PET/CT Imaging and Human Papilloma Virus–Positive Oropharyngeal Squamous Cell Cancer: Evolving Clinical Imaging Paradigm

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Learning Objectives: On successful completion of this activity, participants should be able to (1) understand the clinical pathologic features of human papilloma virus–positive oropharyngeal squamous cell cancer; (2) review the evolving role of 18F-FDG PET/CT in the management of patients with human papilloma virus–positive oropharyngeal squamous cell cancer; and (3) postulate the imaging strategy of management of patients with human papilloma virus–positive oropharyngeal squamous cell cancer.

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More than 85% of head and neck cancers are squamous cell cancers (HNSCC) (1). Tobacco and alcohol have been the major risk factors for development of HNSCC. However, the human papillomavirus (HPV) has been recognized as a major etiologic factor for a subset of HNSCCs arising from the oropharynx (2,3) (HPV-positive oropharyngeal squamous cell carcinoma [OPSCC]) since the early 2000s, especially in the tongue base and palatine and lingual tonsils. Greater than 90% of HPV-positive OPSCCs are associated with a single HPV type, HPV-16 (4). HPV-positive OPSCCs are epidemiologically distinct from HPV-negative OPSCCs. HPV-positive OPSCC is characterized by younger age (usually 40–50 y) at onset, predominance in white men, and a strong association with sexual behaviors (5,6).

PET/CT is a useful imaging test in staging, therapy response assessment, and follow-up of patients with many human solid tumors (7–12), including head and neck cancers (13–17). The objective of this article is to review the evolving role of PET/CT in staging, therapy response assessment, and follow-up of patients with HPV-positive OPSCC.

CLINICOPATHOLOGIC FEATURES

HPV Status

The best method to detect the HPV status of the tumor is controversial, and both in situ hybridization and polymerase chain reaction are commonly used. Immunohistochemistry for p16 protein, a cyclin-dependent kinase inhibitor, could serve as a potential surrogate marker (4). In HPV-positive tumors, transcription of the viral oncoprotein E7 inactivates retinoblastoma protein, which leads to upregulation of p16 to levels that can be detected by immunohistochemistry. Many studies have demonstrated the correlation between HPV and p16 expression status in HNSCC (18–24). p16 immunohistochemistry is easier to interpret than HPV in situ hybridization...
ization (25), as well as less expensive. However, the expression of p16 is not limited to HPV-positive tumors, and using this marker alone as an indicator of biologically relevant HPV infections inevitably entails the risk of including some false-positive results (22,25). Detection of p16 can also indicate disruption of the retinoblastoma protein pathway by other causes, and HPV infection other than HPV-16 type (24) can also lead to false-positives. In a study by Thomas and Primeaux (25), among the 47 HNSCC cases, 17 and 29 cases were positive with HPV in situ hybridization and p16 immunohistochemistry, respectively. p16 immunohistochemistry has been shown to have a sensitivity of 100% and a specificity of 79% in screening for transcriptionally active HPV infection. In a study by Pannone et al. (22), p16 immunohistochemistry showed a sensitivity of 100% and a specificity of 93% in the detection of HPV in 22 OPSCC cases. For clinical purposes, many centers perform p16 immunohistochemistry for detection of HPV-positive HNSCC, as there is more than 90% concordance between p16 expression by immunohistochemistry and in situ hybridization (24).

**Histology**

HPV-positive OPSCCs are histologically distinct from HPV-negative tumors. In contrast to the HPV-negative OPSCCs, which are usually moderately differentiated and keratinizing, HPV-positive OPSCCs are consistently poorly differentiated, demonstrate a high mitotic rate, are nonkeratinizing, and have a distinct basaloid appearance (26–29). There is repression of viral oncogene expression in HPV-positive OPSCC cells, which induce massive apoptosis and restoration of p53 and retinoblastoma protein tumor suppressor pathways. The high mitotic rate, apoptosis, and restoration of tumor suppressor pathways may explain the better survival prognosis in patients with HPV-positive OPSCC.

