

The prognostic value of HPV in head and neck cancer patients undergoing postoperative chemoradiotherapy

Randall J. Kimple, Paul M. Harari

Department of Human Oncology, Carbone Comprehensive Cancer Center, University of Wisconsin School of Medicine and Public Health, Madison, WI 53792, USA

Correspondence to: Randall J. Kimple, MD, PhD, and Paul M. Harari, MD. University of Wisconsin Hospital and Clinics, 600 Highland Ave., K4/B100, Madison, WI 53792, USA. Email: rkimple@humonc.wisc.edu; harari@humonc.wisc.edu.

Submitted Jan 23, 2015. Accepted for publication Jan 26, 2015.

doi: 10.3978/j.issn.2305-5839.2015.01.37

View this article at: <http://dx.doi.org/10.3978/j.issn.2305-5839.2015.01.37>

In a recent issue of *Radiotherapy and Oncology*, Lohaus and colleagues reported (<http://dx.doi.org/10.1016/j.radonc.2014.11.011>) on a subgroup analysis from the German Cancer Consortium Radiation Oncology Group (DKTK-ROG) (1). They reported on 221 patients treated with postoperative radiotherapy with concurrent cisplatin (PORT-C) treated over a 5-year period between 2005 and 2010. They investigate the role of human papilloma virus (HPV) in non-oro-pharynx head and neck cancer and extend findings from several reports that patients with HNC arising in the oropharynx have significantly improved outcomes if their cancer is associated with HPV.

Patients in this study cohort were at high risk for loco-regional recurrence due to locally advanced disease with a tumor stage of pT4, >3 positive lymph nodes, positive margins and/or extracapsular extension. Patients with primary tumors arising in the oral cavity (n=60), oropharynx (n=126), and hypopharynx (n=35) were included. Patients were also required to have formalin-fixed paraffin-embedded (FFPE) material available for both DNA analysis and immunohistochemistry (IHC). HPV was identified by polymerase chain reaction (PCR) using standard primers on genomic DNA extracted from FFPE sections. Several biomarkers including p16 and p53 were also assessed by IHC.

Low incidence of HPV outside the oropharynx

Various forms of HPV testing are now routinely performed for most patients with oropharynx cancer and utilized as both a stratification variable and an entry criterion for

clinical trials. Approximately 50% of oropharynx cancer patients in this study had tumors that tested positive for HPV. This rate corresponds well with recent reports from other European centers and is slightly lower than the 65-70% rate seen in many US reports (2). While the authors did not report a formal correlation analysis; in the oropharynx, similar percentages of patients were positive for HPV DNA and p16 (48% and 54%, respectively). Consistent with the role of the HPV E6 oncoprotein in degrading p53, most patients with HPV-positive tumors demonstrated negative staining for p53.

In contrast to oropharynx cancers, HPV (or p16) was detected in only 12% of oral cavity and 15% of hypopharynx cancers. Similar proportions of tumors in these sites were also positive for p16 (18% and 9%, respectively). These results are quite similar to the 9% of non-oro-pharyngeal cancers found to be positive for HPV by in situ hybridization (19% positive by p16 IHC) in a recent publication by Chung and colleagues (3). Both of these studies suggest a disparity between the detection of HPV DNA and IHC for p16 when the prevalence of HPV is low (e.g., oral cavity, larynx, hypopharynx). The poor positive predictive value of p16 for HPV infection in these disease sites suggests that there may be other explanations for p16 overexpression besides HPV outside the oropharynx.

Improved outcomes in HPV+ (oropharynx) cancer

As in the non-operative setting, patients in this surgery-first study with HPV-positive tumors had significantly better loco-regional tumor control (HR =0.20, P=0.04)

and overall survival (HR =0.36, $P<0.01$) than those with HPV-negative tumors. Improved outcomes in HPV-positive HNC patients have been consistently observed in single institution studies and in large multicenter trials performed by the Radiation Therapy Oncology Group (4), Eastern Cooperative Oncology Group (5), Trans Tasman Radiation Oncology Group (6), and the Danish Head and Neck Cancer Group (7). Although some reports have demonstrated this favorable HPV effect in the postoperative setting (8), much of the data reflects patients treated with non-operative approaches. In this postoperative report by the DTKK-ROG (1), the improved outcomes in HPV-positive patients are strongly confirmed and appear to be due primarily to patients with oropharynx cancer ($n=126$, HR =0.09 and HR =0.36 for loco-regional control and overall survival, respectively). As discussed, 59 of 71 HPV-positive patients had oropharynx cancers. Despite the small number of non-oropharynx cancers, Lohaus and colleagues did analyze outcomes by HPV status in oral cavity cancers and identified no impact on either loco-regional control or overall survival. No data on a similar analysis for hypopharynx cancers was provided in this manuscript. This data contrasts with that recently reported by Chung *et al.*: patients with p16-positive non-oropharynx tumors had significantly better overall survival (HR =0.57) than those with p16-negative tumors (3). In the analysis by Chung *et al.*, no difference in outcomes was seen in patients who were HPV-positive by in situ hybridization.

It has been postulated that the improved outcomes in HPV-positive cancers may be related to increased sensitivity to therapy or enhanced anti-tumor immunity. Preclinical data exists for a key role of the HPV oncoproteins in modulating sensitivity to radiation (9-12) and for an important role for an anti-tumor immune response (13-15). Ongoing studies by a number of groups are studying the role of therapeutic de-intensification for patients with HPV-positive oropharynx cancer (16). The converse, therapeutic intensification, is being studied in HPV-negative cancers due to the poor outcomes in this group of patients.

