COLLEGE of AMERICAN PATHOLOGISTS

Laboratory Quality Solutions

Supplemental Digital Content* | Methodology | December 2017

Human Papillomavirus Testing in Head and Neck Cancers

Guideline from the College of American Pathologists

Corresponding Author:
James S. Lewis, Jr., MD, FCAP

Authors:
Beth Beadle, MD, PhD
Justin A. Bishop, MD, FCAP
Rebecca D. Chernock, MD, FCAP
Carol Colasacco, MLIS, SCT(ASCP)
Christina Lacchetti, MHSc
Joel Todd Moncur, MD, PhD, FCAP
James W. Rocco, MD, PhD
Mary R. Schwartz, MD, FCAP
Raja R. Seethala, MD, FCAP
Nicole E. Thomas, MPH, CT(ASCP)^{cm}
William H. Westra, MD
William C. Faquin, MD, PhD, FCAP

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

*The Supplemental Digital Content was not copyedited by Archives of Pathology and Laboratory Medicine

METHODS USED TO PRODUCE THE GUIDELINE

Panel Composition

The College of American Pathologists (CAP) Pathology and Laboratory Quality Center (the Center) convened an expert panel (EP) consisting of pathologists, a radiation oncologist, an otolaryngologist, and a methodologist consultant to develop an evidence-based guideline to make recommendations for the testing, application, interpretation, and reporting of human papillomavirus (HPV) (and surrogate marker) tests in head and neck carcinomas in order to improve consistency and quality of clinical practice. The CAP approved the appointment of the project co-chairs and panel members. The EP members performed the systematic evidence review (SER). An advisory panel (AP) of two patient advocates, four pathologists, one medical oncologist/molecular epidemiologist, one radiation oncologist, and a methodologist also helped in the development of the guideline. The role of the AP members was to provide guidance and feedback on the key questions for the literature search, vet the draft guideline statements prior to the public comment period, and to review and provide feedback for the manuscript and supplemental digital content.

Conflict of Interest (COI) Policy

Prior to acceptance on the expert or advisory panel, potential members completed the CAP conflict of interest (COI) disclosure process, whose policy and form (in effect April 2010) require disclosure of material financial interest in, or potential for benefit of significant value from, the guideline's development or its recommendations 12 months prior through the time of publication. The potential members completed the COI disclosure form, listing any relationship that could be interpreted as constituting an actual, potential, or apparent conflict. The CAP Center uses the following criteria:

Nominees who have the following conflicts may be excused from the panel:

a. Stock or equity interest in a commercial entity that would likely be affected by the guideline or white paper
b. Royalties or licensing fees from products that would likely be affected by the guideline or white paper
c. Employee of a commercial entity that would likely be affected by the guideline or white paper

Nominees who have the following potentially manageable direct conflicts may be appointed to the panel:

a. Patents for products covered by the guideline or white paper
b. Member of an advisory board of a commercial entity that would be affected by the guideline or white paper
c. Payments to cover costs of clinical trials, including travel expenses associated directly with the trial
d. Reimbursement from commercial entity for travel to scientific or educational meetings

Everyone was required to disclose conflicts prior to beginning and continuously throughout the project's timeline. Expert panel members' disclosed conflicts are listed in the appendix of the manuscript. The CAP provided funding for the administration of the project; no industry funds were used in the development of the guideline. All panel members volunteered their time and were not compensated for their involvement, except for the contracted methodologist.

Literature Review and Analysis

The expert panel met 16 times through teleconference webinars from November 22, 2013 through September 21, 2016. Additional work was completed via electronic mail. The panel met in person February 8-9, 2014 to determine the scope and key questions and again April 9, 2016 to draft recommendations.

The following key questions were developed by the expert and advisory panel for which to base the literature search:

1) Should patients with newly diagnosed oropharyngeal squamous cell carcinoma (OPSCC), nonoropharyngeal SCC (non-OPSCC), oropharyngeal non-SCC, nonoropharyngeal non-SCC), and cervical nodal metastatic carcinomas of unknown and/or known primary be routinely tested for high risk (HR)-HPV?
    a. Do relevant clinical outcomes differ based on:
        i. Testing with immunohistochemistry (IHC) p16 alone?
        ii. Testing with IHC p16 plus one confirmatory test?
            1. Polymerase chain reaction (PCR) for HPV deoxyribonucleic acid (DNA)
            2. in situ hybridization (ISH) for HPV DNA
            3. ISH for E6/E7 ribonucleic acid (RNA)
            4. Reverse transcription (RT)-PCR for E6/E7
            5. Subtyping of HR-HPV
    b. Do relevant clinical outcomes differ if the diagnosis is based on fine needle aspiration (FNA) rather than biopsy?
        i. What is the comparison of testing with FNA on:
            1. IHC p16 alone?
            2. PCR alone?
            3. ISH alone?
            4. Other liquid-based tests alone?
            5. Specific combinations of tests?
        ii. Does testing FNA specimens vary based on the cytologic appearance of the metastatic head and neck SCC/non-SCC?
        iii. Do specific HR-HPV tests differ based on:
            1. The FNA sample preparation method? (eg, liquid-based cytology specimens, smears, cell block, other)
            2. The number of cells in the FNA specimen?
            3. The method of cell block preparation?
                - Thrombin
                - Cellient (Hologic, Marlborough, MA)
                - Other methods
        iv. How should HR-HPV tests on FNAs of metastatic head and neck SCC/non-SCC be validated?
            1. Is HPV status determined by FNA a reliable status of disease?
        v. Do any of these tests or testing algorithms differ based on smoking history? Does smoking history have an impact on the performance of HPV tests?

2) Do relevant clinical outcomes of specific tests or testing algorithms for HR-HPV differ based on:
    a. Specimen size, percent neoplastic cellularity, and cellularity (if so, what is minimum size associated with acceptable test performance?)
    b. Type and length of tissue fixation?
    c. For IHC p16 testing, specific antibodies, dilution, and testing conditions?
    d. For IHC p16, criteria/definition for a positive test?
    e. For ISH and PCR, testing conditions and criteria/definition for a “positive test”?
    f. For ISH, specific probes?
    g. What HPV type specific probes should be included?

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)?
    a. Do the harms and benefits of testing for HR-HPV differ based on the terminology used to report test results?

4) Should patients with recurrent/persistent OPSCC, non-OPSCC, and cervical nodal metastatic SCC be routinely tested for HR-HPV?

5) Should patients with locally and/or regionally recurrent OPSCC, non-OPSCC, and cervical nodal metastatic SCC be routinely tested for HR-HPV?

6) Should patients with distant disease be tested for HR-HPV?

All EP members participated in the SER. Each level of the SER (title-abstract, full text review, and data extraction) was performed in duplicate by two members of the EP. The co-chairs and contracted methodologist performed adjudication of the conflicts. Articles meeting the inclusion criteria were assessed for strength of evidence, methodological rigor, and confirmation of validity by the methodologist. Supplemental Figure 1 displays the results of the literature review. All articles were available as discussion or background references. All members of the EP participated in developing draft recommendations, reviewing open comment feedback, finalizing and approving final recommendations, and writing/editing of the manuscript.

Peer Review

An open comment period was held from July 18, 2016 through August 8, 2016 on the CAP Web site www.cap.org. Fourteen draft recommendations, two demographic questions, and three questions about feasibility/implementability were posted for peer review. An announcement was sent to the following entities deemed to have interest:

- Advanced cell diagnostics (Newark, CA)
- Affymetrix (Santa Clara, CA)
- American Academy of Oral and Maxillofacial Pathology (AAOMP)
- American Cancer Society
- American Dental Association (ADA)
- American Head and Neck Society (AHNS)
- American Society for Clinical Pathology (ASCP)
- American Society of Clinical Oncology (ASCO)
- American Society of Cytopathology (ASC)
- American Society of Radiation Oncology (ASTRO)
- Association of Community Cancer Centers (ACCC)
- Association of Directors of Anatomic and Surgical Pathology (ADASP)
- Association of Molecular Pathology (AMP)
- Association of Pathology Chairs (APC)
- Canadian Association of Pathologists Association - Canadienne des pathologists (CAP-ACP)
- Canadian Partnership Against Cancer (CPAC)
- Cancer Care
- Cancer Leadership Council (CLC)
- Cancer Research and Prevention Foundation (Prevent Cancer Foundation)
- Cancer Support Community
  National Comprehensive Cancer Network (NCCN)
- CAP
- Celgene (Summit, NJ)

- Center for Disease Control and Prevention (CDC) - Division of Laboratory Programs, Standards, and Services
- Centers for Medicare and Medicaid Services (CMS)
- Eastern Cooperative Oncology Group (ECOG)
- European Society for Medical Oncology (ESMO)
- European Society of Pathology (ESP)
- Food and Drug Administration (FDA)
- Genentech (South San Francisco, CA)
- Genomic Health, Inc. (Redwood City, CA)
- Incyte Corporation (Wilmington, DE)
- International Academy of Pathology (IAP)
- Kaiser Permanente / Kaiser Family Foundation
- LIVESTRONG Foundation
- National Academies of Science, Engineering, and Medicine (formerly Institute of Medicine [IOM])
- National Cancer Institute (NCI)
- National Society for Histotechnology (NSH)
- North American Society of Head and Neck Pathology (NASHNP)
- Roche (Basel, Switzerland)
- Society of Surgical Oncology (SSO)
- Support for People with Oral and Head and Neck Cancer
- SurePath (TriPath Imaging, Inc., Burlington, NC)
- SWOG (formerly Southwest Oncology Group)
- Targos Inc. (Munich, Germany)
- ThinPrep (Hologic, Marlborough, MA)
- Union for International Cancer Control (UICC)
- United Kingdom National External Quality Assessment Service (UK NEQAS)
- United States and Canadian Academy of Pathology (USCAP)
- Ventana Medical Systems, Inc. (Tucson, AZ)

“Agree” and “Disagree” responses were captured for every proposed recommendation. The website also received 269 written comments. 13 of the 14 draft recommendations achieved at least 80% agreement. Each expert panel member was assigned one - two draft recommendations to review and summarize participant comments. After consideration of the comments, seven draft recommendations were maintained with the original language and seven were revised. Resolution of all changes was obtained by majority consensus of the EP using nominal group technique (rounds of teleconference webinars, email discussion and multiple edited recommendations) amongst the panel members. The final recommendations were approved by the EP with a formal vote. The panel considered laboratory efficiency and feasibility throughout the entire considered judgment process.[1] Neither formal cost analysis nor cost effectiveness models were performed.

An independent review panel (IRP) was assembled to review and approve the guideline. The IRP was masked to the EP and vetted through the COI process.

Dissemination Plans

CAP plans to host a HPV Testing in Head and Neck resource page which will include a link to the manuscript and supplement; a summary of the recommendations, a teaching PowerPoint (Microsoft Corporation, Redmond, WA) and a frequently asked question (FAQ) document. The guideline will be promoted and presented at various society meetings.

Systematic Evidence Review (SER)

The objective of the SER was to identify articles that would provide data to inform recommendations for appropriate testing of the head and neck for HPV. If of sufficient quality, findings from this review could provide an evidence base to support the development of the guideline. The scope of the SER and the key questions (KQs) were established by the EP in consultation with the methodologist prior to beginning the literature search.

Search and Selection

A comprehensive search for literature was initially performed on 3/3/14 in MEDLINE using the OvidSP interface, encompassing the publication dates of 1/1/1995 to 3/3/14. A supplemental search was performed in PubMed on 3/26/14 encompassing the publication dates of 1/1/1995 to 3/26/14. An additional search for literature published in journals not indexed in MEDLINE was performed utilizing Scopus (3/29/14) to identify relevant articles published between 1/1/1995 and 3/29/14. The literature search of the electronic databases was conducted in two arms; the first combined Medical Subject Headings (MeSH) and keywords to address the concepts “head and neck neoplasms”, “human papillomavirus (HPV)”, and “laboratory testing” , and the second combined MeSH terms and keywords for the concepts “head and neck neoplasms”, “human papillomavirus (HPV)”, and “outcomes”. The results of both arms of the search were combined and deduplicated. Limits were set for human studies published in English, and a publication filter was applied to exclude lower levels of evidence such as letters, commentaries, editorials, and case reports. The Ovid search strategy is included as Supplemental Figure 2. The PubMed and Scopus search strategies were adaptations of the Ovid search strategy.

A search for grey (unindexed) literature included a review of guideline and systematic reviews repository sites (eg, Guidelines International Network, National Guideline Clearinghouse, Cochrane Library, Prospero, Centre for Reviews and Dissemination) and relevant medical organizations’ websites to identify guidelines, protocols and standards. A review of meeting abstracts from pathology and oncology organizations from 2012-2014 (American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), College of American Pathologists (CAP), United States and Canada Academy of Pathology, European Society for Radiotherapy and Oncology, American Society for Radiation Oncology, American Society for Cytopathology, American Head and Neck Society, American Academy of Otolaryngology - Head and Neck Surgery, American Society for Clinical Pathology, International Papillomavirus Society) and expert panel recommendations completed the systematic literature review. The Ovid search was rerun on 7/11/16 to identify articles published since 3/1/2014 that provided new evidence or strength to the evidence informing the recommendations. A focused search for new guidelines, standards, or protocols and expert panel recommendations supplemented the literature refresh. Prior to submission for publication, all included meeting abstracts were checked for subsequent publication, and the data from any published studies was incorporated into the body of evidence.

Inclusion and Exclusion Criteria

Practice guidelines, consensus documents, systematic reviews (SRs), meta-analyses, randomized control trials (RCTs), comparative studies, reviews, case-controlled studies, case series, and evaluation studies were eligible for inclusion.

