COLLEGE of AMERICAN PATHOLOGISTS

Laboratory Quality Solutions

# Human Papillomavirus Testing in Head and Neck Carcinomas

## Guideline from the College of American Pathologists

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**12/18/2017**

# Overview

- **Introduction**
- **Clinical questions addressed and main findings**
- **Guideline development process**
- **Guideline statements**
- **Conclusion**

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# Introduction

- **The incidence of Human Papillomavirus (HPV)-related head and neck carcinomas is rising in the United States (US), with the greatest increase among middle-aged white men.**
- **At least 25% and as much as 60% of head and neck cancers are now associated with high-risk HPV (HR-HPV), although the role and clinical significance of the HPV in cancers is only clearly defined for those arising in the oropharynx.**

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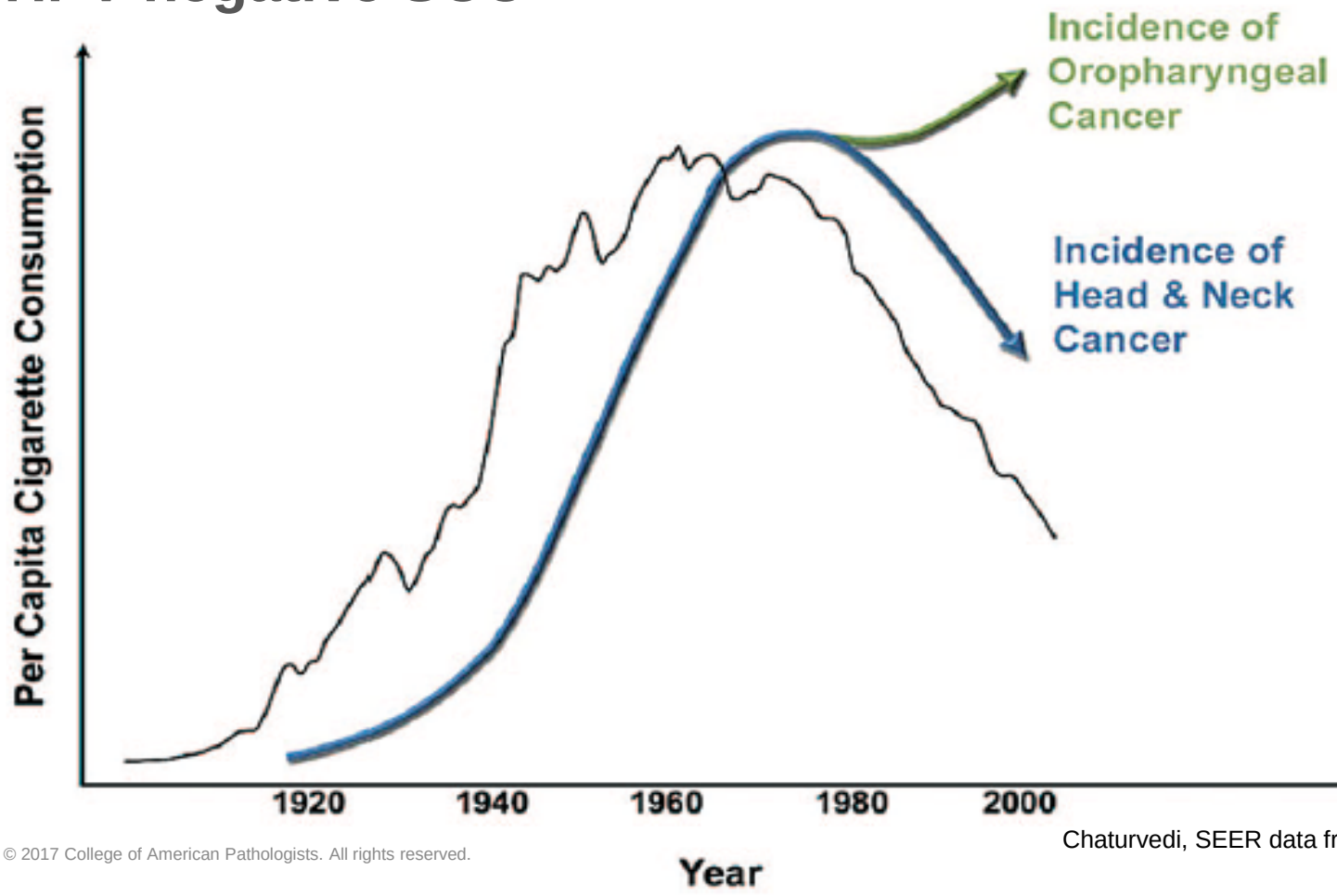
# The HPV head and neck squamous cell carcinoma (SCC) epidemic

**225% increase in HPV-positive SCC vs 50% decrease in HPV-negative SCC**




Chaturvedi, SEER data from 1984-2004

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# Introduction, continued

- **HPV 16 is the most common driver of oropharyngeal carcinoma, implicated in over 90% of these patients.**
- **HPV-positive oropharyngeal squamous cell carcinomas (OPSCCs) have better prognosis, and these patients may be candidates for less aggressive therapy compared to HPV-negative carcinoma patients.**

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# Introduction, continued

- **The clinical role of HPV testing in head and neck SCCs and target populations has previously been established by other studies (Cancer Care Ontario). The College of American Pathologists (CAP) developed recommendations for methods of HR-HPV testing in both histologic and cytologic specimens of head and neck carcinomas.**

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# Clinical questions addressed

1. **Should patients with newly diagnosed OPSCC, nonoropharyngeal squamous cell carcinoma (non-OPSCC), oropharyngeal non-SCC, nonoropharyngeal non-SCC, and cervical nodal metastatic carcinomas of unknown and/or known primary be routinely tested for HR-HPV?**

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# Clinical questions addressed, continued