Implications and future directions

The results presented by Lohaus and colleagues further extend our knowledge base in oropharyngeal cancer: a significant proportion of these cancers are associated with HPV and patients with HPV-positive cancers have a better prognosis than those with HPV-negative cancers. This improved survival outcome is observed whether

patients are treated with surgery followed by postoperative chemoradiation or using definitive chemoradiation. The outstanding loco-regional control demonstrated in this cohort for HPV-positive patients should be kept in perspective: even among patients with HPV-negative disease 3-year local failure rate was only 20% suggesting a more favorable cohort in comparison to major studies in which patients received primary chemoradiation. HPV-negative oropharynx cancer patients treated on RTOG 0522 and 0129 demonstrated a 3-year loco-regional failure rate (30-45%), nearly double that seen in the DTKK-ROG report (17,18).

The last decade has witnessed important advances in our understanding of the prognosis of patients with oropharynx cancer. In 2015, we do not yet have data that the treatment of patients with HPV-positive oropharynx cancers should differ from that of HPV-negative HNCs, outside the context of a clinical trial. However, there are numerous studies in progress to evaluate treatment de-intensification strategies for what appear to be the most favorable cases. Given the variable data regarding the prognostic impact of HPV in non-oropharynx cancers, future clinical studies should consider stratification on the basis of HPV, but there is insufficient data to include HPV-positive non-oropharyngeal patients in ongoing studies of HPV-positive oropharynx cancer.

The global rise in the prevalence of human papillomavirus (approaching 70% of all oropharynx cancers in the United States and a slightly lower percentage in Europe) as a causative factor in HNC has important clinical implications. While vaccination efforts are ongoing in teenagers and young adults, the impact of ongoing vaccination programs will likely not be realized for 20-30 years. Stepwise, systematic clinical investigation should enable us to more accurately identify those subsets of patients who can safely be treated with various forms of treatment de-intensification without compromising overall tumor control and survival.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Lohaus F, Linge A, Tinhofer I, et al. HPV16 DNA status is a strong prognosticator of loco-regional control after postoperative radiochemotherapy of locally advanced oropharyngeal carcinoma: Results from a multicentre

- explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG). *Radiother Oncol* 2014;113:317-23.
2. Stein AP, Saha S, Yu M, et al. Prevalence of human papillomavirus in oropharyngeal squamous cell carcinoma in the United States across time. *Chem Res Toxicol* 2014;27:462-9.
 3. Chung CH, Zhang Q, Kong CS, et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. *J Clin Oncol* 2014;32:3930-8.
 4. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24-35.
 5. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst* 2008;100:261-9.
 6. Rischin D, Young RJ, Fisher R, et al. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. *J Clin Oncol* 2010;28:4142-8.
 7. Lassen P, Overgaard J, Eriksen JG. Expression of EGFR and HPV-associated p16 in oropharyngeal carcinoma: correlation and influence on prognosis after radiotherapy in the randomized DAHANCA 5 and 7 trials. *Radiother Oncol* 2013;108:489-94.
 8. Harari PM, Harris J, Kies MS, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. *J Clin Oncol* 2014;32:2486-95.
 9. Kimple RJ, Smith MA, Blitzer GC, et al. Enhanced radiation sensitivity in HPV-positive head and neck cancer. *Cancer Res* 2013;73:4791-800.
 10. Park JW, Nickel KP, Torres AD, et al. Human papillomavirus type 16 E7 oncoprotein causes a delay in repair of DNA damage. *Radiother Oncol* 2014;113:337-44.
 11. Rieckmann T, Tribius S, Grob TJ, et al. HNSCC cell lines positive for HPV and p16 possess higher cellular radiosensitivity due to an impaired DSB repair capacity. *Radiother Oncol* 2013;107:242-6.
 12. Dok R, Kalev P, Van Limbergen EJ, et al. p16INK4a impairs homologous recombination-mediated DNA repair in human papillomavirus-positive head and neck tumors. *Cancer Res* 2014;74:1739-51.
 13. Spanos WC, Nowicki P, Lee DW, et al. Immune response during therapy with cisplatin or radiation for human papillomavirus-related head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2009;135:1137-46.
 14. Vermeer DW, Spanos WC, Vermeer PD, et al. Radiation-induced loss of cell surface CD47 enhances immune-mediated clearance of human papillomavirus-positive cancer. *Int J Cancer* 2013;133:120-9.
 15. Lyford-Pike S, Peng S, Young GD, et al. Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma. *Cancer Res* 2013;73:1733-41.
 16. Kimple RJ, Harari PM. Is radiation dose reduction the right answer for HPV-positive head and neck cancer? *Oral Oncol* 2014;50:560-4.
 17. Nguyen-Tan PF, Zhang Q, Ang KK, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. *J Clin Oncol* 2014;32:3858-66.
 18. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol* 2014;32:2940-50.

Cite this article as: Kimple RJ, Harari PM. The prognostic value of HPV in head and neck cancer patients undergoing postoperative chemoradiotherapy. *Ann Transl Med* 2015;3(S1):S14. doi: 10.3978/j.issn.2305-5839.2015.01.37