Published studies were selected for full-text review if they met each of the following criteria:

1. Patients with tissue or cytology aspiration material taken from the work-up of:
    - Oropharyngeal primaries
    - Cervical nodal metastasis of unknown primary
    - Regional or distant metastasis from known or suspected oropharyngeal primary

- Other head and neck sites (eg, sinonasal)
- All carcinomas in the head and neck (except non-epithelial origin)
- Human studies

2. Patients of all ages and gender
3. Studies published in English
4. The study compared, prospectively or retrospectively, laboratory testing methodologies or potential testing algorithms for HPV testing
5. The study addressed one of the key questions
6. The study included measureable data such as the negative predictive value (NPV) or positive predictive value (PPV) if testing methodologies used to determine HPV status, alone and in combination; negative and positive concordance across the platforms; sensitivity and specificity of individual tests and accuracy in determining HPV status.

Articles were excluded from the systematic review if they were non-comparative or qualitative studies, including editorials, commentaries, or letters; animal studies; full text articles not available in English; studies that included patients with other tumor types not specified in the inclusion criteria; studies that did not include relevant measureable data; and studies that did not address at least one of the key questions.

Outcomes of Interest

The outcomes of interest were two fold for the SER; clinical/prognostic outcomes and test characteristics. The clinical outcomes of interest included: overall survival, disease-free survival, progression-free survival, and recurrence-free survival. The SER also captured data on time to recurrence, quality of life, cost effectiveness, 3-year survival, 5-year survival, but yielded very limited data. For test characteristics the outcomes of interest included: sensitivity, specificity, reproducibility, concordance, and observer variability.

Data Extraction & Management

The data elements from an included article/document were extracted by one reviewer into standard data formats and tables developed using systematic review database software (DistillerSR, Evidence Partners Inc., Ottawa, Canada); a second reviewer confirmed accuracy and completeness. Any discrepancies in data extraction were resolved by discussion amongst the co-chairs and methodologist. A bibliographic database was established in EndNote (Thomson Reuters, Carlsbad, CA) to track all literature identified and reviewed during the study.

Quality Assessment Methods

An assessment of study quality was performed for all fully published studies meeting inclusion criteria by a research methodologist. Studies only available in abstract form did not undergo formal quality assessment. Formal quality assessment involved determining the risk of bias by assessing key indicators, based on study design and methodological rigor. These items were assessed as being either yes, no, partial, not reported (NR), or not applicable (N/A) in the following way:

Clinical practice guidelines (CPGs) were assessed for quality by confirming the following attributes were considered and incorporated in its design as recommended by the National Academy of Medicine (NAM), formerly the Institute of Medicine (IOM).[2]

- Based on a systematic review
- Included a multidisciplinary panel
- Patient preferences were considered
- Important patient sub-types were considered
- Methods were well-described and reproducible
- Information on potential conflicts of interest were gathered and disclosed
- Quality of the evidence was assessed
- Strength of the evidence was rated

- CPG includes a plan for updating
- Sources of funding are disclosed

Meta-analyses and systematic reviews were assessed based on A Measurement Tool to Assess Systematic Reviews (AMSTAR) tool:[3]

- An 'a priori' design provided
- Duplicate study selection and data extraction
- Comprehensive literature search performed
- Status of publication (ie, grey literature) used as an inclusion criterion
- List of studies (included and excluded) provided
- Characteristics of the included studies provided
- Scientific quality of the included studies assessed and documented
- Scientific quality of the included studies used appropriately in formulating conclusions
- Methods used to combine the findings of studies appropriate
- Likelihood of publication bias assessed
- Conflict of interest included

For studies that re-analyzed results of completed randomized control trials (RCTs), no specific instrument was used, but the following items were considered:

- Was the analysis pre-specified versus post hoc
- Differences in baseline characteristics between patients whose HPV status was assessed and those in which it was not
- Reporting of power calculations for subgroups analyses

Methodological criteria assessed for other study designs were informed by the Newcastle-Ottawa Quality Assessment Scale:[4]

- Study design
- Type of data collection
- Sampling method used
- Blinding of outcome assessment reported
- Sources of funding are disclosed

Each study was assessed individually, and then each study type was summarized. Finally, a summary of the overall quality of the evidence was given considering the evidence in totality.

A rating for the strength of evidence is given for guideline statements where quality was assessed (ie, only studies obtained from our SR). Ultimately, the designation (rating) of the strength of evidence is a judgment by the expert panel of their level of confidence that the evidence from the studies informing the recommendations reflects true effect. Supplemental Table 1 describes the grades for strength of evidence.

Quality Assessment Results

A total of 157 studies were included in our systematic review. This body of evidence comprised one meta-analysis, nine RCTs, 116 observational studies, and 31 studies only reported in abstract form. In the following sections, the quantity of the evidence as determined by the number of studies that met our inclusion criteria and were retained, the evidence type as determined by study design, the quality of that evidence as determined by the risk of bias assessment, and its consistency are all reported, both as individual studies and in totality, statement by statement. Refer to Supplemental Tables 2-6 for these findings.

Assessing the Strength of Recommendations

The central questions that the EP addressed in developing the guideline was:

1) Should patients should be routinely tested for HR-HPV in the head and neck and if so, which ones and by what test or tests?

2) Do clinical outcomes differ based on testing methodology or other testing characteristics?

Development of recommendations required that the panel review the identified evidence and make a series of key judgments:

1) What are the significant findings related to each KQ or outcome? Determine any regulatory requirements and/or evidence that support a specific action.
2) What is the overall strength of evidence supporting each KQ or outcome? Strength of evidence is graded as Convincing, Adequate or Inadequate, based on four published criteria. Strength of evidence is a key element in determining the strength of a recommendation.
3) What is the strength of each recommendation? The method for determining strength of recommendation is described in the manuscript and is based on the strength of evidence and the likelihood that further studies will change the conclusions. Another consideration is the likelihood that additional studies will be conducted to fill gaps in knowledge. Recommendations not supported by evidence (ie, evidence was missing or insufficient to permit a conclusion to be reached) were made based on consensus expert opinion.
4) What is the net balance of benefits and harms? For each guideline statement, the panel considered the desirable effects, the undesirable effects, the resources required, feasibility, and acceptability.

Discussion of Benefits and Risks of Implementing the Recommendations

Statement 1: 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.

Identifying the HPV status of OPSCC is important for prognostication. It is also helpful for diagnosis, staging, and treatment approach, within standard of care. Most of the methodologies used to determine HPV status are already being used in many laboratories (eg, p16 IHC, HPV PCR and ISH). As such, the expertise to perform the testing is already in place.

If an institution had to set up as a laboratory developed test, the risks would include incurring the expenses and validating/verifying prior to offering the test.

The risk of testing without formal treatment or standard of care guidelines is that clinicians and patients may select a therapy based on cancer HPV status when there is so far insufficient evidence to definitively treat these tumors in a manner specific to HPV status. The current recommendation to test all OPSCC patients is done with the trust that clinicians understand the significance for their patients and what to do with the results in the context of our evolving understanding of the prognostic importance of HPV status. The benefits of being able to understand that the patients have oropharyngeal primaries, why the tumors were acquired, and what can be expected regarding recurrence, likely pattern of spread, and likely outcomes, and for appropriate monitoring of patients after treatment outweighs the risks of not testing.

Statement 2: For oropharyngeal tissue specimens (ie, 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.

Identifying the HPV status helps establish diagnosis, staging, therapy, and prognosis. p16 is relatively inexpensive, common, easy to perform for most laboratories and easy to interpret for

most pathologists. There is low interobserver variability in its assessment. The optimal performance of HPV-specific tests will help to clarify patient HPV status in situations where p16 does not perform as well due to variable clinical contexts, tissue fragmentation, technical problems with specimens, or specific clinical/research need to clarify HPV subtype

While p16 is recommended, there are some associated risks. Sensitivity and specificity of the IHC may vary across laboratories. The current literature does not clearly allow for the recommendation of a specific antibody clone nor staining conditions. In the interim, p16 IHC testing should follow the practices used in the large studies which have validated its use, and the testing must be properly validated using CAP standards. Another risk is that pathologists may not use proper interpretive criteria. Several high quality studies have also shown that p16 is sometimes overexpressed in the absence of high risk HPV, so there may be “false positives”. However, even HPV-specific tests have performance variation, with rare false negative and false positive results.

Despite these risks, the panel contends that the benefits of implementing the recommendation outweigh the harms.

Statement 3: Pathologists should *not* routinely perform HR-HPV testing on patients with nonsquamous carcinomas of the oropharynx.

Because the literature does not suggest an etiological role of HPV in nonsquamous carcinomas at this time, the panel concluded that it would not be helpful to perform testing in this context. The statement leaves room for testing to be performed in specific clinical situations, but does not support routine testing. Treating clinicians may push back and desire testing of more tumor subtypes; however, the preponderance of data at this time does not support testing of nonsquamous cancers. Not performing unnecessary testing should lead to cost, time, and laboratory resource savings.

The resources required to implement this guideline statement would be minimal. In essence, it only requires that personnel know when not to test. Laboratories may wish to inform personnel using various communication methods (such as updating standard operating procedures [SOPs]).

Most participants of the open comment period agreed with this guideline statement.

Statement 4: Pathologists should *not* routinely perform HR-HPV testing on patients with nonoropharyngeal primary tumors of the head and neck.

The systematic review did not support the use of HR-HPV testing for patients with non-OP primary tumors of the head and neck. The desirable effects include saving money, time, and resources of the laboratory. This would also trickle down in cost savings for the patients by not incurring the costs of unnecessary testing.

Because the literature does not suggest an etiological role of HPV in nonsquamous carcinomas at this time, the panel concluded that it would not be helpful to perform testing in this context. The statement leaves room for testing to be performed at times, but does not support routine testing. While this should accommodate most physicians, there might be push-back from some. Not performing unnecessary testing should lead to cost, time, and laboratory resource savings.

The resources required to implement this guideline statement would be minimal. In essence, it only requires that personnel know when not to test.

Because the literature does not support this practice, the panel contends that the desirable effects outweigh the undesirable effects for this guideline statement. Most of the participants of the open comment period agreed with this guideline statement.

Statement 5: Pathologists should routinely perform HR-HPV testing on patients with metastatic SCC of unknown primary in a upper or mid jugular chain lymph node. An explanatory note on the significance of a positive HPV result is recommended.

Level II/III metastases are already presumed to be likely oropharyngeal without HPV testing, but HPV testing is supportive evidence and helpful to counsel patient, an, regardless, will be needed later as a prognostic marker in many cases anyway as an metastatic squamous cell carcinoma at this location has a high pretest probability of association with oropharyngeal primary. Laboratories already performing HPV testing can easily add such cases to their workload since the testing methodology would be in place. Laboratories that do not perform HPV testing would incur the costs, time, and resources required to add HPV testing to their laboratory test menu or to send tests to a reference laboratory. The panel could think of no other risks or harms associated with implementing this guideline statement.

Statement 6: 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 (nonroutine testing) in the neck and/or for tumors with keratinizing morphology.

Performing p16 IHC in this context may reduce unnecessary testing for laboratories that routinely perform p16 and HPV-specific testing.

On the other hand, rare cases may be identified as p16 positive/negative without further HPV testing that may be misclassified. The clinical significance of these cases is unknown because they are so rare

Implementing this guideline statement would probably reduce testing in many cases and would save resources; but for laboratories not routinely HPV testing unknown primary SCC, it may require a small investment of resources.

Statement 7: Pathologists should perform HR-HPV testing on head and neck 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 testing, they should validate the criteria (ie, cutoff) for a positive result.

As previously mentioned, identifying the HPV status helps establish diagnosis, staging, therapy, and prognosis. Most laboratories receiving FNAs are likely already equipped to provide HR-HPV testing on these specimens because they are already commonly done on cervical cytology specimens. If this were to be implemented however, proper validation for head and neck specimens would be required. Implementing this guideline statement leverages equipment in the laboratory and expertise of the laboratory personnel. Because no recommendation is made regarding the use of any specific testing methodology, the guideline statement allows laboratories the autonomy to select the methodology of their choice.

Statement 8: Pathologists should report p16 IHC as positive 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.

Implementing this guideline statement would impact all p16 IHC users and provide much needed standardization for what is called “positive.” Since the 70% nuclear and cytoplasmic expression is a professional and somewhat subjective assessment, there is a risk of under- or over-calling borderline cases, as is the case with interpretation of all immunostain studies with cut-off points.

There are no special resources required to implement this guideline statement. It only requires that the individual assessing the staining knows what percentage of staining is necessary to call a case positive.

Ninety percent of respondents agreed with this guideline statement during the open comment period.

Statement 9: Pathologists should *not* routinely perform low-risk HPV testing on patients with head and neck carcinomas.

The literature does not support the use of routine low-risk HPV testing for patients with head and neck carcinomas. The desirable effects of not testing these patients would be saving the money, time, and resources of the laboratory. This would also trickle down to a cost savings for patients by not incurring the costs of unnecessary testing. The statement leaves room for testing to be performed, but does not support routine testing.

Statement 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 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.

The panel believes that there is no benefit in repeating HPV testing on patients with locally recurrent, regionally recurrent, or persistent tumor if HPV status of the primary tumor has previously been established. Again, reducing unnecessary testing saves the laboratory and patient time and money. The guideline statement, however, allows for HPV testing in cases of uncertainty. In such cases, the HPV status might help establish diagnosis as a new primary tumor and for staging, therapy, and prognosis.

Statement 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.

