Human Papillomavirus Testing in Head and Neck Carcinomas: ASCO Clinical Practice Guideline Endorsement Summary of the CAP Guideline

Carole Fakhry, Christina Lacchetti, and Bayardo Perez-Ordonez

Johns Hopkins School of Medicine, Baltimore, MD; American Society of Clinical Oncology, Alexandria, VA; and University Health Network, Toronto, Ontario, Canada

The incidence of oropharyngeal cancers has been increasing dramatically in the United States and in other developed countries. An estimated 16,000 new cases are diagnosed each year in the United States.[1] These incidence trends seem to be driven by human papillomavirus (HPV). Indeed, the prevalence of HPV-positive tumors in the oropharynx in the United Statess has steadily increased, whereas the prevalence of HPV-negative oropharynx cancers has declined.[2,3] By 2020, the incidence of HPV-associated oropharyngeal cancer is forecasted to exceed that of cervical cancer.[2,4]

HPV-related and -unrelated tumors have established differences in terms of epidemiology, clinical and demographic phenotype at presentation, histopathology, and prognosis; therefore, HPV-related oropharynx cancer is now considered to be an entity that is distinct from HPV-unrelated oropharynx cancer, despite residing in the same anatomic site. Whereas HPV may serve as an etiologic infection in oropharyngeal squamous cell carcinoma, its contribution related to nonoropharyngeal cancer appears to be substantially less, and its prognostic and therapeutic significance remain controversial.[5-9]

In 2018, the College of American Pathologists (CAP) released guideline recommendations regarding testing for HPV in head and neck cancers.[10] ASCO has established a process for endorsing other organizations' clinical practice guidelines. The guideline endorsement summarizes the results of that process and presents the endorsed practice recommendations.[11]

The original CAP Recommendations appear in Table 1 and online at https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/human-papillomavirus-testing-in-head-and-neck-carcinomas. Additional information is available at www.asco.org/head-neck-cancer-guidelines. Patient information is available at www.cancer.net. JOP

Acknowledgment

Human Papillomavirus Testing in Head and Neck Carcinomas: ASCO Clinical Practice Guideline Endorsement of the CAP Guideline was developed and written by: Carole Fakhry, Christina Lacchetti, Lisa M. Rooper, Richard C. Jordan, Danny Rischin, Erich M. Sturgis, Diana Bell, Mark W. Lingen, Seema Harichand-Herdt, John Thibo, Jose Zevallos, and Bayardo Perez-Ordonez.

Authors' Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at jop.ascopubs.org.

Author Contributions

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

DOI: https://doi.org/10.1200/JOP.18.00433; published online ahead of print at jop.ascopubs.org on September 7, 2018.

THE BOTTOM LINE

Human Papillomavirus Testing in Head and Neck Carcinomas: ASCO Clinical Practice Guideline Endorsement Summary of the CAP Guideline

ASCO endorses the Human Papillomavirus Testing in Head and Neck Carcinomas Clinical Practice Guideline, with qualifying statements by the ASCO Expert Panel.

Guideline Question

What is the optimal way to test, apply, interpret, and report HPV and surrogate marker tests in head and neck carcinomas.

Target Population

People with head and neck squamous cell carcinoma.

Target Audience

Oncologists, pathologists, and other providers involved in the delivery of care to patients with head and neck squamous cell carcinoma.

Methods

An ASCO Expert Panel was convened to consider endorsing the CAP Human Papillomavirus Testing in Head and Neck Carcinomas Clinical Practice Guideline recommendations that were based on a systematic review of the medical literature. The ASCO Expert Panel considered the methodology used in the CAP guideline by considering the results from the AGREE II review instrument. The ASCO Expert Panel carefully reviewed the CAP guideline content to determine its appropriateness for ASCO endorsement.

Recommendations

ASCO Expert Panel's endorsed recommendations and qualifying statements:

Overall ASCO Qualifying Statement:

CAP guidelines recommend high-risk (HR) HPV testing. ASCO endorses the importance of HPV tumor detection, but qualifies that the term HR HPV cannot be used interchangeably with p16 in all circumstances. HR HPV should only be referred to when HPV-specific testing has been performed, including in situ hybridization or polymerase chain reaction for HR oncogenic HPV types. Instead, we recommend using the general term HPV tumor status, as HR HPV may be misleading. p16 can be considered a surrogate for HPV-positive tumor status strictly for oropharynx tumors, and only when HPV-specific testing has been ascertained can HR HPV be used/asserted.

Recommendation 1:

Pathologists should perform HR HPV testing in all patients with newly diagnosed OPSCC, including all histologic subtypes. This testing may be performed on the primary tumor or on a regional lymph node metastasis when the clinical findings are consistent with an oropharyngeal primary.

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ASCO Qualifying Statement:

The ASCO Endorsement Panel reinforces the need to determine HPV tumor status in newly diagnosed OPSCC.