**Survival Benefit**

HPV-positive OPSCCs are reported to have improved overall and progression-free survival in comparison to their HPV-negative counterparts. In a study by Ang et al. (30), 63.8% of patients with OPSCCs (206/323) had HPV-positive tumors. The authors retrospectively analyzed the association between tumor HPV status and survival among the patients with stage III or IV OPSCC. They found that patients with HPV-positive tumors had better 3-y rates of overall survival (82.4% vs. 57.1%, *P* < 0.001) than patients with HPV-negative tumors. HPV-positive patients had a 58% reduction in the risk of death (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.27–0.66), after adjustment for age, race, tumor and nodal stage, tobacco exposure, and treatment assignment.

In a metaanalysis by O’Rorke et al. (31) including 42 studies, the authors examined the survival differences between HPV-positive and HPV-negative HNSCC patients and found that patients with HPV-positive HNSCC had a 54% better overall survival than HPV-negative patients, with an HR of 0.46 (95% CI, 0.37–0.57). The authors performed further subset analysis for OPSCC, and the pooled HR for overall survival was 0.47 (95% CI, 0.35–0.62). The pooled HR for disease-specific survival was 0.28 (95% CI, 0.19–0.40); similar effect sizes were found irrespective of the adjustment for confounders, HPV detection methods, or study location. Both progression-free survival and disease-free survival were significantly improved in HPV-positive HNSCCs. HPV-positive HNSCC patients and a subgroup of OPSCC patients had a significantly lower disease-specific mortality and were less likely to experience progression or recurrence of their cancer than were HPV-negative patients, in this metaanalysis.
showed an overall sensitivity of 96% in detecting the primary tumor with 20 patients having OPSCC. 18F-FDG PET/enhanced CT and OPSCC. Seventy-three patients were included in the study, 1-step examination in the initial staging of unselected oral SCC protocol used, and usually is about 12–15 mSv (32–34), and the radiation dose from contrast-enhanced neck CT is about 6–10 mSv.

**Evaluation of the Primary Site**

HPV-positive SCC arises predominantly from the lymphoepithelium of the oral cavity and oropharynx, including both palatine tonsils, the lingual tonsil, and the base of the tongue (35). The incidence of HPV-positive OPSCC increased at about 7.5% per year from 1998 to 2004, and therefore the percentage of OPSCC that was HPV-positive went from less than 20% to more than 70%, likely due to sexual practices. HPV infection is responsible for 40%–80% of OPSCC (4). In a study by Gillison et al., 32 of 34 HPV-positive OPSCCs arose from the palatine and lingual tonsils, showing the distinct location of HPV-positive SCC (27). Fakhry et al. also showed that HPV-positive tumors were more likely than HPV-negative tumors to arise from the tonsil or base of the tongue (P < 0.001) (29).

HPV-positive OPSCCs are commonly occult (35). Deep within tonsillar crypts or hidden amid lingual tonsil fronds and mounds, early mucosal alterations due to HPV malignant transformation may grow undetected for many months. HPV-positive OPSCCs often present with smaller primary lesions (Fig. 1) than the HPV-negative OPSCCs, likely related to bulky neck nodal disease and earlier detection. In a study by Fakhry et al. (29), a greater number of HPV-positive than of HPV-negative OPSCCs were in the earlier T category (T2: 58% vs. 33%, T3–T4: 42% vs. 67%; P = 0.02). Ang et al. (30) also showed that HPV-positive OPSCCs were on average smaller at diagnosis (T2: 34.5% vs. 23.9%, T3: 40.8% vs. 36.8%, T4: 24.8% vs. 39.3%; P = 0.006) than were HPV-negative tumors.