The panel believes that there is no benefit in repeating HPV testing on patients with distant metastases if it is clear that the tumor is metastatic oropharyngeal SCC and the HPV status of the primary tumor has previously been established. The guideline statement, however, allows for HPV testing in cases of uncertainty. In such cases, the HPV status might help establish diagnosis as a new primary tumor and for staging, therapy, and prognosis.

Statement 12: Pathologists should report primary OPSCCs that test positive for HR-HPV or its surrogate marker p16 as HPV positive and/or p16-positive.

Consistency in how HPV-positive OPSCCs are reported will help make it very clear to clinicians reading the report whether a tumor is HPV-related or not. The suggested terms in this guideline statement are consistent with the new World Health Organization (WHO) terminology. The risk in

implementing this guideline statement is that other organizations may suggest different terminology which may cause confusion.

Statement 13: Pathologists should *not* provide a tumor grade or differentiation status for HPV-positive/p16-positive OPSCCs.

Consistency in the way pathologists report these cases is optimal. Since one would normally equate a “high” tumor grade with poorer outcomes in OPSCC, as it is in other head and neck SCCs, removing this terminology from HPV-positive oropharyngeal SCC tumor reports will help to avoid this confusion. The only potential risk/harm that is anticipated is that pathologists will not be able to convey the morphology of the SCC clearly enough without using these terms in the reporting. However, the panel strongly believes that the benefit outweighs any potential harms.

Statement 14: Pathologists should *not* alter HR-HPV testing strategy based on patient smoking history.

The panel believes that there is no benefit in altering HR-HPV testing strategy based on patient smoking history because for patients who are active or former smokers prognosis is still better for HPV-positive tumors when compared with HPV-negative ones. The only potential risk of this recommendation is that some treating physicians may not understand the balance between smoking and HPV status in OPSCC. Some physicians may consider all patients with HPV-positive tumors to be similar. However, active smoking is proven to markedly decrease the favorable effects of HPV positivity in a patient’s tumor.

Supplemental Table 1. Grades for Strength of Evidence

Designation	Description	Quality of Evidence
Convincing	High confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect.	High/Intermediate quality evidence
Adequate	Moderate confidence that available evidence reflects true effect. Further research is likely to have an important impact on the confidence in estimate of effect and may change the estimate.	Intermediate/Low quality of evidence
Inadequate	Little confidence that available evidence reflects true effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.	Low/Insufficient evidence and expert panel uses formal consensus process to reach Recommendation
Insufficient	Evidence is insufficient to discern net effect. Any estimate of effect is very uncertain.	Insufficient evidence and expert panel uses formal consensus process to reach Recommendation

Adapted from J Clin Epidemiol, 64(4), Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence, pages 401-406, copyright 2011, with permission from Elsevier.[5]

Supplemental Table 2 – Quality Assessment for Statement 1

Systematic review and meta-analysis:

Author, Year	A priori design	Duplicate study selection & data extraction	Literature search	Grey literature used	List included & excluded studies	Characteristics of included studies provided	Quality assessed & documented	Quality used appropriately for conclusion	Methods to combine used appropriately	Publication bias assessed	Conflicts of Interest (COI)	AMSTAR Score
O'Rorke et al,[6] 2012	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	7/11

Assessed for quality by the AMSTAR tool (Bruyère Research Institute, Ottawa, Ontario Canada)

Randomized Control Trials (RCTs):

Author, Year	Pre-specified or post hoc analysis	Differences in baseline characteristics between patients with known Human Papillomavirus (HPV) status and those with no HPV status testing	Power calculations for subgroup	Overall Risk of bias (ROB)
Ang et al,[7] 2010 (RTOG 0129)	Post hoc	No	No	Moderate

Gillison et al,[8] 2012 (RTOG 9003 & 0129)	Post hoc	No	No	Moderate
Kumar et al,[9] 2008 (UMCC 9921)	Post hoc	No	Unclear	Moderate
Posner et al,[10] 2011 (TAX 324)	Post hoc	Yes, no-HPV status patients more likely to have unresectable and low-curability tumors	No	Moderate
Rischin et al,[11] 2010 (TROG 02.02)	Post hoc	Yes, know HPV status patients had better PS, lower T category, higher haemoglobin, and were less likely to be current smokers	Not Reported (NR)	Moderate
Wu et al,[12] 2012 (TAX 324)	Post hoc	No	No	Moderate
Lassen et al,[13] 2013 (DAHANCA 5 & 7)	Post hoc	Yes, p16-positive tumors were significantly smaller in T-size and were more likely to present with nodal spread compared to p16-negative tumors	No	Moderate
Fakhry et al,[14] 2014 (RTOG 0129 & 0522)	Post hoc	No	No	Moderate

Observational Studies:

Author, Year	**Study Design**	**Data Collection**	**Blinding (Yes/No)**	**Sampling (Consecutive/other)**	**Funding Source**	**Overall Risk of Bias (ROB)**
Gao et al,[15] 2013	Retrospective	Prospective	Not Reported (NR)	NR	Non-industry	Moderate
Holzinger et al,[16] 2012	Retrospective	Prospective	Yes	NR	Non-industry	Low-Moderate
Isayeva et al,[17] 2014	Retrospective	Prospective	Yes	Consecutive	Non-industry	Low
Rietbergen et al,[18] 2013	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Scantlebury et al,[19] 2013	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Schache et al,[20] 2013	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Shi et al,[21] 2009	Retrospective	Prospective	Yes	All patients in database	Non-industry	Low
Ukpo et al,[22] 2011	Retrospective	Prospective	NR	NR	Non-industry	Moderate

Author, Year	Study Design	Data Collection	Blinding (Yes/No)	Sampling (Consecutive/other)	Funding Source	Overall Risk of Bias (ROB)
Al-Swiahb et al,[23] 2010	Retrospective	Prospective	Yes	All patients in database	Non-industry	Low
Chaturvedi et al,[24] 2011	Retrospective	Retrospective	NR	NR	Industry	High
Cooper et al,[25] 2013	Retrospective	Prospective	Yes	NR	NR but report no COIs	Low-Moderate
El-Mofty et al,[26] 2006	Retrospective	Prospective	NR	All patients in database	NR	Moderate
Holzinger et al,[27] 2013	Retrospective	Prospective	Yes	All qualifying patients at hospital	Non-industry	Low
Hong et al,[28] 2013	Retrospective	Prospective	Yes	All qualifying patients in database	Non-industry	Low
Jordan et al,[29] 2012	Retrospective	Prospective	NR	Consecutive	Both industry and Non-industry	Moderate
Licitra et al,[30] 2006	Retrospective	Prospective	NR	Consecutive	NR but report no COIs	Moderate
Lin et al,[31] 2013	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Marklund et al,[32] 2012	Retrospective	Prospective	NR	All patients in database	Non-industry	Low-Moderate
Maxwell et al,[33] 2010	Prospective	Prospective	Yes	Consecutive	Non-industry	Low
Mills et al,[34] 2012	Retrospective	Prospective	Yes	NR	Non-industry	Low-Moderate
Nasman et al,[35] 2013	Retrospective	Prospective	Yes	All patients in database	Non-industry	Low
Nasman et al,[36] 2013	Retrospective	Prospective	Yes	All patients in database	Non-industry	Low
Nichols et al,[37]	Retrospective	Prospective	Yes	All patients in database	Non-industry	Low

Author, Year	Study Design	Data Collection	Blinding (Yes/No)	Sampling (Consecutive/other)	Funding Source	Overall Risk of Bias (ROB)
2010						
Preuss et al,[38] 2008	Retrospective	Prospective	Yes	Consecutive	Non-industry	Low
Reimers et al,[39] 2007	Retrospective	Prospective	Yes	Consecutive	Non-industry	Low
Rietbergen et al,[40] 2013 and Rietbergen et al,[41] 2014	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Rotnaglova et al,[42] 2011	Prospective	Prospective	NR	NR	Non-industry	Low-Moderate
Semrau et al,[43] 2013	Retrospective	Prospective	NR	all patients treated by protocol	NR but report no COIs	Low-Moderate
Tahtali et al,[44] 2013	Retrospective	Prospective	NR	All qualifying patients	NR	Low-Moderate
Thavaraj et al,[45] 2011	Retrospective	Prospective	NR	Consecutive	NR	Moderate
Weinberger et al,[46] 2006	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Weinberger et al,[47] 2009	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Bledsoe et al,[48] 2013	Retrospective	Prospective	NR	All qualifying patients	NR but report no COIs	Low-Moderate
Fujimaki et al,[49] 2013	Retrospective	Prospective	Yes	NR	NR but report no COIs	Low-Moderate
Song et al,[50] 2012	Retrospective	Prospective	NR	All qualifying patients	NR but report no COIs	Low-Moderate
Specto	Retrosp	Prospe	Yes	All qualifying	Non-industry	Low

Author, Year	Study Design	Data Collection	Blinding (Yes/No)	Sampling (Consecutive/other)	Funding Source	Overall Risk of Bias (ROB)
r et al,[51] 2013	ective	ctive		patients		
Vainshtein et al,[52] 2014	Retrospective	Prospective	NR	Consecutive	Non-industry	Low-Moderate
Attner et al,[53] 2011	Retrospective	prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Cerezo et al,[54] 2014	Retrospective	retrospective	Yes	All qualifying patients	Non-industry	Moderate
Cheng et al,[55] 2012	Retrospective	prospective	Yes	All qualifying patients	Non-industry	Low
Cohen et al,[56] 2011	Retrospective	prospective	NR	All qualifying patients	NR	Moderate
Granata et al,[57] 2012	Retrospective	prospective	NR	Consecutive	NR but report no COIs	Low-Moderate
Hong et al,[58] 2013	Retrospective	Prospective	Yes	Consecutive	Non-industry	Low
Hong et al,[59] 2013	Retrospective	Prospective	Yes	Consecutive	Non-industry	Low
Lewis et al,[60] 2010	Retrospective	Prospective	Yes	All qualifying patients	Non-industry	Low
Lindel et al,[61] 2001	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Mizumachi et al,[62] 2013	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Nichols et al,[63] 2013	Retrospective	Prospective	NR	All qualifying patients	Industry	High
O'Sullivan et al,[64] 2012	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
O'Sullivan et al,[65] 2013	Retrospective	Prospective	Yes	All qualifying patients	Non-industry	Low
Park et al,[66]	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate

Author, Year	Study Design	Data Collection	Blinding (Yes/No)	Sampling (Consecutive/other)	Funding Source	Overall Risk of Bias (ROB)
2013						
Psychogios et al,[67] 2012	Retrospective	Prospective	NR	All qualifying patients	NR but report no COIs	Low-Moderate
Rodrigo et al,[68] 2014	Retrospective	Prospective	NR	Consecutive	Non-industry	Low-Moderate
Sedaghat et al,[69] 2009	Retrospective	Prospective	Yes	All qualifying patients	Non-industry	Low
Straetmans et al,[70] 2009	Retrospective	Prospective	NR	All qualifying patients	NR	Moderate
Tural 35 al,[71] 2013	Retrospective	Prospective	NR	All qualifying patients	NR but report no COIs	Low-Moderate
Ukpo et al,[72] 2009	Retrospective	Prospective	NR	All qualifying patients	NR	Moderate
Worden et al,[73] 2008	Prospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Worsham et al,[74] 2013	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Ali et al,[75] 2008	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Cerezo et al,[76] 2014	Retrospective	Prospective	Yes	All qualifying patients	Non-industry	Low
Habbous et al,[77] 2014	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Hess et al,[78] 2014	Retrospective	Prospective	NR	Consecutive	Non-industry	Low-Moderate
Nichols et al,[79] 2013	Retrospective	Prospective	Yes	NR	Industry	Moderate
Chien et al,[80] 2008	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Hannis	Retrosp	Prospe	NR	All qualifying	Non-industry	Low-Moderate

Author, Year	Study Design	Data Collection	Blinding (Yes/No)	Sampling (Consecutive/other)	Funding Source	Overall Risk of Bias (ROB)
dal et al,[81] 2010	ective	ctive		patients		
Kuo et al,[82] 2008	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Mooren et al,[83] 2013	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Ogueji ofor et al,[84] 2013	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Bussu et al,[85] 2014	Prospective	Prospective	Yes	All qualifying patients	Non-industry	Low
Cai et al,[86] 2014	Retrospective	Prospective	NR	All qualifying patients	NR but report no COIs	Low-Moderate
Trosman et al,[87] 2015	Retrospective	Prospective	NR	All qualifying patients	NR but report no COIs	Low-Moderate
Hatakeyama et al,[88] 2014	Retrospective	Prospective	NR	All qualifying patients	NR	Moderate
Barasch et al,[89] 2016	Retrospective	Prospective	NR	Consecutive	Non-industry	Low-Moderate
Liu et al,[90] 2015	Retrospective	Prospective	Yes	All qualifying patients	NR but report no COIs	Low
Rios Velazquez et al,[91] 2014	Retrospective	Prospective	NR	Consecutive	Non-industry	Low-Moderate
Driessen et al,[92] 2016	Retrospective	Prospective	NR	All qualifying patients	NR	Moderate

Abstracts - *Did not undergo quality assessment*

Dunlap et al,[93] 2014
Lorch et al,[94] 2012
Austin et al,[95] 2012
Hasegawa et al,[96] 2011
Guihard et al,[97] 2011
Lorch et al,[98] 2012

