE) was removed from the pathologic nodal staging system. In terms of overall staging, in AJCC 8th ed stage IV disease was reserved for patients with distant metastasis. The ultimate result of these changes is that many patients that were previously stage IV at diagnosis are now stage I, a more accurate depiction of their prognosis

The development and refinement of staging systems is a continuous process, and information regarding the efficacy of the AJCC 8th ed staging updates in predicting outcomes and governing treatment modalities has been eagerly awaited. In the recent issue of Oral Oncology, Hobelmann *et al*. have performed a retrospective analysis of surgically treated patients with HPV-associated OPSCC to determine the impact of the AJCC 8th ed staging changes on predicting treatment outcomes (5). They found that the nodal status as defined by the AJCC 8th ed does not appear to correlate with recurrence rates in their cohort. In fact, no variable associated with N classification had an impact on recurrence rates in their cohort. The use of T classification alone (which did not change significantly between AJCC 7th ed and 8th edition) was a better predictor of recurrence. Importantly, the overall staging system used in AJCC 8th ed but not AJCC 7th ed was significantly associated with recurrence.

The lack of correlation with lymph node size, lymph node number, presence of any positive nodes in the HPV positive cohort, and ENE (which did approach significance) suggests that metastasis to cervical nodes may not be a

critical driver in the outcomes for patients with HPV associated OPSCC provided that they are treated with surgery and post-operative adjuvant treatment.

The authors readily acknowledge the limitations of the study. It is a relatively small single institution cohort with only 10 recurrences. The authors used recurrence as a surrogate marker of survival. Treatment recommendations were guided by AJCC 7th ed and the majority of these patients were treated as if they had stage IVa disease, which could potentially mask survival differences. Moving forward, prospective data collection will be need to clarify these issues, but this is an important step forward in our understanding of HPV-associated OPSCC. The results suggest that lymph node metastasis is not an important driver of recurrence and survival in these patients, and thus by proxy, nodal status should be de-emphasized from the overall staging system. These findings further underscore our developing understanding of the disease process in HPV associated OPSCC and likely reflect the highly successful nature of the current treatment modalities for this disease. It is likely that the current treatment of this disease is so effective that it is difficult to ascertain subtle differences in survival based on nodal status.

Changes to staging systems is an iterative process that requires years of validation, ideally in the setting of prospective data. The study by Hobelmann *et al*. is reassuring in that the AJCC 8th ed staging was associated with improved prognostication of recurrence, though it is possible that N classification will be further de-emphasized in future staging systems if the results from this study are further validated as no pathologic lymph node findings have any prognostic significance in this study. At this point T-classification is the primary driver in HPV associated OPSCC cancer staging, which is already reflected in the AJCC 8th ed. However, T-classification is a better predictor of recurrence than overall stage, further emphasizing its dominant role in HPV associated OPSCC. Analysis of additional molecular markers, smoking status, etc., may ultimately be more important in prognostication than nodal status at presentation. Though counterintuitive given historical precedent and contrasting behavior for other head and neck subsites, it is hypothesis-generating studies such as those by Hobelmann that may advance the field by questioning convention.

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Footnote

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