Contrast-enhanced neck CT provides more anatomic details about the primary tumor, involvement of adjacent structures or muscles, and vascular anatomy than does the attenuation-correction CT done routinely in PET/CT. When enhanced CT and PET are combined as a single study, the study provides more accurate anatomic details along with the biologic functional information about the primary tumor (36). Krabbe et al. (37) conducted a retrospective study of whole-body 18F-FDG PET/enhanced CT as a 1-step examination in the initial staging of unselected oral SCC and OPSCC. Seventy-three patients were included in the study, with 20 patients having OPSCC. 18F-FDG PET/enhanced CT results were correlated to histologic specimens obtained from tumor resection and neck dissection. 18F-FDG PET/enhanced CT showed an overall sensitivity of 96% in detecting the primary tumor and a sensitivity of 100% among patients with OPSCC.

**Evaluation of Locoregional Nodal Metastases**

HPV-positive OPSCC patients frequently present with enlarged neck lymph nodes (Fig. 2). Cervical nodal metastases from HPV-positive OPSCC primary disease are usually in neck nodal levels II–IV. Contralateral nodal metastases are also seen, usually in conjunction with ipsilateral metastases but also occurring as an isolated event (35). HPV-positive OPSCCs are often associated with cystic lymph node metastases (38) and have a higher rate of nodal involvement than do HPV-negative OPSCCs (29,39).

Patients with HPV-positive OPSCCs present with more advanced N-stage disease than patients with HPV-negative OPSCCs (29,39,40). Because the lymph nodes involved in HPV-positive OPSCCs often appear cystic, contrast-enhanced 18F-FDG PET/CT performs better than nonenhanced 18F-FDG PET/CT in detecting cystic lymph node metastases (Fig. 2) (41). In a retrospective study by Haerle et al. (41), 34 patients with tonsillar SCC underwent pretreatment contrast-enhanced 18F-FDG PET/CT followed by neck dissection as a standard of reference. The enhanced CT part, 18F-FDG PET part, nonenhanced 18F-FDG PET/CT part, and enhanced 18F-FDG PET/CT part were assessed separately. The authors found that contrast-enhanced CT and contrast-enhanced 18F-FDG PET/CT perform equally well and that both perform better than nonenhanced 18F-FDG PET/CT in detecting cystic lymph node metastases in tonsillar SCC. Therefore, in patients with tonsillar SCC scheduled for 18F-FDG PET/CT, the authors recommended performing contrast-enhanced 18F-FDG PET/CT.

**Evaluation of Distant Metastases**

There is a striking difference in the clinical behavior and prognosis of distant metastases between HPV-positive and HPV-negative OPSCC patients. Although the overall frequency of distant metastases is not related to HPV status, distant metastases among HPV-positive OPSCCs tend to disseminate to multiple organs and unusual sites (42). These metastases also can manifest later in the disease course, between 3 and 5 y after completion of treatment (42,43). In view of this characteristic pattern, the imaging of distant metastases during follow-up needs to be tailored.