Saraiya et al,[99] 2012
Maxwell et al,[100] 2011
Xu et al,[101] 2013
Shaw et al,[102] 2012
Bahl et al,[103] 2012
Broglie et al,[104] 2012
Zandberg et al,[105] 2014
Ang et al,[106] 2012
Knoedler et al,[107] 2011
Smith et al,[108] 2014
Xu et al,[109] 2012
Rakusic et al,[110] 2012
Brookes et al,[111] 2014
Valduga et al,[112] 2012
Upile et al,[113] 2012
Broglie et al,[114] 2011
Lassen et al,[115] 2012
Sweeney et al,[116] 2013

Supplemental Table 3 – Quality Assessment for Statement 2

Randomized Control Trials (RCTs):

Author, Year	Pre-specified or post hoc analysis	Differences in baseline characteristics between patients with known Human Papillomavirus (HPV) status and those with no HPV status testing	Power calculations for subgroup	Overall Risk of bias (ROB)
Ang et al,[7] 2010 (RTOG 0129)	Post hoc	No	No	Moderate
Gillison et al,[8] 2012 (RTOG 9003 & 0129)	Post hoc	No	No	Moderate
Rischin et al,[11] 2010 (TROG 02.02)	Post hoc	Yes, known HPV status patients had better prognostic significance, lower T category, higher hemoglobin, and were less likely to be current smokers	Not Reported (NR)	Moderate
Lassen et al,[13] 2013 (DAHANCA 5 & 7)	Post hoc	Yes, p16-positive tumors were significantly smaller in T-size and were more likely to present with nodal spread compared to p16-negative tumors	No	Moderate
Fakhry et al,[14] 2014 (RTOG 0129 & 0522)	Post hoc	No	No	Moderate

Observational Studies:

Author, Year	Study Design	Data Collection	Blinding (Yes/No)	Sampling (Consecutive/other)	Funding Source	Overall Risk of Bias (ROB)
Gao et al,[15] 2013	Retrospective	Prospective	Not Reported (NR)	NR	Non-industry	Moderate
Holzinger et al,[16] 2012	Retrospective	Prospective	Yes	NR	Non-industry	Low-Moderate

Author, Year	Study Design	Data Collection	Blinding (Yes/No)	Sampling (Consecutive/other)	Funding Source	Overall Risk of Bias (ROB)
Isayeva et al,[17] 2014	Retrospective	Prospective	Yes	Consecutive	Non-industry	Low
Rietbergen et al,[18] 2013	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Scantlebury et al,[19] 2013	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Schache et al,[20] 2013	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Shi et al,[21] 2009	Retrospective	Prospective	Yes	All patients in database	Non-industry	Low
Ukpo et al,[22] 2011	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Al-Swiahb et al,[23] 2010	Retrospective	Prospective	Yes	All patients in database	Non-industry	Low
Chaturvedi et al,[24] 2011	Retrospective	Retrospective	NR	NR	Industry	High
Cooper et al,[25] 2013	Retrospective	Prospective	Yes	NR	NR but report no Conflicts of Interest (COIs)	Low-Moderate
El-Mofty et al,[26] 2006	Retrospective	Prospective	NR	All patients in database	NR	Moderate
Holzinger et al,[27] 2013	Retrospective	Prospective	Yes	All qualifying patients at hospital	Non-industry	Low
Hong et al,[28] 2013	Retrospective	Prospective	Yes	All qualifying patients in database	Non-industry	Low
Jordan et al,[29] 2012	Retrospective	Prospective	NR	Consecutive	Both industry and Non-industry	Moderate
Licitra et al,[30]	Retrospective	Prospective	NR	Consecutive	NR but report no COIs	Moderate

Author, Year	Study Design	Data Collection	Blinding (Yes/No)	Sampling (Consecutive/other)	Funding Source	Overall Risk of Bias (ROB)
2006						
Lin et al,[31] 2013	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Marklund et al,[32] 2012	Retrospective	Prospective	NR	All patients in database	Non-industry	Low-Moderate
Nasman et al,[35] 2013	Retrospective	Prospective	yes	All patients in database	Non-industry	Low
Nasman et al,[36] 2013	Retrospective	Prospective	yes	All patients in database	Non-industry	Low
Nichols et al,[37] 2010	Retrospective	Prospective	yes	All patients in database	Non-industry	Low
Preuss et al,[38] 2008	Retrospective	Prospective	yes	Consecutive	Non-industry	Low
Reimers et al,[39] 2007	Retrospective	Prospective	yes	Consecutive	Non-industry	Low
Rietbergen et al,[40] 2013 and Rietbergen et al,[41] 2014	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Semrau et al,[43] 2013	Retrospective	Prospective	NR	All patients treated by protocol	NR but report no COIs	Low-Moderate
Weinberger et al,[46] 2006	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Weinberger et al,[47] 2009	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Bledsoe et al,[48]	Retrospective	Prospective	NR	All qualifying patients	NR but report no COIs	Low-Moderate

Author, Year	Study Design	Data Collection	Blinding (Yes/No)	Sampling (Consecutive/other)	Funding Source	Overall Risk of Bias (ROB)
2013						
Fujimaki et al,[49] 2013	Retrospective		Yes	NR		
Song et al,[50] 2012	Retrospective	Prospective	NR	All qualifying patients	NR but report no COIs	Low-Moderate
Cerezo et al,[54] 2014	Retrospective	retrospective	Yes	All qualifying patients	Non-industry	Moderate
O'Sullivan et al,[65] 2013	Retrospective	Prospective	Yes	All qualifying patients	Non-industry	Low
Park et al,[66] 2013	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Psychogios et al,[67] 2013	Retrospective	Prospective	NR	All qualifying patients	NR but report no COIs	Low-Moderate
Rodrigo et al,[68] 2014	Retrospective	Prospective	NR	Consecutive	Non-industry	Low-Moderate
Habbous et al,[77] 2014	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Hess et al,[78] 2014	Retrospective	Prospective	NR	Consecutive	Non-industry	Low-Moderate
Kuo et al,[82] 2008	Retrospective	Prospective	NR	NR	Non-industry	Moderate
Ogueji ofor et al,[84] 2013	Retrospective	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Thavaraj et al,[45] 2011	Retrospective	Prospective	NR	Consecutive	NR	Moderate
Cerezo et al,[76] 2014	Retrospective	Prospective	Yes	All qualifying patients	Non-industry	Low
Hong et al,[58] 2013	Retrospective	Prospective	Yes	Consecutive	Non-industry	Low

Author, Year	Study Design	Data Collection	Blinding (Yes/No)	Sampling (Consecutive/other)	Funding Source	Overall Risk of Bias (ROB)
Hong et al,[59] 2013	Retrospective	Prospective	Yes	Consecutive	Non-industry	Low
Trosman et al,[87] 2015	Retrospective	Prospective	NR	All qualifying patients	NR but report no COIs	Low-Moderate
Barasch et al,[89] 2016	Retrospective	Prospective	NR	Consecutive	Non-industry	Low-Moderate
Liu et al,[90] 2015	Retrospective	Prospective	Yes	All qualifying patients	NR but report no COIs	Low
Bussu et al,[85] 2014	Prospective	Prospective	Yes	Consecutive	Non-industry	Low
Driessen et al,[92] 2016	Retrospective	Prospective	NR	All qualifying patients	NR	Moderate

Abstracts - *Did not undergo quality assessment*

Dunlap et al,[93] 2014
Austin et al,[95] 2012
Guihard et al,[97] 2011
Broglie et al,[104] 2012
Ang et al,[106] 2012
Knoedler et al,[107] 2011
Smith et al,[108] 2014
Rakusic et al,[110] 2012
Brookes et al,[111] 2014
Valduga et al,[112] 2012
Broglie et al,[114] 2011
Lassen et al,[115] 2012
Maxwell et al,[100] 2011
Xu et al,[101] 2013

Supplemental Table 4 – Quality Assessment for Statement 4

Randomized Control Trials (RCTs):

Author, Year	Pre-specified or post hoc analysis	Differences in baseline characteristics between patients with known Human Papillomavirus (HPV) status and those with no HPV status testing	Power calculations for subgroup	Overall Risk of bias (ROB)
Chung et al,[117] 2014 (RTOG 0129 & 0234 & 0522)	Post hoc	No	No	Moderate

Observational Studies:

Author, Year	Study Design	Data Collection	Blinding	Sampling (Consecutive/other)	Funding Source	Risk of Bias
Lingen et al,[118] 2013	Retrospective cohort	Prospective	Yes	Consecutive	Non-industry	Low
Lewis et al,[119] 2012	Cross sectional	Prospective	Yes	Not consecutive, but reports no bias apparent	Industry	High
Laco et al,[120] 2008	Retrospective cohort	Prospective	Not Reported (NR)	NR	Non-industry	Moderate
Alos et al,[121] 2009	Retrospective cohort	Prospective	Yes	All patients with sinonasal carcinoma	Non-industry	Low
Elango et al,[122] 2011	Case control	Prospective	Yes	Consecutive	Non-industry	Low
Larque et al,[123] 2014	Retrospective cohort	Prospective	NR	All qualifying patients	Non-industry	Low-Moderate
Duncan et al,[124] 2013	Retrospective cohort	Prospective	NR	Consecutive	Non-industry	Low-Moderate
Kaminagakura et al,[125] 2012	Retrospective cohort	Prospective	NR	NR	Non-industry	Moderate
Wendt et al,[126] 2014	Retrospective cohort	Prospective	Yes	All qualifying patients	Non-industry	Low
Duray et al,[127] 2012	Retrospective cohort	Prospective	NR	NR	Non-industry	Moderate
Reuschenbach et al,[128] 2013	Retrospective cohort	Prospective	NR	NR	Both industry & non industry	High
Chaudhary et al,[129] 2010	Retrospective cohort	Prospective	Yes	Random sample	Non-industry	Low
Skalova et al,[130] 2013	Retrospective cohort	Prospective	NR	NR	NR	High
Nichols et al,[79] 2013	Retrospective cohort	Prospective	Yes	NR	Industry	High
Zhao et al,[131] 2009	Retrospective cohort	Prospective	NR	NR	Non-industry	Moderate
Sugiyama et al,[132] 2007	Retrospective cohort	Prospective	NR	NR	Non-industry	Moderate
Duray et al,[133] 2011	Retrospective cohort	Prospective	Yes	NR	Non-industry	Low-Moderate
Robinson et	Retrospe	Pros	NR	All qualifying patients	NR, but no conflicts	Low-

al,[134] 2013	ctive cohort	pecti ve			of interest (COI) reported	Moder ate
Jiang et al,[135] 2013	Retrospe ctive cohort	Pros pecti ve	NR	NR	None & no COI	Moder ate
Ernoux-Neufcoeur et al,[136] 2011	Retrospe ctive cohort	Pros pecti ve	Yes	NR	Non-industry	Low-Moder ate
Nemes et al,[137] 2006	Retrospe ctive cohort	Pros pecti ve	NR	NR	Non-industry	Moder ate
Stephen et al,[138] 2012	Retrospe ctive cohort	Pros pecti ve	NR	NR	Non-industry	Moder ate
Morshed et al,[139] 2008	Retrospe ctive cohort	Pros pecti ve	NR	Consecutive	NR, but no COI	Low-Moder ate
Huang et al,[140] 2012	Prospecti ve cohort	Pros pecti ve	NR	NR	Non-industry	Moder ate
Bishop et al,[141] 2013	Retrospe ctive cohort	Pros pecti ve	NR	Consecutive	Non-industry	Low-Moder ate
Chernock et al,[142] 2013	Retrospe ctive cohort	Pros pecti ve	NR	All qualifying patients	Non-industry	Low-Moder ate

Abstracts - *Did not undergo quality assessment*

Kirby et al,[143] 2014
Stenmark et al,[144] 2013

Supplemental Table 5 – Quality Assessment for Statement 5

Author, Year	**Study Design**	**Data Collection**	**Blinding**	**Sampling (Consecutive/ other)**	**Covariates Accounted or Adjusted**	**Funding Source**	**Risk of Bias**
Compton et al,[145] 2011	Retrospective cohort	Prospective	Not Reported (NR)	All patients in database	Yes	None	Low-Moderate
Tribius et al,[146] 2012	Retrospective cohort	Prospective	Yes	All patients in database	Yes	NR but reported no conflicts of interest	Low
Vent et al,[147]	Retrospective cohort	Prospective	NR	All patients in registry	No	Non-industry	Low-Moderate

