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Commentary

Unfinished Business in Classifying HPV-Positive Oropharyngeal Carcinoma: Identifying the Bad Apples in a Good Staging Barrel

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Abstract

This commentary highlights three important findings in the study by Vijayvargiya et al, published in this journal, involving 9554 oropharyngeal cancer patients from the SEER database. Firstly, there is improved performance in outcome prediction with TNM-8 in HPV+ OPC. However, heterogeneity exists, especially in TNM-8 stage I disease, and there is need for ongoing improvement in risk stratification. Several anatomical and non-anatomical prognostic factors have been proposed. Among them, radiologic extranodal extension has emerged as one of the promising parameters to be considered for future staging. These baseline prognostic factors should address sensitivity, specificity, and diagnostic accuracy to serve different clinical needs. Secondly, cure is possible for some patients presenting with M1 disease. Optimal management of such patients remains to be explored, and clinical trials targeting de novo M1 disease should be encouraged to optimize outcomes for this subset. Finally, methodologies to address missing tumor HPV status in historical cohorts have been discussed, including using baseline demographics and clinical characteristics, as well as statistical procedures such as multiple imputation.

Key words: HPV; oropharyngeal carcinoma; staging.

An essential purpose of a stage classification is to describe prognostically relevant subsets defined by anatomic extent of a cancer. Ideally these should stratify a cancer into realistic distinct prognostic groups to serve the needs of clinical care, research, and cancer control activities. Recognizing inadequacies of the 7th edition TNM (TNM-7) in depicting prognosis of HPV-positive (HPV+) oropharyngeal cancer (OPC), the 8th edition UICC/AJCC TNM (TNM-8) introduced a new stage classification for this fast-growing disease that currently dominates OPC population in Western countries, without obvious slackening in tempo in the near future. Many independent institutional series and NCDB data have shown that TNM-8 improves prognostic distinction in HPV+ OPC. The study by Vijayvargiya et al[1] used administrative data comprising 48655 OPC patients from SEER and adds further evidence to the field.

Although current TNM-8 staging enhances the depiction of prognosis of this disease compared with TNM-7, unfinished business in this sphere mandates on-going improvement of current staging systems through data compilation, analysis, and validation.

A useful finding of the study is lack of distinction in overall survival (OS) between stages I and II disease, mainly due to underperformance of the former group. The lower-than-expected OS in stage I disease in the current dataset could be attributable to misclassification of relatively young (<65 years old) OPC patients with TNM-7 T1-2N2b HPV-negative tonsil/base of tongue tumor as stage I HPV-associated disease. It could also be explained by under-appreciated/under-recognized heterogeneity within TNM-8 stage I disease which accounted for 21% of their HPV-selected OPC population. How to identify the "bad apples" in a "good barrel" (stage I disease) remains an important and essential goal for future staging of this disease. Several anatomical parameters and non-anatomical prognostic biomarkers have been proposed but all must cross the bar of practicality, feasibility, and availability, in addition to validation.

Radiologic extranodal extension (rENE) appears to be one of the front-running candidate anatomic variables to identify patients with high risk of distant metastasis and mortality.[2] Billfalk–Kelly et al[2] showed that within cN+ stage I HPV+ OPC, unequivocal rENE-positive patients had increased risk of distant metastasis (>20%) and death (>30%) at 5-years while rENE-negative patients achieved >95% locoregional control and distant control regardless of treatment. Many studies have now consistently shown that rENE is a powerful

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prognostic factor for HPV+ OPC.[3-5] However, it is essential to consolidate the definition of rENE and assessment methods, as well as level of certainty in declaration of rENE, and recognize that ambiguous rENE could dilute its prognostic importance. Indefinite rENE may result from artifactual imaging signal or observer uncertainty, or represent lesser rENE extent, any of which could carry reduced prognostic importance, especially in the era of contemporary treatment.

Among non-anatomic biomarkers, PD-L1 expression appears to be able to identify a group of HPV+ OPC with favorable outcomes.[6,7] Circulating HPV DNA might also serve as a dynamic biomarker following chemoradiotherapy for treatment response assessment and disease surveillance[8] but should ideally also demonstrate baseline characterisation to permit prognostication at the point of diagnosis. Smoking pack-years has been shown to stratify mortality risk in HPV+ OPC[9]; however, its impact on disease control is inconsistent in the literature. Hawkin's et al[10] showed that smoking history seems less important than TNM-8 stage in relation to disease-specific outcomes, and even suggested that deintensification may be appropriate for otherwise low-risk patients with a significant smoking history. Current smoking status appears to have greater impact on outcomes compared with cumulative intensity of tobacco exposure itself (eg, smoking pack-years).[11] This is presumably related to smoking-induced hypoxia which impacts radiotherapy efficacy.[12] In addition, a recent meta-analysis[13] also suggested that smoking during radiotherapy could elevate late toxicity and therefore intensifying treatment in such settings could actually add additional detriment to heavy smokers. Therefore, it is plausible that advocating smoking cessation during radiotherapy represents an important and effective strategy to optimize outcomes for radiotherapy patients.