To our knowledge, no published studies have specifically investigated the value of 18F-FDG PET/CT in the diagnosis of distant metastases in a selected group of patients with HPV-positive OPSCC. However, as a whole-body examination, 18F-FDG PET/CT is especially helpful in the assessment of distant metastases in...
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Pre-/posttreatment PET/CT</th>
<th>Study type</th>
<th>18F-FDG PET/CT with intravenous contrast</th>
<th>Summary and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haerle et al., 2011 (41)</td>
<td>34</td>
<td>Pretreatment</td>
<td>Retrospective</td>
<td>Yes</td>
<td>Enhanced CT and enhanced 18F-FDG PET/CT perform equally well and better than nonenhanced 18F-FDG PET/CT in detecting cystic neck nodal metastases in tonsillar SCC. Therefore, in patients scheduled for 18F-FDG PET/CT, authors suggested performing enhanced 18F-FDG PET/CT, which is not routine in most centers.</td>
</tr>
<tr>
<td>Tahari et al., 2013 (56)</td>
<td>123</td>
<td>Pretreatment</td>
<td>Retrospective</td>
<td>Mixed</td>
<td>Index morphologic (diameter) and glycolytic parameters (SUV$<em>{\text{max}}$, SUV$</em>{\text{peak}}$, SUV$_{\text{mean}}$, MTV, TLG, heterogeneity index) as measured in 18F-FDG PET/CT are significantly larger in HPV-negative than HPV-positive primary OPSCC. Same parameters tended to be larger in HPV-positive regional nodal disease.</td>
</tr>
<tr>
<td>Cheng et al., 2013 (54)</td>
<td>70</td>
<td>Pretreatment</td>
<td>Retrospective</td>
<td>No</td>
<td>Tumor TLG and textural features are prognostic predictors, when adjusted for other clinical parameters, in patients with advanced T-stage OPSCC.</td>
</tr>
<tr>
<td>Joo et al., 2013 (55)</td>
<td>78</td>
<td>Pretreatment</td>
<td>Retrospective</td>
<td>No</td>
<td>Median SUV$_{\text{max}}$ cutoffs of 7.10 or greater are associated with high-risk HPV negativity in OPSCC patients.</td>
</tr>
<tr>
<td>Chan et al., 2012 (66)</td>
<td>77</td>
<td>Posttreatment</td>
<td>Retrospective</td>
<td>Yes</td>
<td>Enhanced PET/CT with SUV$<em>{\text{max}}$ cut-point of 2 had NPV of 100.0% (95% CI, 92.0%–100.0%), and SUV$</em>{\text{max}}$ cut-point of 2.5 had NPV of 95.7% (95% CI, 85.8%–98.8%). PET combined with enhanced CT has better NPV than either imaging modality alone in patients with HPV-positive OPSCC.</td>
</tr>
<tr>
<td>Cheng et al., 2012 (53)</td>
<td>60</td>
<td>Pretreatment</td>
<td>Retrospective</td>
<td>No</td>
<td>Tumor TLG was independent predictor of survival in patients with locally advanced OPSCC.</td>
</tr>
<tr>
<td>Moeller et al., 2009 (67)</td>
<td>98</td>
<td>Posttreatment</td>
<td>Prospective</td>
<td>No</td>
<td>Only 1 of 3 patients had HPV status available. Authors concluded that 18F-FDG PET/CT SUV$<em>{\text{max}}$ provides little value over CT alone in radiation response assessment for unselected patients with locally advanced HNSCC. 18F-FDG PET/CT SUV$</em>{\text{max}}$ improves assessment of treatment response in high-risk patients, such as those with HPV-negative and nonoropharyngeal disease. However, unlike CT reads, PET/CT reads were not dichotomized into positive and negative for residual tumor based on qualitative assessment.</td>
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TLG = total lesion glycolysis; NPV = negative predictive value.
HPV-positive OPSCC, particularly since they may manifest late, involve more than 2 organs, and appear at unusual sites.

A consistent trend toward higher sensitivity and diagnostic capability for PET/CT than for whole-body MR imaging has been shown in OPSCC and hypopharyngeal SCC (44,45). A metaanalysis by Xu et al. (46) involving 15 studies with 1,445 patients with head and neck cancer showed pooled sensitivity and specificity estimates for $^{18}$F-FDG PET/CT of 0.875 (95% CI, 0.787–0.936) and 0.950 (95% CI, 0.931–0.964), respectively, for detection of distant metastases. The superior accuracy of PET/CT for detection of distant metastases in head and neck cancer patients allows it to be deployed in the diagnosis of distant metastases in patients with HPV-positive OPSCC during the longer follow-up period that they require.

