Analyzing the oral HPV infection and cytopathology: Evaluation of an oropharyngeal "Pap-Test Equivalent" in high-risk populations

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Abstract
Human papillomavirus (HPV) is responsible for the rising incidence of oropharyngeal squamous cell cancers (OSCC) in the United States, and yet, no screening strategies have been evaluated. Secondary prevention by means of HPV detection and cervical cytology has led to a decline in cervical cancer incidence in the United States. Here, we explored an analogous strategy by evaluating associations between HPV16 infection, cytopathology, and histopathology in two populations at elevated risk for OSCCs. In the first, a cross-sectional study population (PAP1), cytology specimens were collected by means of brush biopsy from patients presenting with oropharyngeal abnormalities. In the second (PAP2), a nested case-control study, bilateral tonsillar cytology samples were collected at 12-month intervals from HIV-infected individuals. The presence of cytopathologic abnormality in HPV16-positive tonsil brush biopsies (cases) was compared with HPV16-negative samples (controls) matched on age and gender. HPV16 was detected in samples by consensus primer PCR and/or type-specific PCR. Univariate logistic regression was used to evaluate associations. In PAP1, HPV16 alone (OR: 6.1, 95% CI: 1.6–22.7) or in combination with abnormal cytology (OR: 20, 95% CI: 4.2–95.4) was associated with OSCC. In PAP2, 4.7% (72 of 1,524) of tonsillar cytology specimens from HIV-infected individuals without oropharyngeal abnormalities were HPV16 positive. Tonsillar HPV16 infection was not associated with atypical squamous cells of unknown significance (ASCUS), the only cytologic abnormality identified. Therefore, HPV16 was associated with OSCCs among individuals with accessible oropharyngeal lesions but not with cytologic evidence of dysplasia among high-risk individuals without such lesions. An oropharyngeal Pap-test equivalent may not be feasible, likely due to limitations in sampling the relevant tonsillar crypt epithelium.

Introduction
Human papillomavirus (HPV) is etiologically responsible for a distinct and growing subset of oropharyngeal squamous cell cancers (OSCC) that disproportionately affect young men, nonsmokers, and nondrinkers (1,2). In contrast to OSCCs, cervical cancer incidence rates have declined for decades in the United States because of a successful secondary prevention strategy by means of cervical cytology screening (Papanicolaou or "Pap" test; refs. 3–5). Because of its superior sensitivity, cervical HPV detection has been incorporated into the screening algorithm and may replace cervical cytology (6–8). Given this, it is reasonable to investigate whether HPV detection and/or an oral "Pap-test equivalent" could be similarly used to screen for HPV-positive OSCCs.

Oral HPV16 infection is estimated to confer at least a 15-fold increase in risk for OSCCs in case-control studies (1). In cervical cancer screening, the presence of a high-risk HPV infection is associated with an approximate 50-fold increase in risk of cervical cytologic abnormalities (e.g., cervical intraepithelial neoplasia, CIN 1–3) when compared with HPV-negative women (9). We therefore investigated whether or not oral HPV16 infection is associated with cytologic or histologic abnormalities of the oropharynx in 2 populations: (i) patients who present for evaluation of clinical abnormalities of the oropharynx [cross-sectional study population (PAP1)] and (ii) a population known to have a 2 to 6-fold increase in risk for both oral HPV infection and OSCCs, HIV-infected individuals [nested case-control study (PAP2); refs. 10–12].

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Materials and Methods

Study populations, and specimen collection

Cross-sectional study population. Eligible subjects included patients with oropharyngeal abnormalities referred to a head and neck surgeon for diagnostic evaluation. Patients were enrolled at Johns Hopkins Hospital (Baltimore, MD) and affiliated centers (Greater Baltimore Medical Center, Towson, MD), University of Maryland (College Park, MD), University of Pittsburgh (Pittsburgh, PA), and Louisiana State University (New Orleans, LA). Patient demographic characteristics, risk behaviors (alcohol and tobacco use), and clinical characteristics of the lesion (including color, appearance, ulceration, symptoms, location, duration, size, and clinical impression) were obtained by a standardized, clinician-completed questionnaire. Cytology specimens were obtained from all lesions by use of an Oral-CDx brush (Oral CDx Laboratories), as recommended by the manufacturer (13). After transfer of cellular material to a glass slide, the cytobrush was placed into a vial containing 1 mL of Digene Specimen Transport Medium (STM; Qiagen) and stored at −80°C until further processing (see later). Incisional biopsy was conducted for all but one lesion which was benign appearing.