2. **Do relevant clinical outcomes of specific tests or testing algorithms for HR-HPV differ based on:**
   - **Specimen size, percent neoplastic cellularity, and cellularity?**
   - **Type and length of tissue fixation?**
   - **For immunohistochemistry (IHC) p16 testing, specific antibodies, dilution, and testing conditions?**
   - **For IHC p16, criteria/definition for a positive test?**
   - **For in situ hybridization (ISH) and polymerase chain reaction (PCR), testing conditions and criteria/definition for a positive test?**
   - **For ISH, specific probes?**
   - **What HPV type specific probes should be included?**

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# Clinical questions addressed, continued

3. **For patients with OPSCC, non-OPSCC, and cervical nodal metastatic SCC, what is the optimal method of reporting HPV test results to best inform patients and clinicians about the clinical significance of the results (including considerations about uncertainty)?**
4. **Should patients with recurrent/persistent OPSCC, non-OPSCC, and cervical nodal metastatic SCC be routinely tested for HR-HPV?**

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# Clinical questions address, continued

5. **Should patients with locally and/or regionally recurrent OPSCC, non-OPSCC, and cervical nodal metastatic squamous cell carcinoma be routinely tested for HR-HPV?**
6. **Should patients with distant disease be tested for HR-HPV?**

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# Main findings

- **Based on the systematic review:**
  - **there is clear evidence to recommend when routine testing is indicated**
  - **there is little evidence to support routine testing in certain anatomic sites and certain types of carcinomas**
- **p16 is the recommended method for testing HR-HPV in the oropharynx; HPV-specific tests may be used at the discretion of the pathologist/clinician or in the context of clinical trials.**

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# Guideline Development Process

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# Scope

- **The CAP formed an expert panel to systematically review the relevant literature and to establish recommendations for methods of HR-HPV testing in both histologic and cytologic specimens of head and neck carcinomas in the clinical setting, including the performance, interpretation, and reporting of results from those tests.**

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# Guideline expert panel members

- **William C. Faquin, MD, PhD, FCAP, co-chair**
- **James S. Lewis, Jr., MD, co-chair**
- **Beth Beadle, MD, MD**
- **Justin A. Bishop, MD**
- **Rebecca Chernock, MD, FCAP**
- **Joel T. Moncur, MD, PhD**
- **James W. Rocco, MD, PhD**
- **Mary R. Schwartz, MD, FCAP**
- **Raja R. Seethala, MD, FCAP**
- **William H. Westra, MD**
- **Christina Lacchetti, MHSc, Methodology Consultant**

**Portion of the panel**

## CAP Guideline Staff

- **Nicole E. Thomas, MPH, CT(ASCP)$^{cm}$, Senior Manager, Center Guideline Development**
- **Carol Colasacco, MLIS, SCT(ASCP), Medical Librarian Specialist, Center**

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# Systematic evidence review

- **Identify key questions**
- **Literature search**
- **Data extraction**
- **Develop proposed recommendations**
- **Open comment period**
- **Considered judgment process**
  - **Consider risks and benefits, costs, regulatory requirements, patient and/or laboratory preferences, etc.**

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# Systematic evidence review results

- **Initial literature search conducted for studies from 1/1/1995 – 3/3/2014; 1 literature refresh to include studies from March 2014 – July 2016**
- **2,207 articles identified for abstract review**
  - **906 articles submitted for full text review**
  - **157 articles underwent data extraction and quality assessment analysis**
- **14 final guideline statements**
  - **4 recommendations**
  - **10 expert consensus opinions**

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# Systematic evidence review results, continued

- **Results from the open comment period**
  - **July 18 – August 8, 2016: 14 draft statements were presented**
  - **130+ respondents for each draft statement**
  - **269 written comments**
  - **13 draft statements received at least 80% agreement, one received 57% agreement**

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# Definition of strength of recommendations

| Grades for Strength of Recommendations | | |
|---|---|---|
| **Designation** | Recommendation | **Rationale** |
| **Strong Recommendation** | Recommend for or against a particular practice (Can include “must” or “should”) | **Supported by convincing (high) or adequate (intermediate) quality of evidence and clear benefit that outweighs any harms** |
| **Recommendation** | Recommend for or against a particular practice (Can include “should” or “may”) | **Some limitations in quality of evidence (adequate [intermediate] or inadequate [low]), balance of benefits and harms, values, or costs but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation** |
| **Expert Consensus Opinion** | Recommend for or against a particular practice (Can include “should” or “may”) | **Serious limitations in quality of evidence (inadequate [low] or insufficient), balance of benefits and harms, values or costs, but panel consensus is that a statement is necessary** |
| **No Recommendation** | **No recommendation for or against a practice** | **Insufficient evidence or agreement of the balance of benefits and harms, values, or costs to provide a recommendation** |