Recommendation 2:

For oropharyngeal tissue specimens—that is, noncytology—pathologists should perform HR HPV testing by surrogate marker p16 immunohistochemistry (IHC). Additional HPV-specific testing may be done at the discretion of the pathologist and/or treating clinician or in the context of a clinical trial.

ASCO Qualifying Statement:

A small fraction of oropharyngeal tumors are not etiologically driven by HPV, yet overexpress p16. Pathologists should be experienced with and have available confirmatory HPV testing.

Recommendation 3:

Pathologists should *not* routinely perform HR HPV testing on patients with nonsquamous carcinomas of the oropharynx.

ASCO Qualifying Statement:

When oropharyngeal tumors are poorly differentiated and there is uncertainty that the carcinoma is nonsquamous—for example, with neuroendocrine tumors—HPV tumor testing is warranted.

Recommendation 4:

Pathologists should *not* routinely perform HR HPV testing on patients with nonoropharyngeal primary tumors of the head and neck.

Recommendation 5:

Pathologists should routinely perform HR HPV testing on patients with metastatic squamous cell carcinoma (SCC) of unknown primary in a cervical upper- or midjugular chain lymph node. An explanatory note on the significance of a positive HPV result is recommended.

Recommendation 6:

For tissue specimens—that is, noncytology—from patients who present with metastatic SCC of unknown primary in a cervical upper- or midjugular chain lymph node, pathologists should perform p16 IHC. Expert consensus opinion. (NOTE. Additional HR HPV testing on p16-positive cases should be performed for tumors that are located outside of level II or III—nonroutine testing—in the neck and/or tumors with keratinizing morphology.)

ASCO Qualifying Statement:

p16 IHC alone may not be sufficient in this scenario. Additional confirmatory testing should be performed at the discretion of the pathologists and/or clinician. ASCO recommends HPV tumor detection for unknown primary in head and neck squamous cell cancer independent of keratinizing morphology (refer to updated flowchart).

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Recommendation 7:

Pathologists should perform HR HPV testing on head and neck fine-needle aspiration (FNA) SCC samples from all patients with known OPSCC not previously tested for HR HPV, with suspected OPSCC, or with metastatic SCC of unknown primary. (NOTE. No recommendation is made for or against any specific testing methodology for HR HPV testing in FNA samples. If the result of HR HPV testing on the FNA sample is negative, testing should be performed on tissue if it becomes available. If pathologists use cytology samples for p16 IHC testing, they should validate the criteria—that is, cut off—for a positive result.)

ASCO Qualifying Statement:

IHC alone may not be sufficient in this scenario, particularly with cytology material. Additional confirmatory testing should be performed at the discretion of the pathologist and/or clinician. ASCO recommends a 70% cutoff for p16 IHC with use restricted to patients with known OPSCC.

Recommendation 8:

Pathologists should report p16 IHC positivity as a surrogate for HR HPV in tissue specimens—that is, noncytology—when there is at least 70% nuclear and cytoplasmic expression with at least moderate to strong intensity.

ASCO Qualifying Statement:

Tissue specimens that fail to meet the recommended threshold may still warrant more specific HR HPV testing if clinical features are consistent with HPV etiology.

Recommendation 9:

Pathologists should *not* routinely perform low-risk HPV testing on patients with head and neck carcinomas.

Recommendation 10:

Pathologists should *not* repeat HPV testing on patients with locally recurrent, regionally recurrent, or persistent tumor if primary tumor HR HPV status has already been established. If initial HR HPV status was never assessed or if results are unknown, testing is recommended. HPV testing may be performed on a case-by-case basis for diagnostic purposes if there is uncertainty regarding whether the tumor in question is a recurrence or a new primary SCC.

Recommendation 11:

Pathologists should *not* routinely perform HR HPV testing on patients with distant metastases if primary tumor HR HPV status has been established. HPV testing may be performed on a case by-case basis for diagnostic purposes if there is uncertainty regarding whether the tumor in question is a metastasis or a new primary SCC.

Recommendation 12:

Pathologists should report primary OPSCCs that test positive for HR HPV or its surrogate marker p16 as HPV positive and/or p16 positive.

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Recommendation 13:

Pathologists should *not* provide a tumor grade or differentiation status for HPV-positive and/or p16-positive OPSCCs.

Recommendation 14:

Pathologists should *not* alter the HR HPV testing strategy on the basis of patient smoking history.

Additional Resources

More information, including a Data Supplement, Methodology Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/head-neck-cancer-guidelines. Patient information is available at www.cancer.net. A link to Human Papillomavirus Testing in Head and Neck Carcinomas Guideline from the College of American Pathologists can be found at http://www.cap.org.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

Corresponding author: Christina Lacchetti, American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; email: guidelines@asco.org.

Reprint requests: 2318 Mill Road, Suite 800, Alexandria, VA 22314; guidelines@asco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Carole Fakhry
No relationship to disclose

Christina Lacchetti
No relationship to disclose

Bayardo Perez-Ordonez
Honoraria: AstraZeneca