Nested case-control. A case–control study was nested within a prospective cohort study of the natural history of oral HPV infection in HIV-positive men and women (HOPE) at The Johns Hopkins Hospital. Oral samples were obtained for HPV detection every 6 months for a maximum of 6 visits. Oral rinses were collected at 6-month intervals by use of a 30-second oral rinse and gargle with 10 mL of Scope mouthwash. Oral exfoliated cells were centrifuged, washed with PBS, and stored at −80°C until further processing.

Bilateral tonsillar brush biopsies were conducted at 12-month intervals by use of 2 OralCDx brushes. Circumferential pressure was applied along the palatine tonsils or posterior pharyngeal wall (in patients without tonsils) until pinpoint bleeding was elicited. The cytobrush was placed in a vial containing 1 mL of PBS on ice for transport to the laboratory. The samples were vortexed, split into 2 equal aliquots, and centrifuged. One aliquot was resuspended in 0.5 mL of Digene STM (Qiagen) and the second in 0.5 mL of Cytorich Red (BD). Pilot studies were conducted to determine the optimal specimen fixative for preservation of cytoarchitectural features of oropharyngeal biopsies and to establish practicality of the collection process. All specimen processing and analysis was conducted in the Gillison Laboratory (Johns Hopkins Medicine).

Specimen processing and HPV detection

DNA was purified from oral rinse samples by use of a modified protocol for a Puregene DNA purification kit (Gentra Systems; ref. 14). DNA was purified from cytology specimens (both oropharyngeal cytology specimens and tonsillar cytology specimens) in Digene STM by standard protocol. Briefly, half of the STM sample was added to a proteinase K-digestion buffer solution (final concentration 0.4 mg/mL proteinase K, 50 mmol/L Tris-HCl, 1 mmol/L EDTA, 0.5% Tween-20) and incubated at 65°C for 1 hour followed by heat inactivation at 95°C for 10 minutes. DNA was precipitated by standard ammonium acetate ethanol precipitation, washed with 70% ethanol, dried, and resuspended in 20 μL of LoTE buffer (3 mmol/L Tris-HCl and 0.2 mmol/L EDTA).

The presence of HPV16 genomic DNA was detected in oropharyngeal cytology and oral rinse samples by PCR amplification by use of PGMY09/11 L1 consensus primers, followed by hybridization to a prototype HPV probe linear array and β-globin (Roche Molecular Systems, Inc.; ref. 15). A negative control was included for each row of the 96-well plate (1 in 11 experimental samples). Samples that were β-globin negative were considered to be of insufficient quality for analysis.

Type-specific, quantitative, TaqMan real-time PCR (Applied Biosystems) targeted to HPV16 E6 was used to detect HPV16 in oropharyngeal (PAP1) and tonsillar cytology samples (PAP2; ref. 16). A negative control was included for each row of the 96-well plate (1 in 10 experimental samples). Samples with a mean of the duplicates greater than or equal to 1 viral copy were considered positive.

For oropharyngeal and tonsillar cytology samples, the number of epithelial cells in each PCR reaction was estimated by use of a TaqMan real-time PCR targeted to a single-copy human gene on chromosome 7, human endogenous retrovirus 3 (ERV-3; ref. 14). Data were used: (i) to categorize PAP2 tonsillar cytology samples as evaluable if ERV3 was greater than or equal to 3 (lower limit of assay sensitivity); (ii) to adjust HPV16 viral load to cell number; and (iii) to estimate the number of cells evaluated by cytopathology.

All specimen processing and analysis was conducted in the Gillison Laboratory (Johns Hopkins Medicine).

