

Detection of Human Papillomavirus in Clinical Samples

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KEYWORDS

- Oropharyngeal carcinoma • Squamous cell carcinoma of the head and neck
- In situ hybridization • Hybrid capture 2 • p16 immunohistochemistry

KEY POINTS

- Identification of human papillomavirus (HPV) in squamous cell carcinomas of the head and neck is rapidly becoming a means of tracking the presence and progress of disease relating to all aspects of patient care, including prognosis, tumor staging (ie, identifying site of tumor origin), and selection of patients who are most likely to benefit from tailored therapeutic options.
- At present, there is no standard approach for HPV testing of clinical samples. The challenge for the oncologic community is to implement standardized HPV testing using a method that is highly accurate, technically feasible, and cost effective.
- The use of p16 immunohistochemical staining is acceptable as a method of HPV detection, provided it is used and interpreted in a defined context that takes into account certain anatomic factors, histologic findings, and staining characteristics.
- The development of detection assays that are optimized for cytologic samples will lead to more widespread implementation of HPV testing and may obviate tissue acquisition and processing.

INTRODUCTION

Squamous cell carcinoma of the head and neck (HNSCC) has long been regarded as a monotonous disease entity. Important distinctions between anatomic subsites and natural histories have largely been ignored, given the histopathologic uniformity and response to treatment. Recent studies suggest considerable differences between some HNSCCs that go beyond variations related to tumor subsite and stage. In

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particular, a subset of HNSCCs, which is associated with the human papillomavirus (HPV), has emerged as a form of HNSCC with an epidemiologic, demographic, histopathologic, and clinical profile that deviates from the profile of conventional non-HPV-related HNSCC.^{1,2} HPV-associated cancers tend to occur more frequently in younger men, and tobacco smoking does not seem to be a strong cofactor in the development of these tumors.^{3,4} These cancers most frequently occur in the oropharynx,^{2,5} tend to exhibit a nonkeratinizing basaloid morphology,^{6,7} and are associated with improved clinical outcomes.^{2,8-10} In effect, recognition of this association with HPV amounts to the identification of a new and distinct disease entity.

WHY IS HPV TESTING IMPORTANT?

Until recently, clinicians have not been able to rely on prognostic markers other than tumor staging in their care of patients with HNSCC. Although numerous studies have addressed the prognostic relevance of cell proliferation (eg, Ki67, proliferating cell nuclear antigen), p53 immunohistochemical staining, apoptosis, aneuploidy, epidermal growth factor receptor overexpression, and various other markers of biological activity, none of these markers have proved consistently reliable across multiple studies. None of these markers are currently used as a routine part of pathologic evaluation for patient care. The absence of reliable prognostic markers has been offset to some degree by HPV testing. The detection of HPV in HNSCCs has recently emerged as a powerful biomarker, indicating a more favorable clinical outcome. Patients with HPV-positive tumors have a lower risk of tumor progression and death than patients with HPV-negative tumors.^{2,8-10} Accordingly, inclusion of HPV status as a parameter for emerging molecular staging systems is compelling, and routine HPV assessment will soon become part of the standard pathologic evaluation of all oropharyngeal carcinomas. Both the College of American Pathologists and the American Joint Committee on Cancer have recently recommended routine HPV testing as part of the standard pathologic evaluation of resected oropharyngeal squamous cell carcinomas for the purpose of molecular tumor staging.^{11,12}

The value of HPV testing is by no means confined to mere prognostication in patients with HNSCC. A study that analyzed the motivations for HPV testing in the clinical arena found that HPV testing was often initiated by the pathologist to help resolve difficult diagnostic dilemmas.¹³ For example, HPV testing of cervical lymph node metastases is a highly effective strategy for localizing the site of origin in those patients who present with neck metastases in the absence of an obvious primary tumor. In these patients, the detection of HPV in a lymph node metastasis is a reliable predictor of oropharyngeal origin (**Fig. 1**).^{14,15} Similarly, HPV status can be used to clarify second primary or metastatic disease in those patients with HNSCC who subsequently develop squamous cell carcinoma in their lungs.¹⁶ In some instances, HPV status can inform the differential diagnosis, such as squamous-lined cysts of the lateral neck, where an HPV-positive cystic metastasis can easily be confused with an inflamed branchial cleft cyst.¹⁷

As more is understood of the unique natural history of HPV-positive HNSCC, from viral infection to viral persistence to viral-induced malignant transformation, applications for HPV testing will undoubtedly continue to increase. The detection of HPV is emerging as a valid biomarker for discerning the presence and progress of disease, encompassing all aspects of patient care:

- Early cancer detection.¹⁸
- More accurate tumor staging.^{14,15}

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