Notably, the current study also included patients with M1 disease (TNM-8 stage IV) which represented 4% of the authors' cohort. They demonstrated that while these patients have a generally unfavorable outcome, a small proportion (about 15%-20%) can still live beyond 10 years. Long-term survival in HPV+ OPC with oligometastasis has been reported by Huang et al[14] and others.[15] This raises the possibility of "cure" in a subset of patients with de novo or metachronous oligometastasis, supporting consideration of aggressive treatment with curative intent if the metastatic disease is amenable to local ablative treatment. This includes surgery or radical dose radiotherapy with/without systemic agent (chemotherapy and immunotherapy). However, optimal sequencing to address locoregional and distant metastatic disease at presentation remains to be explored, ideally in the clinical trial setting. Identifying the "good apples" in an otherwise "bad barrel" is just as relevant for this group of patients compared with the more favorable subgroups. Therefore, the authors' recommendation to explore genomic profiling in this disease may be even more important for this subset of the HPV+ OPC population.

A uniqueness of the current study is the methodology in handling a historical dataset where HPV status was unavailable. The authors used demographic data (age <65 years, male gender, white race) and disease subsite (tonsil and base of tongue) as surrogates. This method is acceptable in the HPV+ OPC endemic regions where the majority of OPC (estimated >80%) are caused by high-risk HPV infection. However, the choice of parameters and their cutoff values remains debatable and its applicability in areas of lower disease density should be applied with caution. Other methods have been explored to address "missing HPV status" issue. Statistical methods, such as multiple imputation, are useful to ascribe HPV status for missing HPV status subset based on characteristics of HPV status known subset[16,17]; however, this method requires there to be a proportion of cases with ascertained HPV status within the dataset to drive the statistical modelling procedures. Estimating tumor HPV status using patient-specific characteristics has been explored by many authors. D'Souza et al[18] showed a moderate predictivity using demographics and behavioral characteristics to predict HPV+ OPC. Chan et al[19] constructed clinical models using patient demographics plus disease subsite and T/N classifications showed improved predictability in HPV positivity in OPC. Leijenaar et al[20] showed feasibility in predicting tumor HPV status based on radiomic signatures from standard CT images. Although all these methods cannot replace routine HPV testing in OPC, they could be useful to address historical data to help understand time trends of this burgeoning disease in specific jurisdictions.

In summary, as demonstrated by Vijayvargiya et al,[1] current TNM-8 staging represents an improvement in outcome prediction for HPV+ OPC, a new disease for which TNM-7 was never intended. However, it is only the first step in risk stratification of HPV+ OPC. The ability to gather more "wheat" and less "chaff" in favorable stage groups, whether by new and emerging anatomic (eg, rENE) or non-anatomic biomarkers (including genomic profiling), would facilitate clinical care and research for the typical curative population of patients. These baseline prognostic factors should address sensitivity, specificity, and diagnostic accuracy to serve different clinical needs. For factors addressing deintensification trial ineligibility, high sensitivity should be prioritized which would avoid exposing patients to suboptimal treatment. For staging purposes, or eligibility for clinical trials addressing risk of distant metastasis from an adverse feature, high specificity should be emphasized to preserve prognostic importance. Finally, investigations and clinical trials targeting de novo M1 disease should also be useful to optimize outcomes for this subset, some of whom may still be curable with appropriate individualized management.

Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

All authors: conception/design, manuscript writing, final approval of manuscript.

References

1. Vijayvargiya P, Trivedi S, Rupji M, et al. Comparison of the 7th & 8th ed of American Joint Committee on Cancer (AJCC) staging for selected & non-selected oropharyngeal squamous cell carcinomas. *The Oncologist*. 2021.
2. Billfalk-Kelly A, Yu E, Su J, et al. Radiologic extranodal extension portends worse outcome in cN+ TNM-8 stage I human papillomavirus-mediated oropharyngeal cancer. *Int J Radiat Oncol Biol Phys*. 2019;104(5):1017-1027. http://doi.org/10.1016/j.ijrobp.2019.03.047