Cytology PAP1

Cytology slides from patients with oropharyngeal abnormalities were interpreted at Oral CDx Labs by
pathologist-guided computer analysis and reported as "not interpretable" or "interpretable." Samples considered "not interpretable" were incomplete transepithelial biopsies that were not representative of all 3 epithelial layers (13). "Interpretable" slides were further categorized as "negative," "atypical," or "positive."

Cytology PAP2
To evaluate associations between tonsillar HPV16 infection and cytologic abnormality in PAP2, a nested case-control study was conducted. A case was defined as an HPV16-positive tonsillar cytology specimen. A control was defined as an HPV16-negative tonsillar cytology specimen from an individual with a corresponding HPV16-negative oral rinse specimen. Controls were matched to cases in a 2:1 ratio on subject study visit, gender, and age (in 5-year categories). Tonsillar cytology specimens from both cases and controls underwent cytopathologic review. In addition, cytopathologic analysis was conducted on contralateral HPV16-negative tonsillar cytology specimens from cases as well as specimens from all individuals with an HPV16-positive oral rinse sample in the presence of HPV16-negative tonsillar cytology specimens.

Tonsillar cytology specimens in Cytorich Red from the nested case-control study were prepared by thawing to room temperature and applied to slides using cytocentrifugation. Briefly, approximately 300 μL of each specimen was combined with 300 μL of Shandon Cytospin Collection Fluid (Thermo Fisher Scientific) and applied to 2 cytospin slides (6-mm area each) using a cytospin funnel and centrifugation. Slides were then stained using routine Papanicolaou stain.

A case report form for interpretation of the tonsillar cytology specimens was created to standardize cytomorphologic evaluation and reporting and was derived from the Bethesda System criteria used for evaluating squamous lesions in cervical cytology (17). Specimens were evaluated for adequacy based on the presence of at least 1,000 squamous cells and lack of obscuring factors such as blood or inflammation. Slides were assigned to one of the following categories: (i) negative for dysplasia or malignancy; (ii) positive for atypical squamous cells of undetermined significance (ASCUS); (iii) positive for dysplasia (mild, moderate, or severe dysplasia); (iv) positive for squamous cell carcinoma. All slides were screened by an experienced cytopathologist (B.T. Rosenthal) and interpreted by an experienced cytopathologist (D.P. Clark). Both reviewers were masked to HPV status and clinical features of individual cases during evaluation.

In situ hybridization
Available tumors were evaluated for the presence of HPV16 DNA by use of the in situ hybridization (ISH)-catalyzed signal amplification method for biotinylated probes (GenPoint; Dako), as previously described (18, 19). Slides were scored as positive for HPV16 if a punctate signal specific to tumor cell nuclei was present.

Statistical analysis
Characteristics of each study population were summarized using descriptive statistics. PAP1 cytology and histopathology were categorized as dichotomous variables of normal or abnormal (including "atypical" or "positive") and non-SCC or SCC, respectively. ISH1 scoring was categorized as a dichotomous variable of negative and positive. In PAP2, HPV16 infection status was categorized by sample (oral rinse or tonsillar cytology), study visit (1–6), and by study subject (n = 401). Detection of HPV16 infection was described as visit specific or cumulative prevalence. A subject was considered infected if HPV16 was present at each visit (prevalence) or detected in any samples collected over the course of the study (cumulative prevalence).

Associations between HPV16 and abnormal cytology or histology were evaluated using univariate logistic regression (ORs and 95% CIs). A 2-sided value of P < 0.05 was considered statistically significant. Stata IC 11 software (StataCorp LP) was used to conduct the analysis.

Results
PAP1
A total of 92 individuals with clinically apparent lesions of the oropharynx were enrolled in PAP1. The majority was male (78.3%) and Caucasian (85.9%). Median age was 56.5 years (range: 22–85). The majority had a history of tobacco smoking (65.2%), and current smokers had a median of 40.5 [interquartile range (IQR): 30–60] pack-years of use. Twenty-three of 92 (25%) reported heavy current alcohol use (>5 drinks per day). The anatomic site distribution of the oropharyngeal abnormality that underwent cytopathologic analysis was tonsil (n = 36, 39.1%), base of tongue (n = 34, 37.0%), posterior pharyngeal wall (n = 6, 6.5%), retromolar trigone (n = 4, 4.4%), and mixed/other (n = 8, 8.6%). Cytology specimens were collected under general anesthesia (82.6%), in an outpatient clinic (9.8%) or location unknown (7.6%). The clinical characteristics of the oropharyngeal abnormalities in PAP1 are summarized in the Supplementary Table.