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# Guideline Statements

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# Guideline statement 1

**Strong Recommendation – Pathologists should perform HR-HPV testing on 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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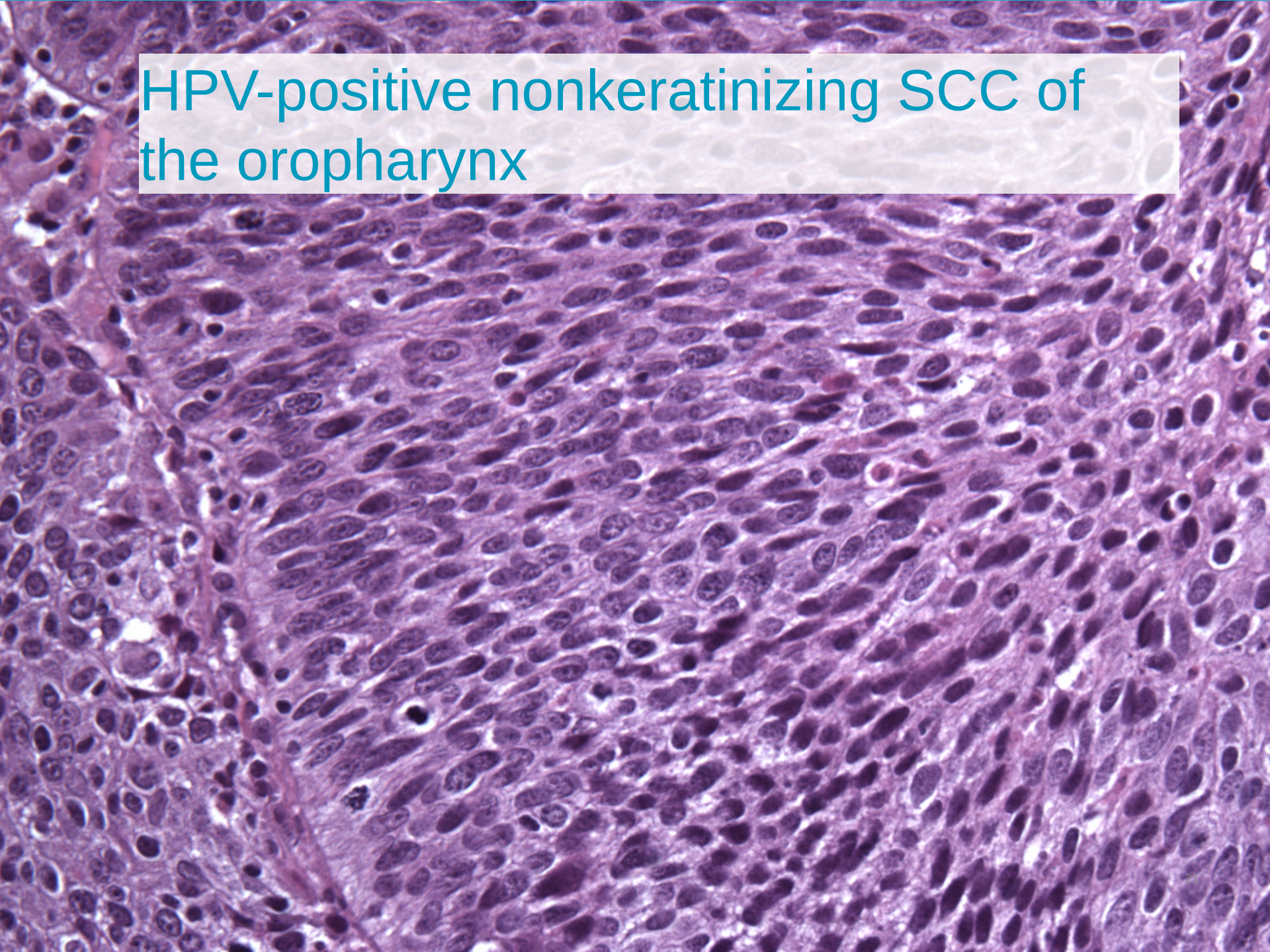
# HPV-positive nonkeratinizing SCC of the oropharynx



# Guideline statement 1 rationale

- **The literature overwhelmingly supports the conclusion that HPV status is an important and independent predictor of overall and disease-specific survival for patients with OPSCC.**
- **The survival benefit of HPV-positive OPSCC is maintained across nearly all studies, despite significant heterogeneity in patient populations, sample size, methods of HPV detection, tumor stage, tumor treatment, comorbidity, and inclusion of various other prognostic factors in the analysis.**

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# Guideline statement 2

**Recommendation – For oropharyngeal tissue specimens (ie, noncytology), pathologists should perform HR-HPV testing by surrogate marker p16 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.**

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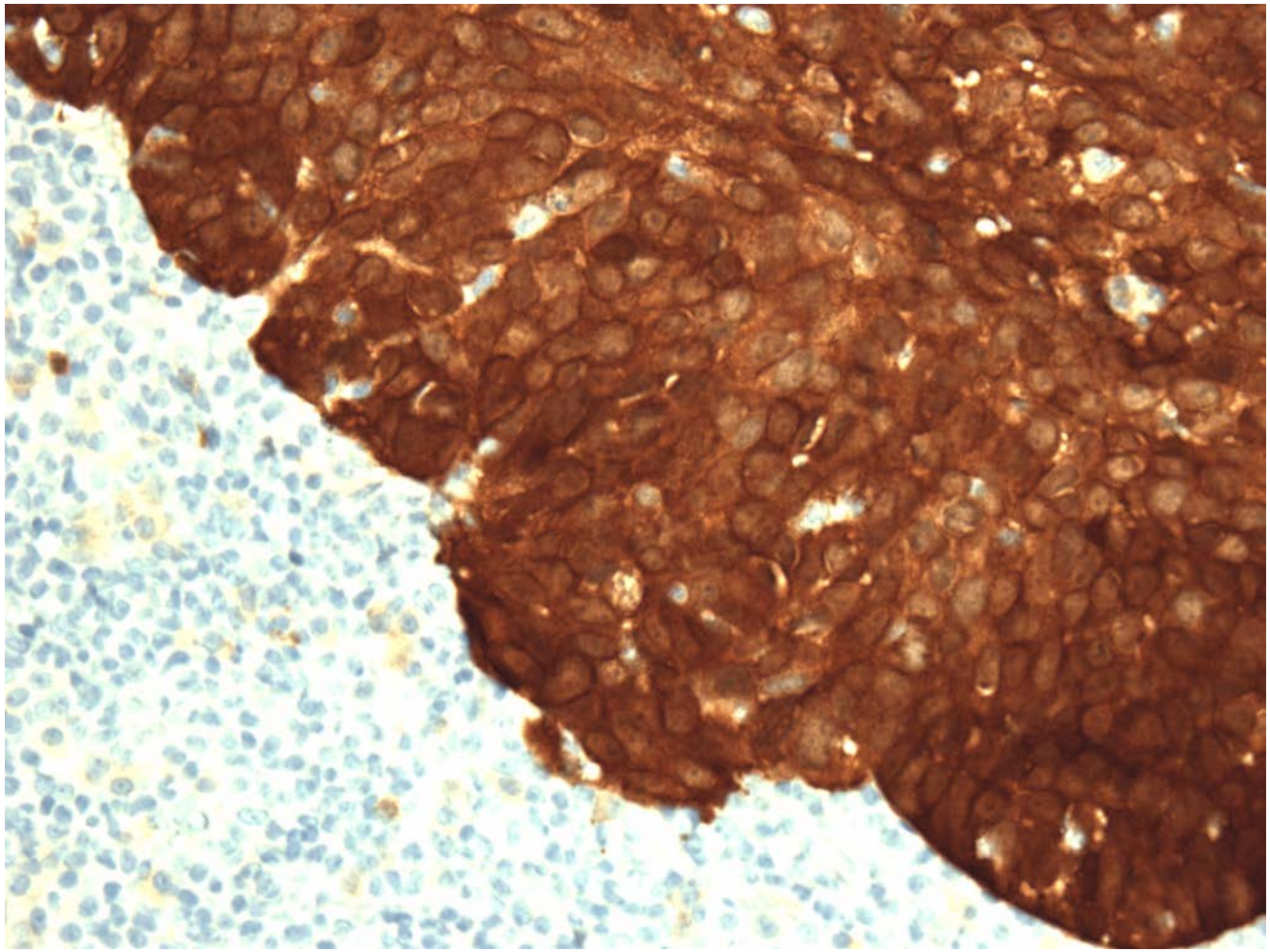
# OPSCC: IHC for p16