2013							
Sivars et al,[148] 2014	Retrospective cohort	Prospective	Yes	All patients in database	Yes	Non-industry	Low

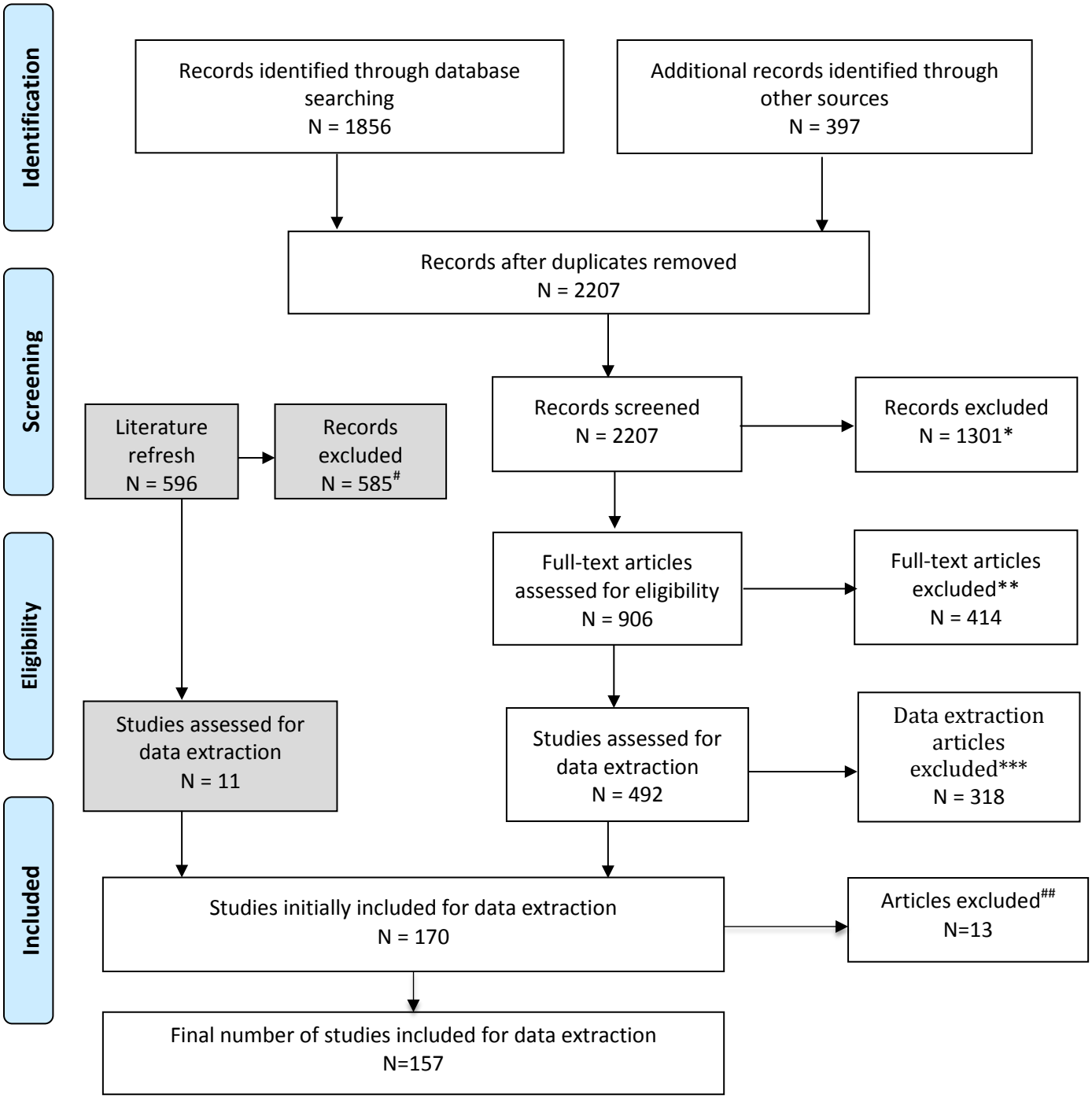
Supplemental Table 6 – Quality Assessment for Statement 7

Author, Year	Study Design	Data Collection	Blinding	Sampling (Consecutive/other)	Funding Source	ROB
Begum et al,[149] 2007	Retrospective cohort	Prospective	Not Reported (NR)	Consecutive	NR	Moderate
Bishop et al,[150] 2012	Retrospective cohort	Prospective	NR	Consecutive	Non-Industry	Low-Moderate
Guo et al,[151] 2014	Retrospective cohort	Prospective	NR	NR	Non-Industry	Moderate
Lastra et al,[152] 2013	Retrospective cohort	Prospective	NR	All patients in database	NR	Moderate
Vent et al,[147] 2013	Retrospective cohort	Prospective	NR	NR	Non-Industry	Moderate
Jakscha et al,[153] 2013	Cross sectional study	Prospective	Yes	All qualifying cases	NR	Low-Moderate
Jannapureddy et al,[154] 2010	Retrospective cohort	Prospective	NR	All qualifying cases	NR	Moderate
Baldassarri et al,[155] 2015	Retrospective cohort	Prospective	NR	NR	NR	High
Holmes et al,[156] 2015	Retrospective cohort	Prospective	NR	All qualifying cases	Non-Industry	Low-Moderate
Jalaly et al,[157] 2015	Retrospective cohort	Prospective	Yes	Consecutive	Both industry and non-industry	Low-Moderate
Kerr et al,[158] 2014	Retrospective cohort	Prospective	NR	Consecutive	No specific funding was disclosed but some conflicts of Interest (COIs)	Moderate

Abstracts - *Did not undergo quality assessment*

Smith et al, 2014[159]
Fowler et al,[160] 2012
Davis et al,[161] 2014
Fatima et al,[162] 2012
Inohara et al,[163] 2012

Supplemental Figure 1. Literature Review Flow Diagram



*Excluded based on expert opinion, did not address the project scope or key questions or meet inclusion criteria (1301)
**Excluded based on expert opinion, did not meet inclusion criteria (414)
***Excluded based on expert opinion, presented incomplete data or data that were not in useable formats (318)
#Excluded based on expert opinion, did not provide unique information or evidence to either refute or upgrade the strength of recommendations (585)
##Excluded based on duplicate data or did not report data for outcomes of interest (13)

Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(6):e1000097[164]
doi:10.1371/journal.pmed1000097

Supplemental Figure 2: Human Papillomavirus Testing in Head and Neck Cancers Ovid Search Strings

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Ovid
MEDLINE(R) Daily Update <February 28, 2014> Search Strategy:

---

1 larynx/ (13110)
2 glottis/ (4571)
3 epiglottis/ (2073)
4 laryngeal mucosa/ (759)
5 exp mouth/ (230875)
6 exp jaw/ (83249)
7 pharynx/ (14204)
8 exp hypopharynx/ (1527)
9 exp nasopharynx/ (9031)
10 oropharynx/ (3190)
11 exp nasal mucosa/ (20687)
12 nasal cavity/ (8343)
13 exp salivary glands/ (32821)
14 exp paranasal sinuses/ (19364)
15 or/1-14 (354276)
16 exp "head and neck neoplasms"/ (235360)
17 HNSCC.ti,ab. (3657)
18 or/16-17 (235769)
19 exp "neoplasms, glandular and epithelial"/ (643550)
20 carcinoma, adenosquamous/ (1467)
21 neuroendocrine carcinoma/ (1860)
22 or/19-21 (643550)
23 (oropharyn$ or mouth or "oral cavity" or salivary or parotid or submandibular or laryn$ or hypopharyn$ or pharyn$ or nasal or sinus or sinonasal or tongue or head or neck).ti,ab. (661572)
24 (carcinoma? or malignan$ or neoplas$ or cancer? or tumo?r? or metastatic or metastas?s).ti,ab. (2179000)
25 lymph nodes/ (66561)
26 neck/ (22086)
27 25 and 26 (2244)
28 ("cervical lymph node?" or (neck and node)).ti,ab. (11544)
29 neoplasms, unknown primary/ (2745)
30 ("unknown primar?" or CUP).ti,ab. (14052)
31 or/29-30 (15601)
32 or/27-28 (12674)
33 15 or 23 (902767)
34 22 or 24 (2312553)
35 33 and 34 (148643)
36 31 and 32 (380)
37 18 or 35 or 36 (293791)
38 Papillomavirus infections/ (15099)
39 papillomaviridae/ (18891)
40 exp alphapapillomavirus/ (4286)
41 papillomavirus e7 proteins/ (1902)
42 oncogene proteins, viral/ (6352)
43 dna virus infections/ (1158)
44 (HPV or papillomavir$).ti,ab. (32166)
45 ((E6 or E7) and (oncoprotein$ or protein$)).ti,ab. (4797)
46 or/38-45 (41061)
47 immunohistochemistry/ (241626)

48 human papillomavirus dna tests/ (88)
49 fixatives/ (4858)
50 tissue array analysis/ (4411)
51 tissue fixation/ (5183)
52 formaldehyde/ (17337)
53 paraffin embedding/ (5129)
54 gene expression regulation, viral/ (12319)
55 polymerase chain reaction/ (209591)
56 reverse transcriptase polymerase chain reaction/ (131686)
57 real-time polymerase chain reaction/ (18054)
58 repressor proteins/ (37051)
59 in situ hybridization/ (46443)
60 nucleic acid probes/ (492)
61 dna probes, hpv/ (1033)
62 blotting, southern/ (29765)
63 molecular diagnostic techniques/ (5143)
64 cyclin-dependent kinase inhibitor p16/ (5499)
65 tumor markers, biological/ (82274)
66 tumor suppressor protein p53/ (38343)
67 receptor, epidermal growth factor/ (27389)
68 transcription, genetic/ (146782)
69 oligonucleotide array sequence analysis/ (54752)
70 Genes, p16/ (1918)
71 exp "microarray analysis"/ (71474)
72 p16$.ti,ab. (11429)
73 (IHC or ICC or immunohistochemi$ or immunocytochemi$ or immunoenzyme$).ti,ab. (308856)
74 (PCR or ?ISH or RT?PCR).ti,ab. (327287)
75 (polymerase adj2 chain adj2 reaction).ti,ab. (164400)
76 (in adj2 situ adj2 hybridization).ti,ab. (77492)
77 (hybrid adj2 capture).ti,ab. (1230)
78 ((HPV or papillomavirus or microarray$ or lab$ or test$) adj2 (method$ or platform$ or assay$)).ti,ab. (62877)
79 ("molecular probe$" or immunostain$).ti,ab. (50979)
80 ("formalin?fix$" or "paraffin?embedded" or FFPE).ti,ab. (1253)
81 "fixation time".ti,ab. (529)
82 ((alcohol?fixed or air?dried) and smear?).ti,ab. (3)
83 (cell block or liquid?based or fine?needle or FNA).ti,ab. (7043)
84 (cytopathol$ or histopathol$ or "surgical patholog$" or cytolog?).ti,ab. (185545)
85 ("Roche cobas" or Aptima or "Hybrid capture II" or "Hybrid capture 2" or Cervista or ProX?c or RNAscope).ti,ab.(1282)
86 or/47-85 (1517217)
87 predictive value of tests/ (137511)
88 prognosis/ (349649)
89 "sensitivity and specificity"/ (271240)
90 chi-square distribution/ (59803)
91 disease-free survival/ (40924)
92 false positive reactions/ (23883)
93 risk factors/ (544479)
94 observer variation/ (30765)
95 reproducibility of results/ (264771)
96 analysis of variance/ (191062)
97 cluster analysis/ (39228)
98 decision support techniques/ (11672)
99 diagnosis, differential/ (374192)
100 disease progression/ (98469)
101 exp early diagnosis/ (19288)

102 kaplan-meier estimate/ (27405)
103 multivariate analysis/ (81150)
104 predictive value of tests/ (137511)
105 risk assessment/ (168898)
106 exp survival analysis/ (177162)
107 survival rate/ (121996)
108 exp treatment outcome/ (627762)
109 quality of life/ (113308)
110 ((improve$ or overall or disease$ or time or rate$) and survival).ti,ab. (399138)
111 ((prognos$ or predict$ or therap$ or treatment) and (marker$ or value or respons$ or factor$)).ti,ab. (1553346)
112 ((progression$ or recurrence$) adj3 (rate$ or time or survival)).ti,ab. (75462)
113 (response rate or non?respon$).ti,ab. (71115)
114 (clinical usefulness or (prediction adj3 ability) or predictability).ti,ab. (16282)
115 (statistical$ adj3 significan$).ti,ab. (309566)
116 prognos$.ab. /freq=2 (98457)
117 prevalence.ab. /freq=2 (131125)
118 ("confidence interval" or concordance).ab. (200900)
119 (de?escalation or deintensification).ti,ab. (76)
120 or/87-119 (4340970)
121 37 and 46 and 86 (2306)
122 37 and 46 and 120 (1968)
123 121 or 122 (3099)
124 limit 123 to (english language and yr="1995 -Current") (2472)
125 ("in vitro" or animal or mice or mouse).tw. (1865564)
126 "cell line$".ti. (65689)
127 125 or 126 (1909516)
128 124 not 127 (2271)
129 Meta-Analysis as Topic/ (13247)
130 meta analysis.pt. (44479)
131 meta?analy$.tw. (1288)
132 (pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw. (4752)
133 (systematic adj (review$ or overview?)).tw. (50300)
134 or/129-133 (96823)
135 exp Review Literature as topic/ or review.pt. (1842343)
136 (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).tw. (187488)
137 (study adj selection).ab. (7899)
138 136 or 137 (188983)
139 135 and 138 (67804)
140 (clinical trial or clinical trial, phase II or controlled clinical trial).pt. (511253)
141 (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt. (365903)
142 random allocation/ or double blind method/ or single blind method/ (210273)
143 exp clinical trial/ or exp clinical trials as topic/ (939003)
144 (randomi$ control$ trial? or rct or phase?I or phase?II or phase?III or phase?IV or phase?1 or phase?2 or
phase?3 or phase?4).tw. (81848)
145 or/140-144 (1027414)
146 ((singl$ or doubl$ or treb$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw. (127848)
147 (allocated adj3 random).tw. (758)
148 (clinic$ adj3 trial$1).tw. (218310)
149 or/146-148 (328792)
150 *practice guidelines/ (25568)
151 (practice adj3 guideline?).tw. (16612)
152 practice guideline.pt. (18653)

153 or/150-152 (53859)
154 evaluation studies.pt. (188738)
155 consensus development conference.pt. (8790)
156 consensus development conference, nih.pt. (722)
157 or/154-156 (197737)
158 research support, nih, extramural.pt. (755471)
159 research support, nih, intramural.pt. (35998)
160 research support, non us gov't.pt. (5561325)
161 research support, us gov't, non phs.pt. (672037)
162 research support, us gov't, phs.pt. (1452452)
163 or/158-162 (6961843)
164 (cohort or case?control or non?randomized or longitudinal or cross?sectional or observational or retrospective$ or prospective$ or consecutive$ or multivariate).tw. (1357657)
165 comparative study.pt. (1657022)
166 prospective studies/ (355462)
167 retrospective studies/ (476896)
168 cohort studies/ (157745)
169 case-control studies/ (174099)
170 follow-up studies/ (483687)
171 risk factors/ (544479)
172 epidemiologic studies/ (5794)
173 or/164-172 (3675751)
174 134 or 139 or 145 or 149 or 153 or 157 or 163 or 173 (9703576)
175 (comment or interview or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or in vitro or historical article).pt. (3627967)
176 174 not 175 (9040746)
177 128 and 176 (1566)
178 remove duplicates from 177 (1541)

REFERENCES

1. Verkerk K, Van Veenendaal H, Severens JL, Hendriks EJ, Burgers JS. Considered judgement in evidence-based guideline development. *Int J Qual Health Care*. 2006;18(5):365-369.
2. Institute of Medicine (IOM). *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press; 2011.
3. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7:10. doi: 10.1186/1471-2288-7-10
4. Wells G, Shea B, O'Connell D, et al.The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Institute website. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed June 6, 2017.
5. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406.
6. O'Rorke MA, Ellison MV, Murray LJ, Moran M, James J, Anderson LA. Human papillomavirus related head and neck cancer survival: a systematic review and meta-analysis. *Oral Oncology*. 2012;48(12):1191-1201.
7. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35.