All but one of the oropharyngeal cytology specimens were β-globin positive and therefore evaluable for HPV. HPV DNA was detected by Roche linear array in 52.8% (48 of 91) of evaluable samples. The HPV type-specific distribution for positive samples was HPV16 (n = 41, 85.4%), HPV33 (n = 4, 8.3%) and HPV11, 18, 35, 52, 67, 72, 81, and 83 (for each, n = 1, 2.1%). Five samples were coinfected with 2 distinct HPV infections. HPV16 was detected by type-specific quantitative PCR in 97.6% (40 of 41) of samples positive by linear array and 2 additional samples were positive. The median HPV16 viral load among the 43 positive samples was 1.49 copies per cell (95% CI: 0.25–6.52). As measured by ERV3, a median of 17,267 cells (IQR: 3,934–60,933) were evaluated per sample by realtime PCR for presence of HPV16 in oropharyngeal cytology specimens.

In cytopathologic analysis, 84.8% (78 of 92) of oropharyngeal cytology specimens were interpretable, and of these
Table 1. Associations between HPV16 and cytopathology

<table>
<thead>
<tr>
<th>Cytology</th>
<th>Cytology</th>
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<tr>
<td>Normal</td>
<td>Abnormal</td>
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<td><strong>PAP1</strong></td>
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<td>HPV16 by linear array</td>
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<td>Negative</td>
<td>10</td>
<td>30</td>
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<tr>
<td>Positive</td>
<td>4</td>
<td>33</td>
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<td>HPV16 by real-time PCR</td>
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<td>Negative</td>
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<td><strong>PAP2</strong></td>
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<td>HPV16</td>
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<td>Negative</td>
<td>120</td>
<td>6</td>
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<tr>
<td>Positive</td>
<td>64</td>
<td>6</td>
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</table>

aHPV16 infection status determined by linear array and RT-PCR in PAP1 and linear array in PAP2. There were a differing number of evaluable samples depending on HPV16 assay type.

bReferent category.

78 samples, 14 (17.9%) were normal, 59 (75.6%), were atypical and 5 (6.4%) were positive. Therefore, a total of 64 samples (82.1%) were considered abnormal in our analysis. Detection of HPV16 by type-specific PCR was associated with a nonsignificant 3-fold increased in odds of abnormal cytology (OR: 3.2, 95% CI: 0.9–11.3; Table 1). Furthermore, the presence of high-risk HPV by linear array (OR: 4.6, 95% CI: 1.4–15.4) or HPV16 by real-time PCR (OR: 6.1, 95% CI: 1.6–22.7; Table 2) was strongly associated with a histopathologic diagnosis of squamous cell carcinoma among the 91 lesions for which histopathology was available. Abnormal cytology was also strongly associated with squamous cell carcinoma (OR: 8.0, 95% CI: 2.2–29.6; Table 2). The combination of HPV16 and abnormal cytology was strongly associated with OSCCs (OR: 20, 95% CI: 4.2–95.4).

To explore whether or not the presence of the HPV-negative subset of OSCCs could explain the weak association between HPV and abnormal cytology, a stratified analysis was conducted. Tumor HPV16 status was available for 67% of biopsy specimens (61 of 91). HPV16 was indeed detectable in a higher proportion of abnormal cytology samples (49 of 61) from study subjects with HPV16-ISH positive than negative tumors [91.3% (21 of 23) vs. 38.5% (10 of 26)]. HPV16 presence in cytology samples appeared to be associated with HPV16-positive (OR: 23, 95% CI: 0.75–702.6) but not HPV16-negative OSCCs (OR: 0.8, 95% CI: 0.6–10.0).