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# Guideline statement 2 rationale

- **Based on abundant literature on p16 IHC as an independent predictor of improved patient prognosis in OPSCC, on its widespread availability, ease and reproducibility of interpretation, and excellent performance on small specimen samples such as small biopsies and tissue microarray punches, the expert panel recommends that p16 testing be performed for oropharyngeal tissue specimens.**

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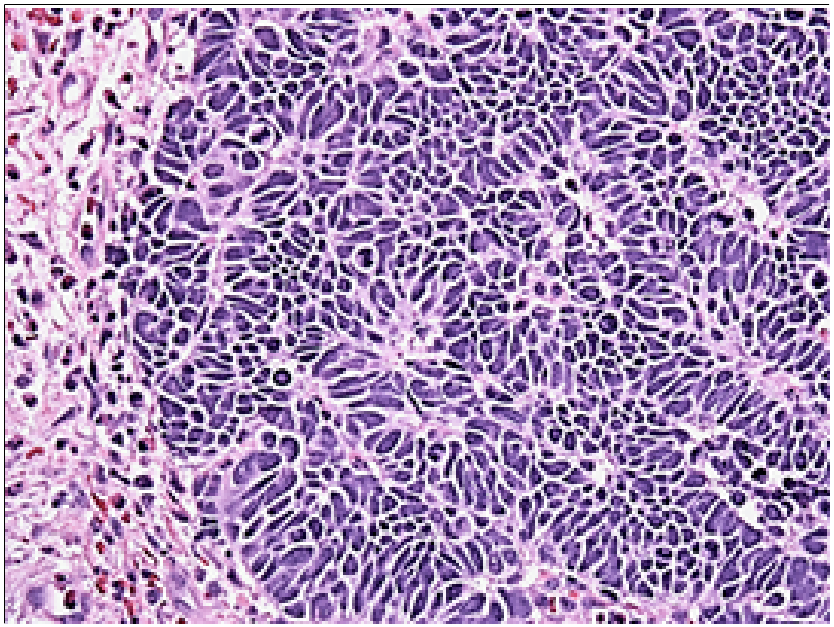
# Guideline statement 3

**Expert Consensus Opinion – Pathologists should *not* routinely perform HR-HPV testing on patients with non-SCCs of the oropharynx.**



**SCC of oropharynx**

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# Guideline statement 3 rationale

- **HPV status does not appear to be a reliable marker for separating aggressive and nonaggressive tumors when it comes to high grade neuroendocrine carcinomas of the oropharynx.**
- **For carcinomas of salivary gland origin, there is currently insufficient evidence to support an etiologic role of HPV in these tumors, or to validate the practice of HPV testing them for prognostic purpose.**

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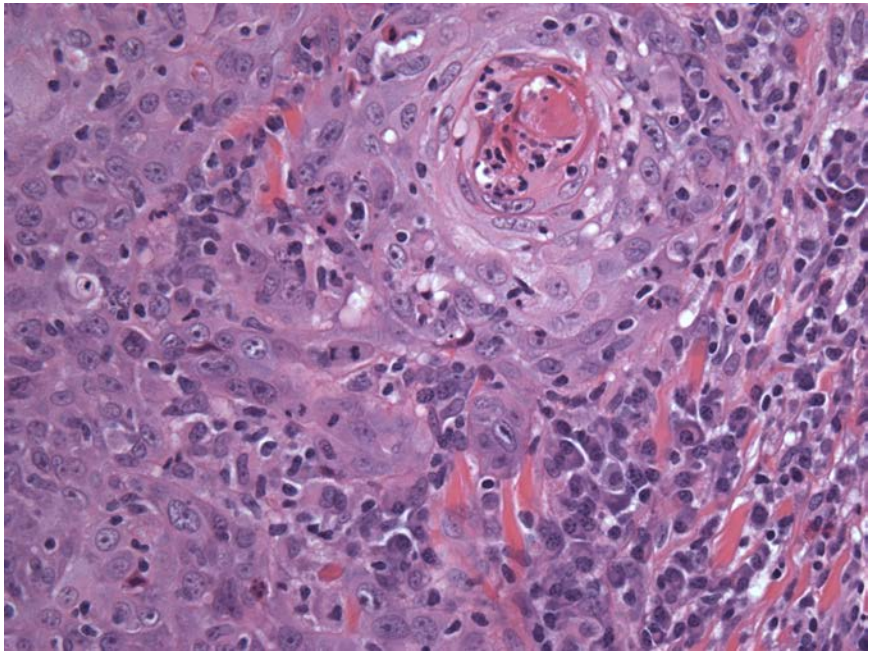
# Guideline statement 4

