Editorial

HPV in non-oropharyngeal head and neck cancer: does it matter?

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The incidence of head and neck squamous cell carcinoma (HNSCC) varies across the globe due to the prevalence of different risk factors. Exposure to carcinogens such as tobacco, alcohol and betel nut remain common in some parts of the world, while parts of Africa and Asia have higher incidence of nasopharyngeal carcinoma related to Epstein Barr virus. Over the past two decades, it has become increasingly clear that a subset of HNSCC, primarily in the oropharynx, is driven by human papillomavirus (HPV). It is now well established that HPV-driven oropharyngeal squamous cell carcinoma (OPSCC) is associated with favorable treatment responses and survival outcomes compared with HPV-negative OPSCC (1). However, the significance of HPV detected in head and neck tumors outside of the oropharynx is unclear. The existence of tumors in other anatomic sites that contain transcriptionally-active virus and histologic features of HPV-positive OPSCC (non-keratinizing, endophytic growth) has been reported, suggesting that the oncogenesis of these tumors is truly HPV-driven (2).

Prior studies investigating whether the presence of HPV affects survival outcomes in non-oropharyngeal HNSCC have shown mixed results. Most of these prior studies are not adequately powered to detect a difference in survival, since the proportion of non-oropharyngeal HNSCC specimens harboring evidence of HPV is relatively small. This proportion varies from about 2–39% depending on the anatomic subsite, with a larger proportion of HPV-positive tumors in the larynx/hypopharynx versus the oral cavity (3-11). As a result of these factors, most single-institution studies with a few hundred cases or less have not shown a statistically significant improvement in survival for HPV-positive tumors outside of the oropharynx (4-7,9,12,13). A few larger studies including several hundred or more patients have shown improved outcomes for HPV-driven tumors, particularly for laryngeal cancers treated with chemoradiation (3,14-17). Interestingly, a few studies have shown that patients with HPV-positive tumors in the oral cavity had worse survival outcomes (18-20). Another important factor to consider is the variable methodology used to detect HPV in these studies. The more stringent studies used both molecular methods to detect HPV DNA and immunohistochemistry to detect p16, a well-validated surrogate marker of HPV; other studies favored one of these methods or accepted either as evidence of HPV-positivity (3). Some of the studies included only HPV 16, the most common high-risk subtype associated with OPSCC, while other studies also included less common subtypes. Importantly, the presence of HPV DNA and p16 are often discordant, especially outside of the oropharynx, where p16 is not necessarily associated with transcriptionally active virus or HPV-driven tumor biology (21,22).

In a recent study published in *Annals of Translational Medicine*, Zhu and colleagues investigated the relationship between HPV 16 status and survival outcomes in a large cohort of 1,539 patients with non-oropharyngeal HNSCC at a single institution in China (17). In 8.5% of cases (n=131), HPV 16 DNA was detected. In attempt to limit some of the biases inherent to retrospective studies, the authors used propensity score matching (PSM). Though propensity scoring has limitations, it attempts to adjust post-hoc for unbalanced factors among cohorts in order to better approximate what a randomized, controlled trial would show (23). Following PSM, the authors compared disease-specific and overall survival in patients with HPV-positive versus negative tumors in the larynx, hypopharynx, and oral

cavity. Although survival was clearly not different based on HPV 16 status for patients with tumors in the oral cavity or hypopharynx, those with HPV+ laryngeal cancers had statistically significant improvements in DSS and OS (17). These significant differences were seen for the laryngeal subsite in the entire patient cohort but were more striking in the propensity-adjusted cohort.

Zhu and colleagues did acknowledge that these results from their single-institution study may not necessarily be generalizable to other patient populations (17). A large study from the United States analyzed the effects of HPV status on survival outcomes in cases from the National Cancer Database (NCDB), with similar overall methodology but different results (16). In the NCDB study by Tian *et al.*, non-oropharyngeal cases of HNSCC that were positive for HPV 16, 18, or other high-risk HPV types were compared to HPV-negative cases, again using PSM (16). After excluding cases with insufficient information, a total of 9,907 patients with non-OPSCC were included in the analysis. Cases were further stratified into stage I/II versus III/IV, except for the hypopharynx due to lower cases numbers for that anatomic site. In contrast to the study by Zhu *et al.*, survival differences based on HPV status in the NCDB study were more striking in the hypopharynx and oral cavity, whereas the smaller difference in OS for HPV-positive versus negative tumors was not quite statistically significant for the larynx (P=0.063). While reasons for this major difference in results among subsites between the Zhu *et al.* and Tian *et al.* studies are not entirely clear, they are likely related in part to different patient populations from two different continents, with variable rates of other genetic and environmental risk factors. Tian and colleagues also acknowledged that major limitations are present when using a cancer database, including a lack of information on how HPV testing was performed (16). Though Zhu *et al.* only included HPV 16 (17), their detection methods were uniform.

For OPSCC, information on HPV status is critical for patient counseling and enrollment in clinical trials of de-escalated therapy, since the majority of oropharyngeal tumors are HPV-related with a favorable prognosis. Currently, testing for HPV is rarely performed on non-oropharyngeal HNSCC tumors due to the lack of information on how this information can be used in clinical practice. Data on how HPV-driven tumors outside the oropharynx respond to different modalities of therapy are lacking, and the possibility of prognostic information in the minority of HPV-driven cases is not sufficiently motivating for routine testing of all non-OPSCCs.

In summary, large, prospective studies investigating HPV status in non-oropharyngeal HNSCC are lacking, and retrospective studies showed mixed results. These discrepancies may be related to limited sample sizes, different study populations, and varying methods of detecting HPV. Larger studies, including the two discussed above, do suggest that a real survival difference exists for the minority of HPV-driven head and neck tumors arising outside the oropharynx. The prospective studies that would be needed to validate these findings have not yet been a research priority, since the potential effects on treatment options and shared decision making are unclear. As more is learned about equally-effective, less toxic treatment de-escalation strategies for HPV-positive OPSCC with its favorable prognosis, it will be important to revisit whether HPV-driven tumors of the larynx, hypopharynx, and oral c may also portend a favorable prognosis with a need for alternative treatment strategies.

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Footnote

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