**PAP2**

Given the findings noted above, a study was designed to evaluate associations between HPV16 infection and tonsillar cytology in a population at high risk for HPV infection and tonsillar cancer, HIV-infected individuals.

A total of 401 HIV-infected men and women were enrolled in the HOPE cohort study. The HOPE cohort was 60.1% (n = 241) male and 86.3% (n = 346) African-American, and the overwhelming majority were non-Hispanic (n = 390, 97.3%). Median age was 46.4 years (range: 20.7–73.9). Median CD4 count was 304 cells per μL (IQR: 176–602) and median HIV viral load was 354.0 copies per mL (IQR: 55.5–26,470.0). There were no discernable clinical abnormalities of the oropharynx.

A total of 1,198 oral rinse samples were collected at visits 1 to 5 and 99.1% (1,187 of 1,198) were evaluable for HPV16 by linear array. The prevalence of oral HPV16 infection among 1,187 evaluable oral rinses collected was 2.8% (95% CI: 1.8–3.7). The prevalence of oral HPV16 infection in the study population was 2.6%, 1.3%, 2.8%, 2.7%, and 5.9% at visits 1 to 5, respectively.

Bilateral tonsillar brush biopsy samples were collected at the baseline visit from all 401 enrolled subjects and from 247 and 136 subjects at the 12- and 24-month visits, respectively. Thus, a total of 1,551 tonsillar cytology samples were collected (17 individuals refused to undergo collection of second tonsillar brush biopsy at one of the visits) and 1,524 (98.3%) were evaluable as determined by ERV3. Overall, HPV16 was detected by quantitative PCR in 4.7% (95% CI: 3.7%–5.8%). Median HPV16 viral copy number among positive samples was 2 per 1,000 ERV3 copies (IQR: 0.3–39.3).

The cumulative prevalence of individuals with tonsillar HPV16 infection at last visit was 11.8% (47 of 397). Tonsillar cytology specimens were HPV16 positive for 6.9% (27 of 394) at visit 1, 9.1% (22 of 242) at visit 3, and 6.0% (8 of 133) at visit 5 (Fig. 2A). Among the 47 individuals who had tonsillar HPV16 infection, 10 had concurrent bilateral tonsillar infections. Patterns of HPV16 infections among all individuals with a detectable tonsillar...
infection are shown in Figure 2A. In total, 72 HPV16-positive tonsillar cytology samples were collected from 47 individuals and these comprised the case population. The majority of oral HPV16 infections (76%, 19 of 25) identified at visits 1, 3, and 5 were found in the presence of a tonsillar HPV16 infection (Fig. 2B) and conversely only 34.5% (19 of 55 evaluable paired oral rinse samples) of tonsillar infections were found in the presence of an oral HPV infection.

To evaluate the association between tonsillar HPV16 infection and cytopathology, all 72 HPV16-positive tonsillar cytology samples and 134 matched HPV16-negative cytology specimens underwent cytopathologic review. Samples from 2 cases and 8 controls were categorized as unevaluable by the pathologist. As estimated by ERV3, a median of 65,509 (IQR: 29,285–128,589) tonsillar epithelial cells were evaluated per Pap-test equivalent.

On cytologic review, koilocytosis, a marker of nuclear changes consistent with HPV infection, was not detected in tonsillar cytology specimens (99.7%, 284 of 285). ASCUS was present in 8.6% (6 of 70) and 4.8% (6 of 126) of evaluable cases and controls, respectively (Fig. 1 is representative of normal and abnormal cytology.) Neither dysplasia nor cancer was detected in any of the specimens. The presence of tonsillar HPV16 infection was associated with a nonsignificant increase in odds of ASCUS (OR: 1.9, 95% CI: 0.48–7.3; Table 1). ASCUS was also observed in 11.9% (5 of 42) of evaluable cytology specimens from the contralateral tonsil of individuals with a tonsillar HPV16 infection. All individuals without tonsillar HPV16 infection but with a detectable oral HPV16 infection were without any detectable cytopathology (n = 26).