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



SCC of the oral cavity

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# Guideline statement 4 rationale

- **Routine HPV testing for nonoropharyngeal head and neck carcinomas is not indicated because there is no proven prognostic or therapeutic difference based on its presence or absence (either by any of the various HPV-specific tests or the surrogate marker p16).**

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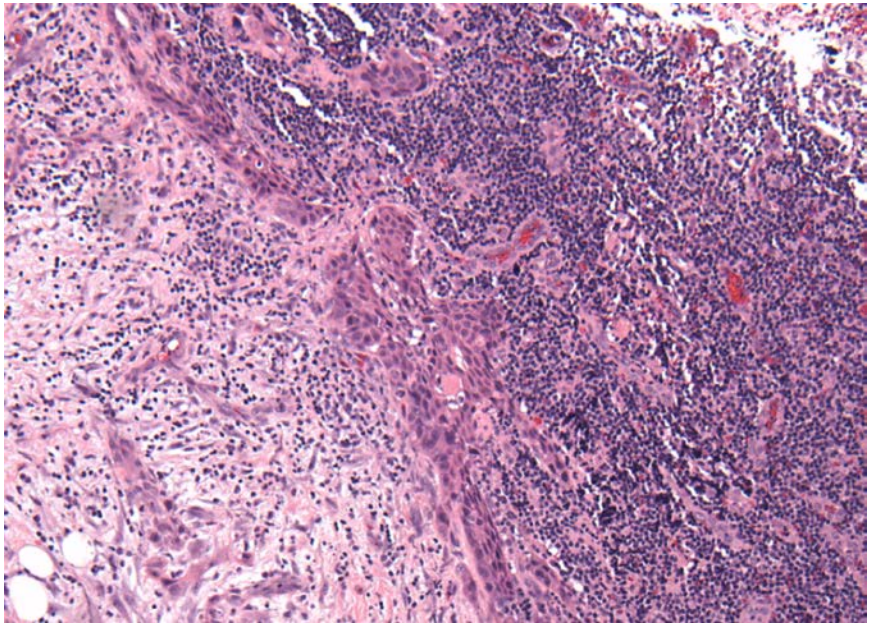
# Guideline statement 5

**Recommendation – Pathologists should routinely perform HR-HPV testing on patients with metastatic SCC of unknown primary in a cervical upper or mid jugular chain lymph node. An explanatory note on the significance of a positive HPV result is recommended.**



**Metastatic SCC of unknown primary to a cervical lymph node**

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# Guideline statement 5 rationale

- **HR-HPV status is important for the management of patients with unknown primary as it informs the clinical team where to search for the primary, or limits the likely area of primary if a definitive lesion is not identified.**

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# Guideline statement 6

- **Expert Consensus Opinion – For tissue specimens (ie, noncytology) from patients presenting with metastatic SCC of unknown primary in a cervical upper or mid jugular chain lymph node, pathologists should perform p16 IHC.**

**Note: Additional HR-HPV testing on p16-positive cases should be performed for tumors located outside of level II or III (noncytology testing) in the neck and/or for tumors with keratinizing morphology.**

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# Guideline statement 6 rationale

- **Three studies concluded that IHC alone is sufficient to determine HR-HPV tumor status when the metastasis is located in one of the upper or mid jugular chain (level II and III) lymph node groups and the tumor morphology is nonkeratinizing.**
- **HR-HPV-specific testing is required to confirm a positive p16 IHC test result only when the tumor morphology is keratinizing and/or the metastasis is located outside of the upper or mid jugular chain.**

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# Guideline statement 7

- **Expert Consensus Opinion – 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 (ie, cutoff) for a positive result.**