8. Gillison ML, Zhang Q, Jordan R, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. *J Clin Oncol*. 2012;30(17):2102-2111.

9. Kumar B, Cordell KG, Lee JS, et al. EGFR, p16, HPV Titer, Bcl-xL and p53, sex, and smoking as indicators of response to therapy and survival in oropharyngeal cancer. *J Clin Oncol*. 2008;26(19):3128-3137.

10. Posner MR, Lorch JH, Goloubeva O, et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. *Ann Oncol*. 2011;22(5):1071-1077.

11. 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(27):4142-4148.

12. Wu Y, Posner MR, Schumaker LM, et al. Novel biomarker panel predicts prognosis in human papillomavirus-negative oropharyngeal cancer: an analysis of the TAX 324 trial. *Cancer*. 2012;118(7):1811-1817.

13. 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(3):489-494.

14. Fakhry C, Zhang Q, Nguyen-Tan PF, et al. Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. *J Clin Oncol*. 2014;32(30):3365-3373.

15. Gao G, Chernock RD, Gay HA, et al. A novel RT-PCR method for quantification of human papillomavirus transcripts in archived tissues and its application in oropharyngeal cancer prognosis. *Int J Cancer*. 2013;132(4):882-890.

16. Holzinger D, Schmitt M, Dyckhoff G, Benner A, Pawlita M, Bosch FX. Viral RNA patterns and high viral load reliably define oropharynx carcinomas with active HPV16 involvement. *Cancer Res*. 2012;72(19):4993-5003.

17. Isayeva T, Xu J, Dai Q, et al. African Americans with oropharyngeal carcinoma have significantly poorer outcomes despite similar rates of human papillomavirus-mediated carcinogenesis. *Hum Pathol*. 2014;45(2):310-319.

18. Rietbergen MM, Leemans CR, Bloemena E, et al. Increasing prevalence rates of HPV attributable oropharyngeal squamous cell carcinomas in the Netherlands as assessed by a validated test algorithm. *Int J Cancer*. 2013;132(7):1565-1571.

19. Scantlebury JB, Luo J, Thorstad WL, El-Mofty SK, Lewis JS Jr. Cyclin D1-a prognostic marker in oropharyngeal squamous cell carcinoma that is tightly associated with high-risk human papillomavirus status. *Hum Pathol*. 2013;44(8):1672-1680.

20. Schache AG, Liloglou T, Risk JM, et al. Validation of a novel diagnostic standard in HPV-positive oropharyngeal squamous cell carcinoma. *Br J Cancer*. 2013;108(6):1332-1339.

21. Shi W, Kato H, Perez-Ordonez B, et al. Comparative prognostic value of HPV16 E6 mRNA compared with in situ hybridization for human oropharyngeal squamous carcinoma. *J Clin Oncol*. 2009;27(36):6213-6221.

22. Ukpo OC, Flanagan JJ, Ma X-J, Luo Y, Thorstad WL, Lewis JS Jr. High-risk human papillomavirus E6/E7 mRNA detection by a novel in situ hybridization assay strongly correlates with p16 expression and patient outcomes in oropharyngeal squamous cell carcinoma. *Am J Surg Pathol*. 2011;35(9):1343-1350.

23. Al-Swiahb JN, Huang C-C, Fang F-M, et al. Prognostic impact of p16, p53, epidermal growth factor receptor, and human papillomavirus in oropharyngeal cancer in a betel nut-chewing area. *Arch Otolaryngol Head Neck Surg*. 2010;136(5):502-508.

24. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29(32):4294-4301.

25. Cooper T, Biron V, Adam B, Klimowicz AC, Puttagunta L, Seikaly H. Prognostic utility of basaloid differentiation in oropharyngeal cancer. *J Otolaryngol Head Neck Surg*. 2013;42:57. doi: 10.1186/1916-0216-42-57

26. El-Mofty SK, Patil S. Human papillomavirus (HPV)-related oropharyngeal nonkeratinizing squamous cell carcinoma: characterization of a distinct phenotype. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006;101(3):339-345.

27. Holzinger D, Flechtenmacher C, Henfling N, et al. Identification of oropharyngeal squamous cell carcinomas with active HPV16 involvement by immunohistochemical analysis of the retinoblastoma protein pathway. *Int J Cancer*. 2013;133(6):1389-1399.

28. Hong A, Jones D, Chatfield M, et al. HPV status of oropharyngeal cancer by combination HPV DNA/p16 testing: biological relevance of discordant results. *Ann Surg Oncol*. 2013;20(Suppl 3):S450-458.

29. Jordan RC, Lingen MW, Perez-Ordonez B, et al. Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. *Am J Surg Pathol*. 2012;36(7):945-954.

30. Licitra L, Perrone F, Bossi P, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. *J Clin Oncol*. 2006;24(36):5630-5636.

31. Lin RJ, Lubpairee T, Liu KY, Anderson DW, Durham S, Poh CF. Cyclin D1 overexpression is associated with poor prognosis in oropharyngeal cancer. *J Otolaryngol Head Neck Surg*. 2013;42:23. doi: 10.1186/1916-0216-42-23

32. Marklund L, Nasman A, Ramqvist T, Dalianis T, Munck-Wikland E, Hammarstedt L. Prevalence of human papillomavirus and survival in oropharyngeal cancer other than tonsil or base of tongue cancer. *Cancer Med*. 2012;1(1):82-88.

33. Maxwell JH, Kumar B, Feng FY, et al. Tobacco use in human papillomavirus-positive advanced oropharynx cancer patients related to increased risk of distant metastases and tumor recurrence. *Clin Cancer Res*. 2010;16(4):1226-1235.

34. Mills AM, Beck AH, Pourmand N, Le QT, Kong CS. Evaluation of ProExC as a prognostic marker in oropharyngeal squamous cell carcinomas. *Am J Surg Pathol*. 2012;36(8):1158-1164.

35. Nasman A, Andersson E, Marklund L, et al. HLA class I and II expression in oropharyngeal squamous cell carcinoma in relation to tumor HPV status and clinical outcome. *PLoS One*. 2013;8(10):e77025. doi: 10.1371/journal.pone.0077025

36. Nasman A, Nordfors C, Grun N, et al. Absent/weak CD44 intensity and positive human papillomavirus (HPV) status in oropharyngeal squamous cell carcinoma indicates a very high survival. *Cancer Med*. 2013;2(4):507-518.

37. Nichols AC, Finkelstein DM, Faquin WC, et al. Bcl2 and human papilloma virus 16 as predictors of outcome following concurrent chemoradiation for advanced oropharyngeal cancer. *Clin Cancer Res*. 2010;16(7):2138-2146.

38. Preuss SF, Weinell A, Molitor M, et al. Nuclear survivin expression is associated with HPV-independent carcinogenesis and is an indicator of poor prognosis in oropharyngeal cancer. *Br J Cancer*. 2008;98(3):627-632.

39. Reimers N, Kasper HU, Weissenborn SJ, et al. Combined analysis of HPV-DNA, p16 and EGFR expression to predict prognosis in oropharyngeal cancer. *Int J Cancer*. 2007;120(8):1731-1738.

40. Rietbergen MM, Brakenhoff RH, Bloemena E, et al. Human papillomavirus detection and comorbidity: critical issues in selection of patients with oropharyngeal cancer for treatment De-escalation trials. *Ann Oncol*. 2013;24(11):2740-2745.

41. Rietbergen MM, Snijders PJ, Beekzada D, et al. Molecular characterization of p16-immunopositive but HPV DNA-negative oropharyngeal carcinomas. *Int J Cancer*. 2014;134(10):2366-2372.

42. Rotnaglova E, Tachezy R, Salakova M, et al. HPV involvement in tonsillar cancer: prognostic significance and clinically relevant markers. *Int J Cancer*. 2011;129(1):101-110.

43. Semrau R, Duerbaum H, Temming S, et al. Prognostic impact of human papillomavirus status, survivin, and epidermal growth factor receptor expression on survival in patients treated with radiochemotherapy for very advanced nonresectable oropharyngeal cancer. *Head Neck*. 2013;35(9):1339-1344.

44. Tahtali A, Hey C, Geissler C, et al. HPV status and overall survival of patients with oropharyngeal squamous cell carcinoma--a retrospective study of a German head and neck cancer center. *Anticancer Res*. 2013;33(8):3481-3485.

45. Thavaraj S, Stokes A, Guerra E, et al. Evaluation of human papillomavirus testing for squamous cell carcinoma of the tonsil in clinical practice. *J Clin Pathol*. 2011;64(4):308-312.

46. Weinberger PM, Yu Z, Haffty BG, et al. Molecular classification identifies a subset of human papillomavirus--associated oropharyngeal cancers with favorable prognosis. *J Clin Oncol*. 2006;24(5):736-747.

47. Weinberger PM, Yu Z, Kountourakis P, et al. Defining molecular phenotypes of human papillomavirus-associated oropharyngeal squamous cell carcinoma: validation of three-class hypothesis. *Otolaryngol Head Neck Surg*. 2009;141(3):382-389.

48. Bledsoe TJ, Noble AR, Hunter GK, et al. Oropharyngeal squamous cell carcinoma with known human papillomavirus status treated with definitive chemoradiotherapy: patterns of failure and toxicity outcomes. *Radiat Oncol*. 2013;8:174. doi: 10.1186/1748-717X-8-174

49. Fujimaki M, Fukumura Y, Mitani K, et al. Histological subtypes and characteristic structures of HPV-associated oropharyngeal carcinoma; study with Japanese cases. *Diagn Pathol*. 2013;8(1):211.

50. Song JS, Kim MS, Park JW, Lee YS, Kang CS. Expression of human papillomavirus-related proteins and its clinical implication in tonsillar squamous cell carcinoma. *Korean J Pathol*. 2012;46(2):177-186.

51. Spector ME, Gallagher KK, Bellile E, et al. Patterns of nodal metastasis and prognosis in human papillomavirus-positive oropharyngeal squamous cell carcinoma. *Head Neck*. 2013;36(9):1233-1240.

52. Vainshtein JM, Spector ME, McHugh JB, et al. Refining risk stratification for locoregional failure after chemoradiotherapy in human papillomavirus-associated oropharyngeal cancer. *Oral Oncol*. 2014;50(5):513-519.

53. Attner P, Du J, Nasman A, et al. Human papillomavirus and survival in patients with base of tongue cancer.[Erratum appears in Int J Cancer. 2012 Nov 1;131(9):E1182]. *Int J Cancer*. 2011;128(12):2892-2897.

54. Cerezo L, de la Torre A, Hervas A, et al. Oropharyngeal cancer related to Human Papilloma Virus: incidence and prognosis in Madrid, Spain. *Clin Transl Oncol*. 2014;16(3):301-306.

55. Cheng N-M, Chang JT-C, Huang C-G, et al. Prognostic value of pretreatment 8F-FDG PET/CT and human papillomavirus type 16 testing in locally advanced oropharyngeal squamous cell carcinoma. *Eur J Nucl Med Mol Imaging*. 2012;39(11):1673-1684.

56. Cohen MA, Weinstein GS, O'Malley BW, Jr., Feldman M, Quon H. Transoral robotic surgery and human papillomavirus status: oncologic results. *Head Neck*. 2011;33(4):573-580.

57. Granata R, Miceli R, Orlandi E, et al. Tumor stage, human papillomavirus and smoking status affect the survival of patients with oropharyngeal cancer: an Italian validation study. *Ann Oncol*. 2012;23(7):1832-1837.

58. Hong AM, Martin A, Armstrong BK, et al. Human papillomavirus modifies the prognostic significance of T stage and possibly N stage in tonsillar cancer. *Ann Oncol*. 2013;24(1):215-219.

59. Hong AM, Martin A, Chatfield M, et al. Human papillomavirus, smoking status and outcomes in tonsillar squamous cell carcinoma. *Int J Cancer*. 2013;132(12):2748-2754.

60. Lewis JS, Jr., Thorstad WL, Chernock RD, et al. p16 positive oropharyngeal squamous cell carcinoma:an entity with a favorable prognosis regardless of tumor HPV status. *Am J Surg Pathol*. 2010;34(8):1088-1096.