3. Benchetrit L, Torabi SJ, Givi B, Haughey B, Judson BL. Prognostic significance of extranodal extension in HPV-mediated oropharyngeal carcinoma: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2021;164(4):720-732. http://doi.org/10.1177/0194599820951176
4. Huang SH, O'Sullivan B, Su J, et al. Prognostic importance of radiologic extranodal extension in HPV-positive oropharyngeal carcinoma and its potential role in refining TNM-8 cN-classification. *Radiother Oncol*. 2020;144:13-22. http://doi.org/10.1016/j.radonc.2019.10.011
5. Gal TJ, O'Brien KJ, Chen Q, Huang B. Clinical vs microscopic extranodal extension and survival in oropharyngeal carcinoma in the human papillomavirus era. *Otolaryngol Head Neck Surg*. 2020;162(5):693-701. http://doi.org/10.1177/0194599820910431
6. Solomon B, Young RJ, Bressel M, et al. Prognostic significance of PD-L1+ and CD8+ immune cells in HPV+ oropharyngeal squamous cell carcinoma. *Cancer Immunol Res*. 2018;6(3):295-304. http://doi.org/10.1158/2326-6066.CIR-17-0299
7. Young RJ, Bressel M, Porceddu S, et al. Validation and characterisation of prognostically significant PD-L1+ immune cells in HPV+ oropharyngeal squamous cell carcinoma. *Oral Oncol*. 2020;101:104516. http://doi.org/10.1016/j.oraloncology.2019.104516
8. Chera BS, Kumar S, Shen C, et al. Plasma circulating tumor HPV DNA for the surveillance of cancer recurrence in HPV-associated oropharyngeal cancer. *J Clin Oncol*. 2020;38(10):1050-1058. http://doi.org/10.1200/JCO.19.02444
9. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35. http://doi.org/10.1056/NEJMoa0912217
10. Hawkins PG, Mierzwa ML, Bellile E, et al. Impact of American Joint Committee on Cancer Eighth Edition clinical stage and smoking history on oncologic outcomes in human papillomavirus-associated oropharyngeal squamous cell carcinoma. *Head Neck*. 2019;41(4):857-864. http://doi.org/10.1002/hed.25336
11. Gillison ML, Zhang Q, Jordan R, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. *J Clin Oncol*. 2012;30(17):2102-2111. http://doi.org/10.1200/JCO.2011.38.4099
12. Hoff CM, Grau C, Overgaard J. Effect of smoking on oxygen delivery and outcome in patients treated with radiotherapy for head and neck squamous cell carcinoma–a prospective study. *Radiother Oncol*. 2012;103(1):38-44. http://doi.org/10.1016/j.radonc.2012.01.011
13. Smith J, Nastasi D, Tso R, Vangaveti V, Renison B, Chilkuri M. The effects of continued smoking in head and neck cancer patients treated with radiotherapy: a systematic review and meta-analysis. *Radiother Oncol*. 2019;135:51-57. http://doi.org/10.1016/j.radonc.2019.02.021
14. Huang SH, Perez-Ordonez B, Weinreb I, et al. Natural course of distant metastases following radiotherapy or chemoradiotherapy in HPV-related oropharyngeal cancer. *Oral Oncol*. 2013;49(1):79-85. http://doi.org/10.1016/j.oraloncology.2012.07.015
15. McBride SM, Busse PM, Clark JR, Wirth LJ, Ancukiewicz M, Chan AW. Long-term survival after distant metastasis in patients with oropharyngeal cancer. *Oral Oncol*. 2014;50(3):208-212. http://doi.org/10.1016/j.oraloncology.2013.10.020
16. Habbous S, Chu KP, Lau H, et al. Human papillomavirus in oropharyngeal cancer in Canada: analysis of 5 comprehensive cancer centres using multiple imputation. *CMAJ*. 2017;189(32):E1030-E1040. http://doi.org/10.1503/cmaj.161379
17. Habbous S, Chu KP, Qiu X, et al. The changing incidence of human papillomavirus-associated oropharyngeal cancer using multiple imputation from 2000 to 2010 at a Comprehensive Cancer Centre. *Cancer Epidemiol*. 2013;37(6):820-829. http://doi.org/10.1016/j.canep.2013.09.011
18. D'Souza G, Zhang HH, D'Souza WD, Meyer RR, Gillison ML. Moderate predictive value of demographic and behavioral characteristics for a diagnosis of HPV16-positive and HPV16-negative head and neck cancer. *Oral Oncol*. 2010;46(2):100-104. http://doi.org/10.1016/j.oraloncology.2009.11.004
19. Chan MW, Yu E, Bartlett E, et al. Morphologic and topographic radiologic features of human papillomavirus-related and -unrelated oropharyngeal carcinoma. *Head Neck*. 2017;39(8):1524-1534. http://doi.org/10.1002/hed.24764
20. Leijenaar RT, Bogowicz M, Jochems A, et al. Development and validation of a radiomic signature to predict HPV (p16) status from standard CT imaging: a multicenter study. *Br J Radiol*. 2018;91(1086):20170498. http://doi.org/10.1259/bjr.20170498.