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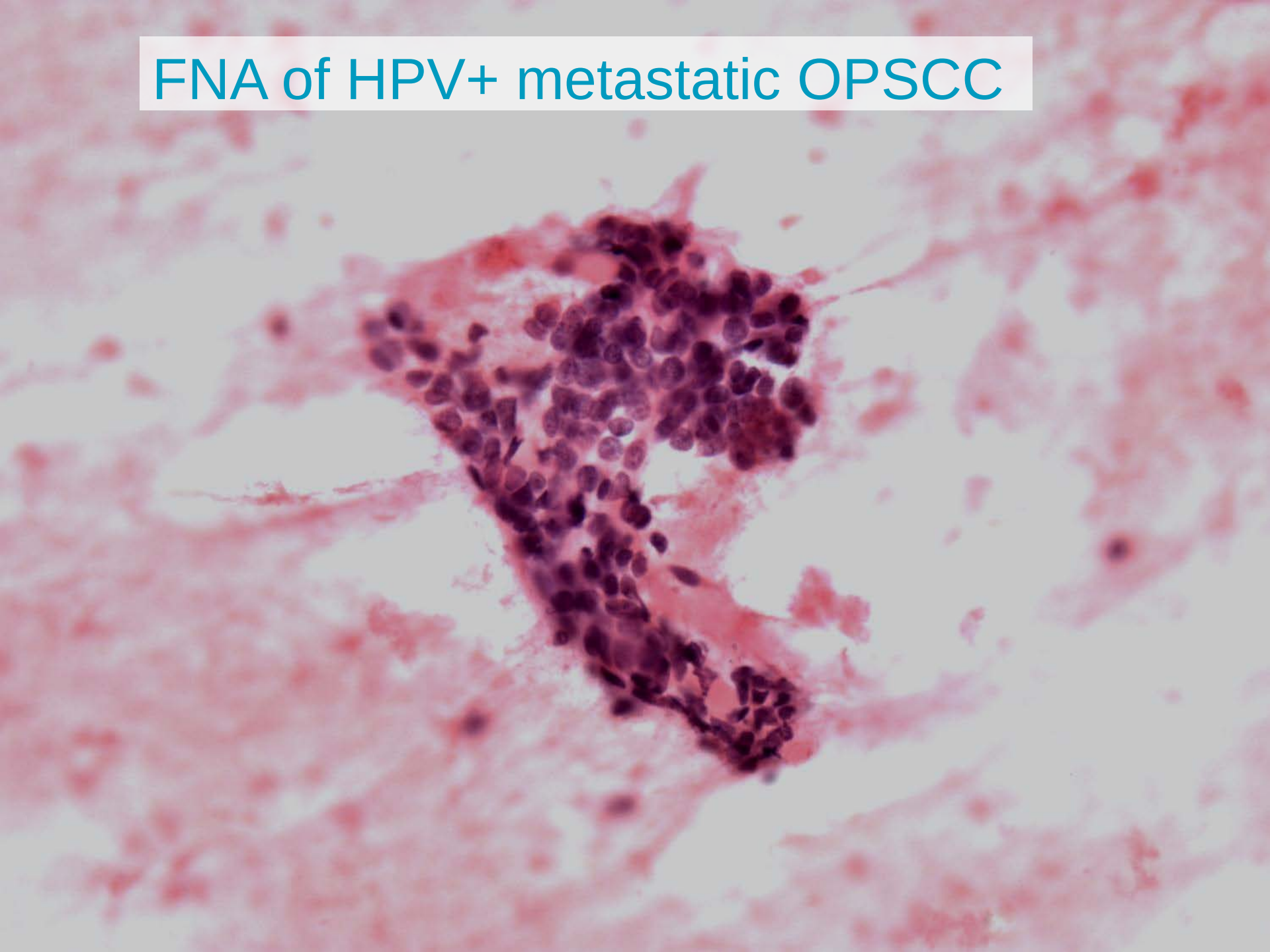
# FNA of HPV+ metastatic OPSCC



# Guideline statement 7 rationale

- **Because of the marked tendency for HPV-positive head and neck SCC to metastasize to cervical lymph nodes, FNA plays a very important diagnostic role in the initial detection of these cancers.**
- **The literature supports the use of FNA as a valid method for obtaining material for HR-HPV testing.**

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# Guideline statement 8

**Expert Consensus Opinion – Pathologists should report p16 IHC positivity as a surrogate for HR-HPV in tissue specimens (ie, noncytology) when there is at least 70% nuclear and cytoplasmic expression with at least moderate to strong intensity.**

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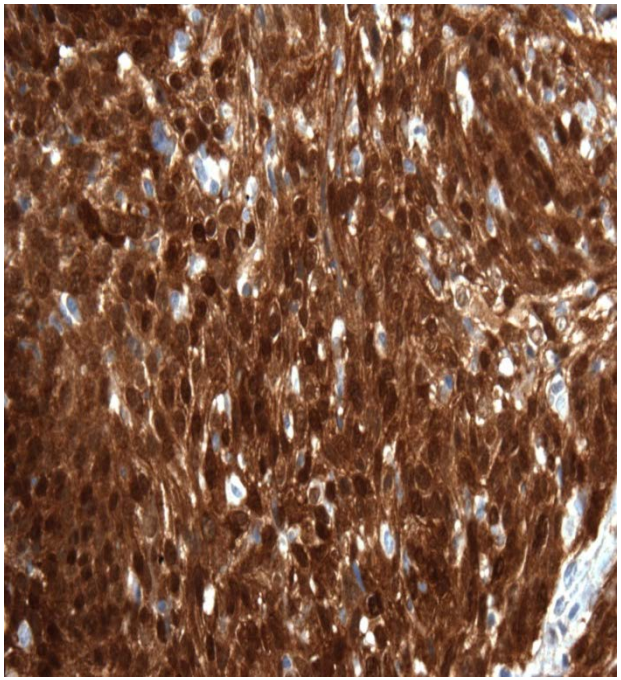
# p16+ OPSCC

## p16 IHC



**Nuclear & cytoplasmic positivity in >70% of tumor cells**

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# Guideline statement 8 rationale

- **Definitions for what percentage of positive cells are necessary has varied substantially; however, some of the largest and prospective studies, such as Ang et al, have supported a stringent cutoff of 70-75%.**
- **In high incidence areas, such as the US, lesser staining cutoffs may function similarly.**

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# Guideline statement 9

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

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# Guideline statement 9 rationale

- **While low-risk HPV types are an established etiologic agent in benign squamous papillomas and warts of various sites, they do not play a significant role in the development of HPV-positive OPSCC.**
- **Because there is little (if any) benefit of identifying low-risk HPV types in the head and neck, the expert panel determined that there is no role for routine low-risk HPV in this context.**