61. Lindel K, Beer KT, Laissue J, Greiner RH, Aebersold DM. Human papillomavirus positive squamous cell carcinoma of the oropharynx: a radiosensitive subgroup of head and neck carcinoma. *Cancer*. 2001;92(4):805-813.

62. Mizumachi T, Kano S, Sakashita T, et al. Improved survival of Japanese patients with human papillomavirus-positive oropharyngeal squamous cell carcinoma. *Int J Clin Oncol*. 2013;18(5):824-828.

63. Nichols AC, Palma DA, Dhaliwal SS, et al. The epidemic of human papillomavirus and oropharyngeal cancer in a Canadian population. *Curr Oncol*. 2013;20(4):212-219.

64. O'Sullivan B, Huang SH, Perez-Ordonez B, et al. Outcomes of HPV-related oropharyngeal cancer patients treated by radiotherapy alone using altered fractionation. *Radiother Oncol*. 2012;103(1):49-56.

65. O'Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. *J Clin Oncol*. 2013;31(5):543-550.

66. Park K, Cho KJ, Lee M, Yoon DH, Kim S-B. Importance of FOXP3 in prognosis and its relationship with p16 in tonsillar squamous cell carcinoma. *Anticancer Res*. 2013;33(12):5667-5673.

67. Psychogios G, Mantsopoulos K, Agaimy A, et al. Prognostic factors in limited (T1-2, N0-1) oropharyngeal carcinoma treated with surgery + adjuvant therapy. *Head Neck*. 2013;35(12):1752-1758.

68. Rodrigo JP, Heideman DAM, Garcia-Pedrero JM, et al. Time trends in the prevalence of HPV in oropharyngeal squamous cell carcinomas in northern Spain (1990-2009). *Int J Cancer*. 2014;134(2):487-492.

69. Sedaghat AR, Zhang Z, Begum S, et al. Prognostic significance of human papillomavirus in oropharyngeal squamous cell carcinomas. *Laryngoscope*. 2009;119(8):1542-1549.

70. Straetmans JMJAA, Olthof N, Mooren JJ, de Jong J, Speel E-JM, Kremer B. Human papillomavirus reduces the prognostic value of nodal involvement in tonsillar squamous cell carcinomas. *Laryngoscope*. 2009;119(10):1951-1957.

71. Tural D, Elicin O, Batur S, et al. Human papillomavirus is independent prognostic factor on outcome of oropharyngeal squamous cell carcinoma. *Tumour Biol*. 2013;34(6):3363-3369.

72. Ukpo OC, Pritchett CV, Lewis JE, Weaver AL, Smith DI, Moore EJ. Human papillomavirus-associated oropharyngeal squamous cell carcinomas: primary tumor burden and survival in surgical patients. *Ann Otol Rhinol Laryngol*. 2009;118(5):368-373.

73. Worden FP, Kumar B, Lee JS, et al. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number. *J Clin Oncol*. 2008;26(19):3138-3146.

74. Worsham MJ, Stephen JK, Chen KM, et al. Improved survival with HPV among African Americans with oropharyngeal cancer. *Clin Cancer Res*. 2013;19(9):2486-2492.

75. Ali SMA, Awan MS, Ghaffar S, et al. Human papillomavirus infection in oral squamous cell carcinomas: correlation with histologic variables and survival outcome in a high risk population. *Oral Surg*. 2008;1(2):111-113.

76. Cerezo L, Lopez C, de la Torre A, et al. Incidence of human papillomavirus-related oropharyngeal cancer and outcomes after chemoradiation in a population of heavy smokers. *Head Neck*. 2014;36(6):782-786.

77. Habbous S, Harland LT, La Delfa A, et al. Comorbidity and prognosis in head and neck cancers: differences by subsite, stage, and human papillomavirus status. *Head Neck*. 2014;36(6):802-810.

78. Hess CB, Rash DL, Daly ME, et al. Competing causes of death and medical Ccomorbidities among patients with human papillomavirus-positive vs human papillomavirus-negative oropharyngeal carcinoma and impact on adherence to radiotherapy. *JAMA Otolaryngol Head Neck Surg*. 2014;140(4):312-316.

79. Nichols AC, Dhaliwal SS, Palma DA, et al. Does HPV type affect outcome in oropharyngeal cancer? *J Otolaryngol Head Neck Surg*. 2013;429.

80. Chien CY, Su CY, Fang FM, et al. Lower prevalence but favorable survival for human papillomavirus-related squamous cell carcinoma of tonsil in Taiwan. *Oral Oncology*. 2008;44(2):174-179.

81. Hannisdal K, Schjolberg A, De Angelis PM, Boysen M, Clausen OPF. Human papillomavirus (HPV)-positive tonsillar carcinomas are frequent and have a favourable prognosis in males in Norway. *Acta Oto-Laryngologica*. 2010;130(2):293-299.

82. Kuo KT, Hsiao CH, Lin CH, Kuo LT, Huang SH, Lin MC. The biomarkers of human papillomavirus infection in tonsillar squamous cell carcinoma-molecular basis and predicting favorable outcome. *Mod Pathol*. 2008;21(4):376-386.

83. Mooren JJ, Kremer B, Claessen SMH, et al. Chromosome stability in tonsillar squamous cell carcinoma is associated with HPV16 integration and indicates a favorable prognosis. *Int J Cancer*. 2013;132(8):1781-1789.

84. Oguejiofor KK, Hall JS, Mani N, et al. The prognostic significance of the biomarker p16 in oropharyngeal squamous cell carcinoma. *Clin Oncol (R College Radiol)*. 2013;25(11):630-638.

85. Bussu F, Sali M, Gallus R, et al. Human papillomavirus (HPV) infection in squamous cell carcinomas arising from the oropharynx: detection of HPV DNA and p16 immunohistochemistry as diagnostic and prognostic indicators--a pilot study. *Int J Radiat Oncol Biol Phys*. 2014;89(5):1115-1120.

86. Cai C, Chernock RD, Pittman ME, El-Mofty SK, Thorstad WL, Lewis JS, Jr. Keratinizing-type squamous cell carcinoma of the oropharynx: p16 overexpression is associated with positive high-risk HPV status and improved survival. *Am J Surg Pathol*. 2014;38(6):809-815.

87. Trosman SJ, Koyfman SA, Ward MC, et al. Effect of human papillomavirus on patterns of distant metastatic failure in oropharyngeal squamous cell carcinoma treated with chemoradiotherapy. *JAMA Otolaryngol Head Neck Surg*. 2015;141(5):457-462.

88. Hatakeyama H, Mizumachi T, Sakashita T, Kano S, Homma A, Fukuda S. Epithelial-mesenchymal transition in human papillomavirus-positive and –negative oropharyngeal squamous cell carcinoma. *Oncol Rep*. 2014;32(6):2673-2679.

89. Barasch S, Mohindra P, Hennrick K, Hartig GK, Harari PM, Yang DT. Assessing p16 status of oropharyngeal squamous cell carcinoma by combined assessment of the number of cells stained and the confluence of p16 staining: a validation by clinical outcomes. *Am J Surg Pathol*. 2016;40(9):1261-1269

90. Liu SZ, Zandberg DP, Schumaker LM, Papadimitriou JC, Cullen KJ. Correlation of p16 expression and HPV type with survival in oropharyngeal squamous cell cancer. *Oral Oncol*. 2015;51(9):862-869.

91. Rios Velazquez E, Hoebers F, Aerts HJ, et al. Externally validated HPV-based prognostic nomogram for oropharyngeal carcinoma patients yields more accurate predictions than TNM staging. *Radiother Oncol*. 2014;113(3):324-330.

92. Driessen CM, Janssens GO, van der Graaf WT, et al. Toxicity and efficacy of accelerated radiotherapy with concurrent weekly cisplatin for locally advanced head and neck carcinoma. *Head Neck*. 2016;38(Suppl 1):E559-565.

93. Dunlap NE, Narayan R, Shaughnessy J, et al. HPV/p16 status and patterns of failure for squamous cell carcinoma of the oropharynx after definitive chemoradiation: establishing a relationship to elective nodal irradiation: definitive management of head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2014;88(2):483-484.

94. Lorch JH, Hanna G, Dai W, et al. HPV and survival in patients with oropharyngeal squamous cell cancer of the head and neck (OPC) treated with induction chemotherapy followed by chemoradiotherapy (ST) versus chemoradiotherapy alone (CRT): the Dana-Farber experience [ASCO abstract 5582]. *J Clin Oncol*. 2012;30(Suppl 15):5582.

95. Austin M, Schmidt R, Parvathaneni U, et al. Expression of p16, ERCC1, and EGFR amplification as predictors of responsiveness of locally advanced squamous cell carcinomas of head and neck (SCCHN) to cisplatin, radiotherapy, and erlotinib: a phase II randomized trial [ASCO abstract 5515]. *J Clin Oncol*. 2012;30(Suppl 15):5515.

96. Hasegawa M, Meda H, Agena S, Suzuki M. HPV E6/E7 mRNA expression in oropharyngeal carcinoma [AAO-AHNS abstract P168]. *Otolaryngol Head Neck Surg*. 2011;145(Suppl 2):P168.

97. Guihard S, Jung AC, Abecassis J, et al. Prognostic value of HPV E6/E7 mRNA expression in a retrospective series of 144 French patients. *Int J Radiat Oncol Biol Phys*. 2011;81(2):S491-S492.

98. Lorch J, Thotakura V, Posner M, et al. HPV and survival in patients with oropharyngeal squamous cell cancer of the head and neck (OPC) treated with induction chemotherapy followed by chemoradiotherapy (ST) versus chemoradiotherapy alone (CRT): a retrospective analysis [ASTRO abstract 145]. Multidisciplinary Head Neck Cancer Symposium, January 26-28, 2012, Phoenix, AZ. http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=b1c590bb-c362-40ea-bf96-b8f21b8936d8&cKey=2c0d661a-453a-4dbd-8d42-32fa94f6c890&mKey=82897973-8a41-4f26-bb8e-7e358fc53b94. Accessed June 6, 2017.

99. Saraiya M, Thompson T, Lynch C, et al. HPV genotype -specific survival of orpharyngeal cancers - United States, 1994-2005 [IPS abstract 315] ; 28th International Papillomavirus Conference, San Juan, Puerto Rico, November 30-December 6, 2012.

100. Maxwell J, Ferris R. Effect of HPV and smoking on survival and recurrence in oropharyngeal cancer patients [AHNS abstract S035]; Annual Meeting of the American Head and Neck Society, April 27-28, 2011, Chicago, IL.

101. Xu J, Isayeva T, Brandwein-Gensler M. p16 overexpression: a better prognostic discriminator than transcriptionally active human papillomavirus 16 [CAP abstract 4]. *Arch Pathol Lab Med.* 2013;137(10):1481.

102. Shaw R, Schache A, Jones T, Risk J, Robinson M, Liloglou L. Smoking may not influence prognosis in HPV-16 mediated oropharyngeal squamous cell carcinoma [AAO-AHNS abstract 1948]; AAO-AHNS 8th International Conference on H&N Cancer. Toronto, ON, Canada. 2012.

103. Bahl A, Dar L, Mohanti B, et al. Prevalence, trends, and survival impact of human papillomavirus on oropharyngeal cancer in Indian population [ASCO abstract 5540]. *J Clin Oncol*. 2012;30(Suppl 15):5540.

104. Broglie M, Soltermann A, Pawlita M, Huber G, Studer G, Stoeckli S. Impact of p16, p53, smoking, alcohol and staging on survival in oropharyngeal squamous cell carcinoma [AHNS abstract S220]. 8th International Conference on Head & Neck Cancer, July 21-25, 2012, Toronto, ON, Canada.

105. Zandberg DP, Liu SZ, Goloubeva O, Schumaker LM, Cullen KJ. HPV-positive oropharyngeal cancer increased for both black and white patients over time, 1992-2007: epidemiology and prevention [ASTRO abstract 107]. *Int J Rad Oncol Biol Phys*. 2014;88(Suppl 2):494-495.

106. Ang M-K, Ang SH, Krishna SS, et al. Association of smoking status with p16 and cyclin D1 (CCND1) expression with clinical characteristics and overall survival (OS) in oropharyngeal squamous cell carcinoma (OSC) [ASCO abstract 5551]. *J Clin Oncol.* 2012;30(Suppl 15):5551.

107. Knoedler M, Zakarneh A, Zimmermann U, Woelke K, Kaschke O, Keilholz U. Effects of human papillomavirus (HPV) and other potential risk factors on survival in patients with oropharyngeal cancer [ASCO abstract 5577]. *J Clin Oncol.* 2011;29(Suppl 15):5577.

108. Smith G, Muller S, Moore C, et al. Racial disparity in p16 positive oropharyngeal squamous cell carcinoma [USCAP abstract 1340]. *Mod Pathol.* 2014;27(Suppl 2):328A.

109. Xu J, Dai Q, Isayeva T, Hebert-Magee S, Brandwein-Gensler M. African Americans with oropharyngeal carcinoma: decreased transcriptionally active high-risk human papillomavirus contributes to poorer survival [USCAP abstract 1340]. *Mod Pathol;* 2012;92(Suppl 1):318A.

110. Rakusic Z, Seiwerth S, Jakovčević A, Prgomet D, Juretić A. Impact of human papillomavirus on clinicopathological characteristics of oropharyngeal carcinomas [ASTRO abstract 2677]. *Int J Rad Oncol Biol Phys*. 2012;84(3):S473-S474.

111. Brookes L, Allibone R, Christian JA. The impact of human papillomavirus on oropharyngeal cancer in Nottingham, UK [ESTRO abstract EP-1142]. *Radiother Oncol.* 2014;111(Suppl 1):S34-35.

