An Analysis of 356 Tumor Specimens Shows p16 Expression Is Not a Reliable Indicator of Human Papillomavirus (HPV) in Oral Cavity, Hypopharynx, and Larynx Cancers

Research published online last week in the Journal of Clinical Oncology reported results of an investigation that pooled head and neck tumor specimens for analysis that were collected as part of three clinical trials conducted by the Radiation Therapy Oncology Group, which is now conducting research as NRG Oncology.

The expression of p16 in oropharyngeal squamous cell carcinoma (OPSCC) is a validated biomarker of HPV positivity. Patients with HPV-positive OPSCC have significantly better outcomes than those with HPV-negative OPSCC. The strong correlation between p16 expression and HPV positivity led to the use of p16 expression as a biomarker for patient selection in clinical trials evaluating if patients with HPV positive OPSCC can undergo less intense therapy than standard-of-care treatment and, thereby, reduce treatment-related side effects without negatively affecting survival outcomes.

Investigators led by Christine H. Chung, MD, Associate Professor of Oncology at Johns Hopkins University, evaluated the prognostic significance of p16 expression in oral cavity, hypopharynx and larynx, collectively referred to as non-OPSCC, where HPV infection is less common than in the oropharynx. Their analysis employed the widely used tests of immunohistochemistry (IHC) for p16 expression and in situ hybridization (ISH) for HPV detection.

A total of 683 eligible patients with non-OPSCC tumors were identified among the 1,921 patients enrolled in the RTOG 0129, RTOG 0234 and RTOG 0522 clinical trials. Three hundred and fifty-six tumors were tested for p16 expression and 311 tumors were evaluated for HPV testing. Their results show, for non-OPSCC tumors, the correlation between p16 IHC and HPV ISH is moderate, especially in tumors of the oral cavity. “Given the strong correlation we see between p16 expression and HPV positivity for oropharyngeal cancer and the associated prognosis for superior outcomes, it was important to evaluate p16 as a prognostic biomarker for non-oropharyngeal cancers,” says Chung. “We learned that p16 determined by IHC is not a reliable surrogate for HPV infection in patients with non-oropharyngeal cancer and it is unclear based on our study whether p16 expression is due to a false negativity in the HPV detection or due to an alternate molecular mechanism resulting in p16 expression in these patients.”

Patients with non-OPSCC whose tumor tested positive for p16 expression were reported to have better progression free survival (a 35% reduction in tumor progression) and overall survival (a 43% reduction in the death rate) than those whose tumor tested negative for p16 expression. However, the analysis showed that patients with HPV-positive tumors did not have significantly better progression free survival or overall survival than patients with HPV-negative tumors. The authors’ note, “While the relevance of p16 expression as a prognostic biomarker is well established in the context of p16 as a surrogate for HPV status, the significance of p16 expression decoupled from HPV in non-OPSCC is unclear requiring further investigation. “Survival outcomes based on p16 status and smoking status were also evaluated. The majority of the patients with non-OPSCC (75% of p16-positive and 84% of p16-negative patients) were heavy smokers (> 10 pack years), and the investigators found smoking history did not impact survival differences between the two groups.

“This multidisciplinary translational research is part of our global strategy to provide personalized oncology care for our patients. Using molecular pathology diagnostic techniques, validated on prospective trials conducted by NRG Oncology, allows us to design clinical strategies which tailor cancer therapies to patients.
for the goals of improving cure rates while at the same time minimizing the toxicity of treatment,” says Adam Dicker, MD, PhD, a chair of the NRG Oncology Translational Research Committee and Professor and Chair in the Department of Radiation Oncology at Thomas Jefferson University, Philadelphia, PA.

For next steps, the authors recommend further development of a p16 IHC scoring system in non-OPSCC and improvement of HPV detection methods prior to broad application in a clinical setting.

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NRG Oncology conducts practice-changing, multi-institutional clinical and translational research to improve the lives of patients with cancer. Founded in 2012, NRG Oncology is a Pennsylvania-based nonprofit corporation that integrates the research strengths of the National Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group and the Gynecologic Oncology Group. The research organization seeks to carry clinical trials with emphases on gender-specific malignancies including gynecologic, breast, and prostate cancers and on localized or locally advanced cancers of all types. NRG Oncology’s extensive research organization is comprised of multidisciplinary investigators including medical oncologists, radiation oncologists, surgeons, physicists, pathologists, and statisticians and encompasses more than 1300 research sites located world-wide with predominance in the United States and Canada. NRG Oncology is supported primarily through grants from the National Cancer Institute (NCI) and is one of five research groups in the NCI’s National Clinical Trials Network.