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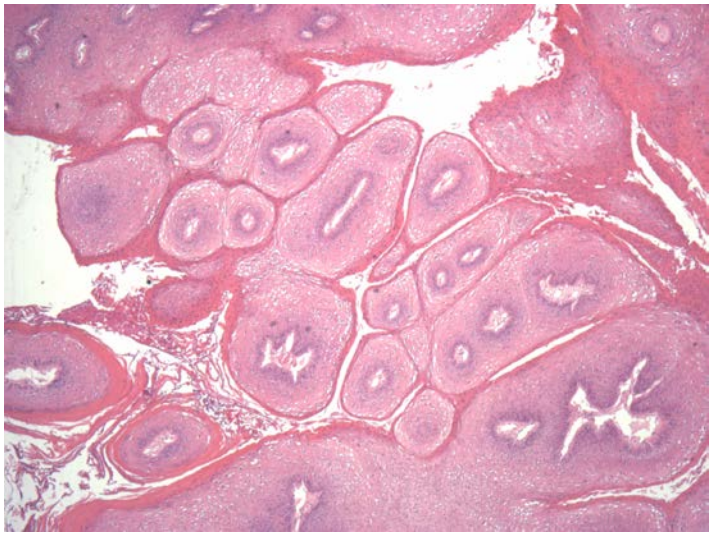
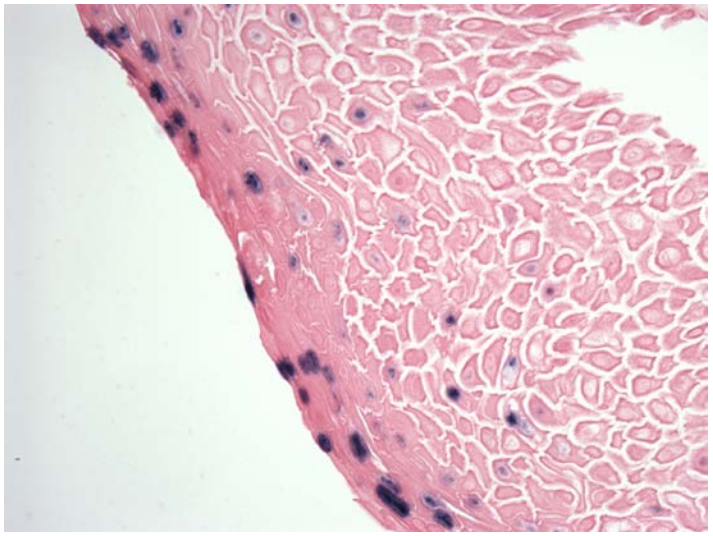
# Low-risk HPV is associated with squamous papillomas





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# Guideline statement 10

**Expert Consensus Opinion – 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 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.**

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# Guideline statement 10 rationale

- **Recurrences have been demonstrated to show the same HR-HPV status as the primary. As such, there is no documented value of repeating testing for HR-HPV on locoregionally recurrent or persistent head and neck SCC.**

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# Guideline statement 11

**Expert Consensus Opinion – 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.**

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# Guideline statement 11 rationale

- **Limited data shows that distant metastases retain the same HR-HPV status, including p16 overexpression. As such, there is no documented value of repeating testing on a metastatic tumor.**
- **However, HR-HPV testing on a metastasis when the status of the primary is unknown would accurately reflect the HPV status of the primary head and neck SCC and is thus recommended.**

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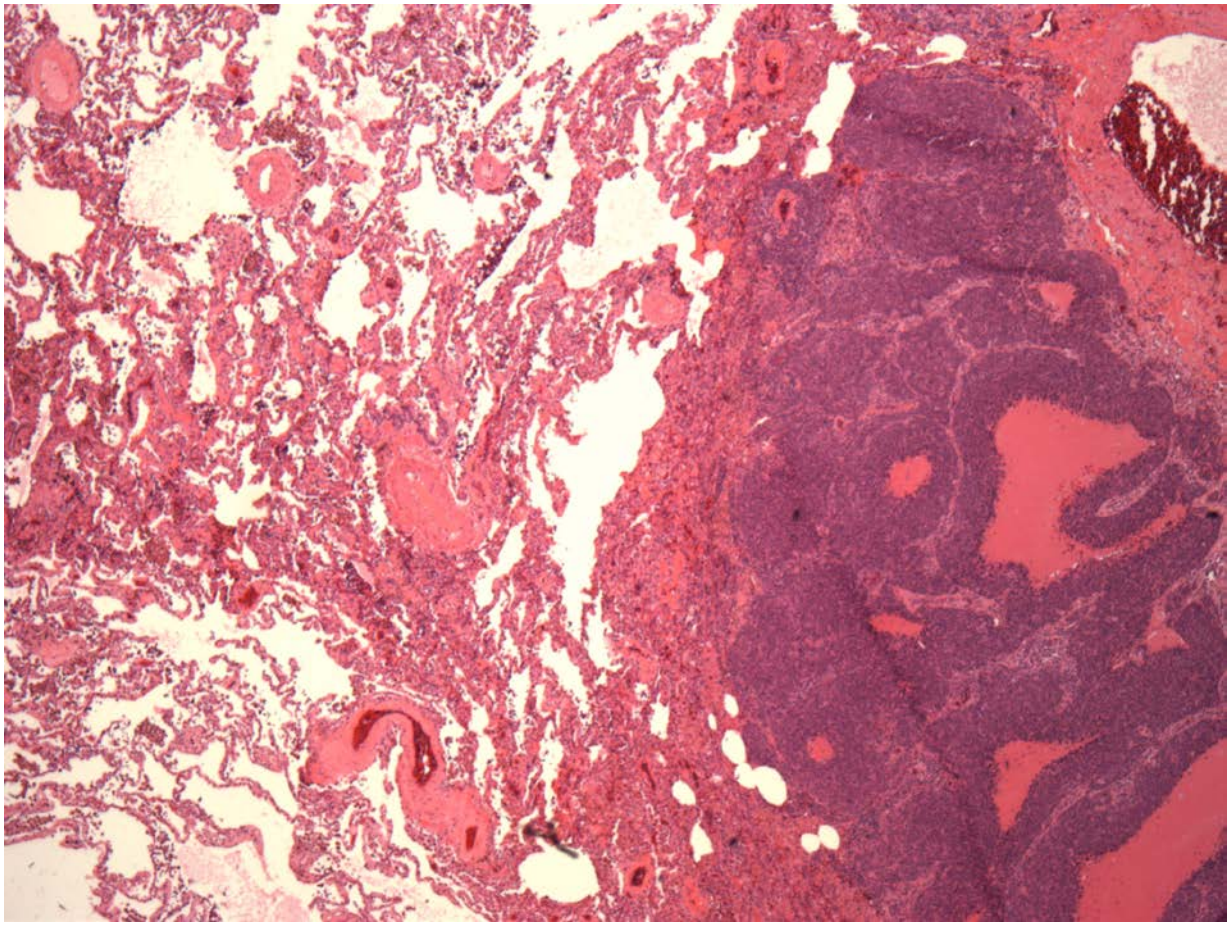
# Metastatic OPSCC to lung