Discussion

In a study population with high prevalence of HPV and clinical oropharyngeal abnormalities (PAP1), the combination of HPV16 and abnormal cytology was strongly associated with OSCCs. In contrast, in a study population (PAP2) with high prevalence of oral HPV16 infection (20)
and elevated risk for tonsillar SCC (10–12). HIV-infected individuals, tonsillar HPV16 infection was not associated with cytologic changes consistent with HPV infection or dysplasia. The only cytopathologic abnormality detected in the study population was ASCUS, and its presence was not associated with tonsillar HPV16 infection.

The primary purpose of a screening test is to identify individuals with precursor lesions or early stage cancer more amenable to treatment (e.g., PAP2). Although HPV16 infection and abnormal cytology were strongly associated with OSCCs in those with oropharyngeal abnormalities (PAP1), we could not detect tonsillar dysplasia among individuals with either a tonsillar or oral HPV16 infection (PAP2). These results suggest that an oropharyngeal Pap-test equivalent may not be feasible as a secondary prevention tool for HPV-positive OSCCs. However, our study had limitations, and therefore, further study may be warranted.

There are several possible explanations for why we may not have observed an association between HPV16 and tonsillar cytopathology. Although HIV-infected individuals have a 2- to 6-fold increased risk for tonsillar SCCs (10, 11, 21, 22), tonsillar cancer is a rare disease, and therefore, our study population may not have provided sufficient power to detect an association. Despite the high cumulative prevalence (11%) of tonsillar HPV16 infection, we observed no cellular changes consistent with dysplasia. In studies of comparable sample size, strong associations between high-risk cervical HPV infections and dysplasia have been observed (23).

We acknowledge that we may have misclassified individuals as high-risk HPV-negative by focusing exclusively upon HPV16. However, approximately 95% of HPV-positive tonsillar cancers are HPV16 positive (24, 25) and no dysplasia was observed in HPV16-negative samples. This is therefore unlikely to explain our null associations. By analogy to cervical disease, persistent high-risk HPV infection would be expected to be a reasonable surrogate for those at risk for tonsillar dysplasia (26). Although our study design allowed us to identify some individuals with a persistent tonsillar HPV16 infection, the majority of infections were transient. However, in cervical cancer, even transient infections are associated with a 5-fold increased risk of squamous intraepithelial lesion (27).

Laboratory contamination is unlikely to explain our results because all negative controls were appropriately negative. The high agreement we observed between HPV16 detection in tonsillar cytology and oral rinse samples collected at the same visit argues against contamination, as samples were independently processed and evaluated. This high agreement might reflect "contamination" of tonsillar samples by HPV16 infection at other sites within the oral cavity. However, we have previously found HPV16 detected in oral rinse samples to be identical in sequence to the HPV16 detected in individuals with tonsillar cancer (28).

We believe that the most likely explanation for our results is related to an inability to sample the relevant tonsillar epithelium. We observed associations between HPV16 and squamous cell carcinoma in oropharyngeal lesions that could be sampled with direct visualization. Despite the majority of oropharyngeal and tonsillar cytology specimens being evaluable with adequate cellularity, the squamous epithelium of significance may have been inaccessible with the oropharyngeal Pap-test equivalent in PAP2. HPV-positive tonsillar cancers are believed to arise from deep within the involuted tonsillar crypt epithelium (29), rendering a superficial brush biopsy insufficient for sampling the relevant cells. This is analogous to the known limitation of cervical Pap tests for screening of cervical adenocarcinomas (30). Cervical Pap tests efficiently sample the superficial squamous epithelium of the ectocervix; however, they do not thoroughly sample the glandular cells of the endocervix. In support of this is the significant increased incidence of cervical adenocarcinoma in the United States whereas squamous cell carcinoma incidence has declined in the same time period (31).

Despite our study limitations, this study represents the first attempt to evaluate an oropharyngeal Pap-test equivalent for HPV-positive cancers at this anatomic site. Our data indicate that any screening modality for OSCCs will have to allow both visualization and sampling of lesions deep within the tonsillar crypts. We envision using such a screening modality in a population at increased risk for development of OSCC such as individuals with persistent oral HPV16 infection.

Disclosure of Potential Conflicts of Interest

M.L. Gillison is a consultant for Merck, GSK, Amgen, and BMS.

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