112. Valduga F, Caldara A, Vanoni V, et al. Clinical outcome according to p16 status and treatment modalities in oropharyngeal cancer (OC) patients (PTS) [ASTRO abstract 220]. Multidisciplinary Head Neck Cancer Symposium, January 26-28, 2012. Phoenix, AZ. http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=b1c590bb-c362-40ea-bf96-b8f21b8936d8&cKey=da2c4be7-f301-46c7-9ff2-93d0285d561e&mKey=%7b82897973-8A41-4F26-BB8E-7E358FC53B94%7d. Accessed June 14, 2017.

113. Upile N, Lancaster J, Kinshuck A, et al. Is human papillomavirus (HPV) status really important? Transoral laser surgery in the management of oropharyngeal squamous cell carcinoma (OPSCC) [AHNS abstract P467]. 8th International Conference on Head & Neck Cancer, July 21-25, 2012, Toronto, ON, Canada.

114. Broglie M, Soltermann A, Pawlita M, Probst R, Stoeckli S. Risk stratification based on p16-expression and other factors in OPSCC [IPS abstract P-16.23]. 27th Annual International Papillomavirus Conference & Clinical Workshops, Berlin, Germany, September 17-September 22, 2011.

115. Lassen P, Primdahl H, Johansen J, et al. HPV, smoking and RT-outcome in advanced OPC treated without chemotherapy – analysis of DAHANCA patients [ESTRO abstract OC-0149]. *Radiother Oncol.* 2012;103(Suppl 1):S58.

116. Sweeney BJ, Ring L, Rego M, Smith HL, Faquin W, Wilbur DC. Automated extraction of FFPE (formalin fixed paraffin embedded) tissue for head and neck HR-HPV (high risk human papillomavirus) testing on the Roche Cobas® 4800 System [ASC abstract 120]. *J Am Soc Cytopathol*. 2013;2(1):S52-S53.

117. Chung CH, Zhang Q, Kong C, et al. p16 expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. *J Clin Oncol*. 2014;32(35):3930-3938.

118. Lingen MW, Xiao W, Schmitt A, et al. Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. *Oral Oncology*. 2013;49(1):1-8.

119. Lewis JS, Jr., Ukpo OC, Ma X-J, et al. Transcriptionally-active high-risk human papillomavirus is rare in oral cavity and laryngeal/hypopharyngeal squamous cell carcinomas--a tissue microarray study utilizing E6/E7 mRNA in situ hybridization. *Histopathology*. 2012;60(6):982-991.

120. Laco J, Slaninka I, Jirasek M, Celakovsky P, Vosmikova H, Ryska A. High-risk human papillomavirus infection and p16INK4a protein expression in laryngeal lesions. *Pathol Res Pract*. 2008;204(8):545-552.

121. Alos L, Moyano S, Nadal A, et al. Human papillomaviruses are identified in a subgroup of sinonasal squamous cell carcinomas with favorable outcome. *Cancer*. 2009;115(12):2701-2709.

122. Elango KJ, Suresh A, Erode EM, et al. Role of human papilloma virus in oral tongue squamous cell carcinoma. *Asian Pac J Cancer Prev*. 2011;12(4):889-896.

123. Larque AB, Hakim S, Ordi J, et al. High-risk human papillomavirus is transcriptionally active in a subset of sinonasal squamous cell carcinomas. *Mod Pathol*. 2014;27(3):343-351.

124. Duncan LD, Winkler M, Carlson ER, Heidel RE, Kang E, Webb D. p16 immunohistochemistry can be used to detect human papillomavirus in oral cavity squamous cell carcinoma. *J Oral Maxillofac Surg*. 2013;71(8):1367-1375.

125. Kaminagakura E, Villa LL, Andreoli MA, et al. High-risk human papillomavirus in oral squamous cell carcinoma of young patients. *Int J Cancer*. 2012;130(8):1726-1732.

126. Wendt M, Romanitan M, Nasman A, et al. Presence of human papillomaviruses and p16 expression in hypopharyngeal cancer. *Head Neck*. 2014;36(1):107-112.

127. Duray A, Descamps G, Decaestecker C, et al. Human papillomavirus DNA strongly correlates with a poorer prognosis in oral cavity carcinoma. *Laryngoscope*. 2012;122(7):1558-1565.

128. Reuschenbach M, Kansy K, Garbe K, et al. Lack of evidence of human papillomavirus-induced squamous cell carcinomas of the oral cavity in southern Germany. *Oral Oncol*. 2013;49(9):937-942.

129. Chaudhary AK, Pandya S, Mehrotra R, Bharti AC, Singh M, Singh M. Comparative study between the Hybrid Capture II test and PCR based assay for the detection of human papillomavirus DNA in oral submucous fibrosis and oral squamous cell carcinoma. *Virol J*. 2010;7:253. doi: 10.1186/1743-422X-7-253

130. Skalova A, Kaspirkova J, Andrle P, Hosticka L, Vanecek T. Human papillomaviruses are not involved in the etiopathogenesis of salivary gland tumors. *Cesk Patol*. 2013;49(2):72-75.

131. Zhao D, Xu QG, Chen XM, Fan MW. Human papillomavirus as an independent predictor in oral squamous cell cancer. *Int J Oral Sci*. 2009;1(3):119-125.

132. Sugiyama M, Bhawal UK, Kawamura M, et al. Human papillomavirus-16 in oral squamous cell carcinoma: clinical correlates and 5-year survival. *Br J Oral Maxillofac Surg*. 2007;45(2):116-122.

133. Duray A, Descamps G, Arafa M, et al. High incidence of high-risk HPV in benign and malignant lesions of the larynx. *Int J Oncol*. 2011;39(1):51-59.

134. Robinson M, Suh YE, Paleri V, et al. Oncogenic human papillomavirus-associated nasopharyngeal carcinoma: an observational study of correlation with ethnicity, histological subtype and outcome in a UK population. *Infect Agents Cancer*. 2013;8(1):30. doi: 10.1186/1750-9378-8-30

135. Jiang H, Lin PF. Human papillomavirus infection a favorable prognostic factor in laryngeal squamous cell carcinoma is associated with the expression of proliferating cell nuclear antigen. *Pak J Med Sci*. 2013;29(5):1173-1177.

136. Ernoux-Neufcoeur P, Arafa M, Decaestecker C, et al. Combined analysis of HPV DNA, p16, p21 and p53 to predict prognosis in patients with stage IV hypopharyngeal carcinoma. *J Cancer Res Clin Oncol*. 2011;137(1):173-181.

137. Nemes JA, Deli L, Nemes Z, Marton IJ. Expression of p16(INK4A), p53, and Rb proteins are independent from the presence of human papillomavirus genes in oral squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006;102(3):344-352.

138. Stephen JK, Chen KM, Shah V, et al. Human papillomavirus outcomes in an access-to-care laryngeal cancer cohort. *Otolaryngol Head Neck Surg*. 2012;146(5):730-738.

139. Morshed K, Polz-Dacewicz M, Szymanski M, Polz D. Short-fragment PCR assay for highly sensitive broad-spectrum detection of human papillomaviruses in laryngeal squamous cell carcinoma and normal mucosa: clinico-pathological evaluation. *Eur Arch Otorhinolaryngology*. 2008;265(Suppl 1):S89-96.

140. Huang SF, Li HF, Liao CT, et al. Association of HPV infections with second primary tumors in early-staged oral cavity cancer. *Oral Dis*. 2012;18(8):809-815.

141. Bishop JA, Guo TW, Smith DF, et al. Human papillomavirus-related carcinomas of the sinonasal tract. *Am J Surg Pathol*. 2013;37(2):185-192.

142. Chernock RD, Wang X, Gao G, et al. Detection and significance of human papillomavirus, CDKN2A(p16) and CDKN1A(p21) expression in squamous cell carcinoma of the larynx. *Mod Pathol*. 2013;26(2):223-231.

143. Kirby S, Marcinow A, Teknos T, Iwenofu O. Does p16 status matter in the larynx? A study of overall survival in p16 positive squamous cell carcinomas of the larynx regardless of HPV status [USCAP abstract 1326]. *Mod Pathol.* 2014;27(S2):321A.

144. Stenmark MH, McHugh JB, Schipper M, et al. High frequency of HPV-associated nasopharyngeal carcinoma (NPC) in North American patients: association with poor prognosis. *Int J Rad Oncol Biol Phys*. 2013;87(2):S79-S80.

145. Compton AM, Moore-Medlin T, Herman-Ferdinandez L, et al. Human papillomavirus in metastatic lymph nodes from unknown primary head and neck squamous cell carcinoma. *Otolaryngol Head Neck Surg*. 2011;145(1):51-57.

146. Tribius S, Hoffmann AS, Bastrop S, et al. HPV status in patients with head and neck of carcinoma of unknown primary site: HPV, tobacco smoking, and outcome. *Oral Oncol*. 2012;48(11):1178-1184.

147. Vent J, Haidle B, Wedemeyer I, et al. p16 expression in carcinoma of unknown primary: diagnostic indicator and prognostic marker. *Head Neck*. 2013;35(11):1521-1526.

148. Sivars L, Nasman A, Tertipis N, et al. Human papillomavirus and p53 expression in cancer of unknown primary in the head and neck region in relation to clinical outcome. *Cancer Med*. 2014;3(2):376-384.

149. Begum S, Gillison ML, Nicol TL, Westra WH. Detection of human papillomavirus-16 in fine-needle aspirates to determine tumor origin in patients with metastatic squamous cell carcinoma of the head and neck. *Clin Cancer Res*. 2007;13(4):1186-1191.

150. Bishop JA, Maleki Z, Valsamakis A, et al. Application of the hybrid capture 2 assay to squamous cell carcinomas of the head and neck: a convenient liquid-phase approach for the reliable determination of human papillomavirus status. *Cancer Cytopathol*. 2012;120(1):18-25.

151. Guo M, Khanna A, Dhillon J, et al. Cervista HPV assays for fine-needle aspiration specimens are a valid option for human papillomavirus testing in patients with oropharyngeal carcinoma. *Cancer Cytopathol*. 2014;122(2):96-103.

152. Lastra RR, Pramick MR, Nakashima MO, et al. Adequacy of fine-needle aspiration specimens for human papillomavirus infection molecular testing in head and neck squamous cell carcinoma. *Cytojournal*. 2013;1021. doi: 10.4103/1742-6413.120789

153. Jakscha J, Zlobec I, Storck C, et al. The clinical impact of p16 status in fine-needle aspirates of cervical lymph node metastasis of head and neck squamous cell carcinomas. *Eur Arch Otorhinolaryngology*. 2013;270(2):661-667.

154. Jannapureddy S, Cohen C, Lau S, Beitler JJ, Siddiqui MT. Assessing for primary oropharyngeal or nasopharyngeal squamous cell carcinoma from fine needle aspiration of cervical lymph node metastases. *Diagn Cytopathol*. 2010;38(11):795-800.

155. Baldassarri R, Aronberg R, Levi AW, Yarbrough WG, Kowalski D, Chhieng D. Detection and genotype of high-risk human papillomavirus in fine-needle aspirates of patients with metastatic squamous cell carcinoma is helpful in determining tumor origin. *Am J Clin Pathol*. 2015;143(5):694-700.

156. Holmes BJ, Maleki Z, Westra WH. The fidelity of p16 staining as a surrogate marker of muman papillomavirus status in fine-needle aspirates and core biopsies of neck node metastases: implications for HPV testing protocols. *Acta Cytol*. 2015;59(1):97-103.

157. Jalaly JB, Lewis JS, Jr., Collins BT, et al. Correlation of p16 immunohistochemistry in FNA biopsies with corresponding tissue specimens in HPV-related squamous cell carcinomas of the oropharynx. *Cancer Cytopathol*. 2015;123(12):723-731.

158. Kerr DA, Pitman MB, Sweeney B, Arpin RN III, Wilbur DC, Faquin WC. Performance of the Roche cobas 4800 high-risk human papillomavirus test in cytologic preparations of squamous cell carcinoma of the head and neck. *Cancer Cytopathol*. 2014;122(3):167-174.

159. Smith DF, Maleki Z, Coughlan D, et al. Human papillomavirus status of head and neck cancer as determined in cytologic specimens using the hybrid-capture 2 assay. *Oral Oncol*. 2014;50(6):600-604.

160. Fowler N, Manzoor N, Rajasekaran K, et al. Prevalence of human papilloma virus and p16 and predictors of survival in patients with cervical unknown primary squamous cell caricnoma [AAO-AHNS abstract S168]. 8th International Conference on Head and Neck Cancer. July 21-25, 2012, Toronto, ON, Canada. http://ahns.jnabstracts.com/2012/Detail?ID=0168. Accessed June 6, 2017.

161. Davis D, Braxton D, Fatima N, Momin S, Cynthia C. HPV L1 in oropharyngeal squamous cell carcinomas: comparison and correlation with p16, HPV ISH, and outcome [USCAP abstract 1309]. *Mod Pathol.* 2014;27(Supp 2):317A..

162. Fatima N, Cohen C, Siddiqui M. Comparing HPV ISH and p16 in assessing metastatic oropharyngeal carcinoma [USCAP abstract 361]. *Mod Pathol.* 2012;25(Supp 2):89A.

163. Inohara H, Yasui T, Maruyama H. Human papilloma virus in nek metastasis from head and neck carcinoma and unknown primary carcinoma [AHNS abstract P346]; 8th International Conference on Head & Neck Cancer, July 21-25, 2012, Toronto, IN, Canada.

164. Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoSMed.* 2009; 6(6):e1000097. doi:10.1371/journal.pmed1000097