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# Guideline statement 12

**Expert Consensus Opinion – Pathologists should report primary OPSCCs that test positive for HR-HPV or its surrogate marker p16 as HPV-positive/p16-positive.**

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# Guideline statement 12 rationale

- **This expert opinion is consistent with the terminology used in contemporary classifications of OPSCCs.**
- **If the term “p16-positive” is used in clinical reporting on its own, a comment should be added that describes the strong relationship between p16 immunopositivity and HPV in the respective setting.**

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# Guideline statement 13

**Expert Consensus Opinion – Pathologists should *not* provide a tumor grade or differentiation status for HPV-positive/p16-positive OPSCCs.**

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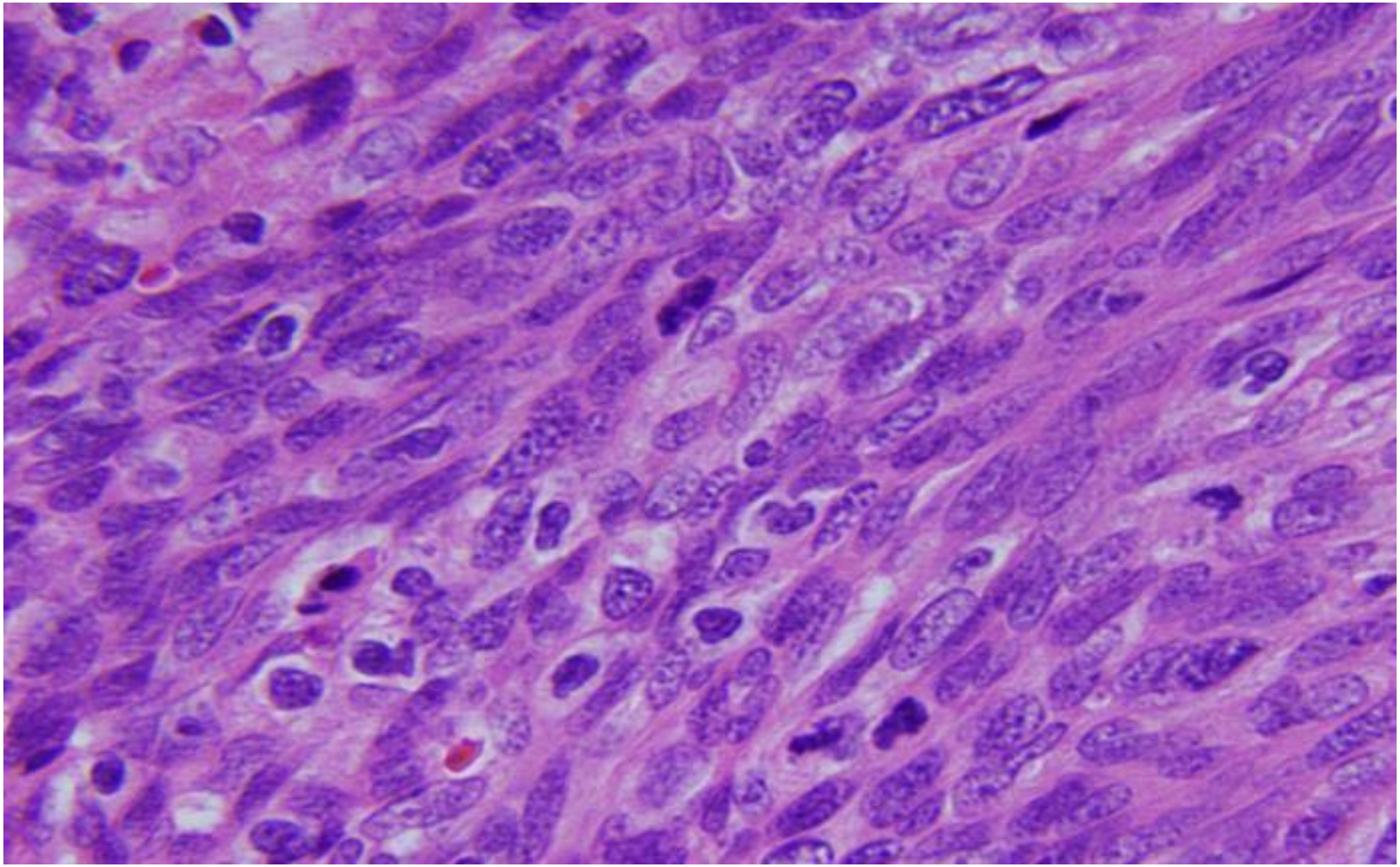
# Nonkeratinizing HPV+ OPSCC with basaloid features



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# Guideline statement 13 rationale

- **Most HPV-positive OPSCCs are usually nonkeratinizing, with high nuclear to cytoplasmic ratios, hyperchromatic nuclei, and are arranged in lobules and sheets; they have often been classified as poorly differentiated or high grade carcinomas.**
- **However, these classifiers were developed in head and neck SCC in general and not specifically for HPV-positive OPSCC. In these tumors, this morphology does not predict poor outcomes.**

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# Guideline statement 14

**Expert Consensus Opinion - Pathologists should *not* alter HR-HPV testing strategy based on patient smoking history.**

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# Guideline statement 14 rationale

- **There is no published evidence that smoking changes the results of any of the HPV-specific tests or p16 IHC.**

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# Conclusion

- **Based on the systematic review and on expert panel consensus, HR-HPV testing is recommended for all new OPSCC patients, but not routinely recommended for other head and neck carcinomas.**
- **The guideline recommendations will evolve with future research and will be reviewed at least every 4 years.**

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# Link to guideline

- **http://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2017-0286-CP**

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