**Prognosis**

The high-dose chemotherapy and altered radiotherapy fractionation strategies used for treatment of OPSCC have improved survival rates. However, these strategies are also associated with an increased risk of developing late swallowing complications (47,48). Studies have consistently demonstrated that HPV-positive OPSCC patients have better survival than HPV-negative OPSCC patients (20,29–31,39,49). This difference in prognosis appears to be independent of the treatment modality used and suggests a fundamental difference in the biology of HPV-positive OPSCC. HPV-positive patients are typically younger, have fewer competing comorbidities, and, hence, are more likely to experience survivorship issues from current treatment approaches. With a diagnosis of head and neck cancer at a younger age and increased survival rates, the development of late swallowing complications becomes significant and is most likely to contribute to poor quality of life (50). To reduce treatment-related complications and improve quality of life for these patients, current research is evaluating deintensification of treatment to maintain the current survival rates while reducing long-term complications (such as swallowing dysfunction) (51). Such a possibility offers the potential to further improve patient selection at initial staging and to use PET/CT to assess the effectiveness of the deintensified treatment to avoid high treatment failure.

Metabolic tumor volume (MTV) is the $^{18}$F-FDG-avid volume of the tumor or lesion. Many segmentation methods are available for calculation of MTV, the most common being use of a fixed percentage maximum standardized uptake value (SUV$_{\text{max}}$) (such as 40% or 50%), an absolute SUV$_{\text{max}}$ threshold (such as 2.5 or 3.0 or 5.0), and gradient segmentation (17). Tang et al. (52) prospectively studied the role of MTV obtained from pretreatment $^{18}$F-FDG PET/CT in predicting treatment outcome in patients with head and neck cancer. The investigators also explored the interaction with p16 status as a surrogate marker for HPV. MTV and SUV$_{\text{max}}$ were calculated for 83 patients with HNSCC who underwent $^{18}$F-FDG PET/CT before receiving definitive radiotherapy. The primary endpoint was to evaluate the relation between MTV and progression-free and overall survival. The investigators found that the primary tumor MTV predicted progression-free (HR, 1.94; $P < 0.0001$) and overall (HR, 1.57; $P < 0.0001$) survival, whereas nodal MTV did not. In the p16-positive oropharynx subset ($n = 64$), total MTV remained a robust predictor of progression-free (HR, 4.23; $P < 0.0001$) and overall (HR, 3.21; $P = 0.0029$) survival.

More studies have evaluated the characteristics and prognostic value of MTV, total lesion glycolysis, and HPV status in OPSCC at initial staging (Table 1) (53–56). Tahari et al. studied 123 newly diagnosed OPSCC patients (98 HPV-positive and 25 HPV-negative) who underwent $^{18}$F-FDG PET/CT at initial staging (56). HPV-negative primary tumors were significantly larger as measured by longest diameter ($P = 0.002$) and slightly more heterogeneous as measured by the $^{18}$F-FDG heterogeneity index ($P = 0.07$) and had a higher SUV$_{\text{max}}$ ($P = 0.01$), SUV peak ($P = 0.01$), SUV mean ($P = 0.01$), MTV ($P = 0.002$), and total lesion glycolysis ($P = 0.001$). There was no significant difference in the metabolic parameters of primary tumors or nodal metastases for HPV-positive patients with and without a smoking history. Cheng et al. (54) studied 70 patients with advanced OPSCC (13 patients HPV-positive and 57 patients HPV-negative), and the patients were followed up for at least 24 mo or until death. Multivariate Cox regression analysis showed that age, tumor total lesion glycolysis, and uniformity were independently associated with progression-free survival and disease-specific survival. Total lesion glycolysis, uniformity, and HPV positivity were significantly associated with overall survival.

**THERAPY RESPONSE ASSESSMENT**

Many studies have proposed that PET/CT imaging may improve the accuracy of posttreatment evaluation for HNSCC (57–61). It has been demonstrated that the metabolic response closely correlates with the histopathologic response, and survival is far better in responders than in nonresponders (Figs. 3 and 4). The timing of posttherapy PET/CT is crucial in the posttherapy assessment. The optimum timing after chemotherapy and radiotherapy is not known, but an interval of 12 wk has been generally recommended to balance the drawbacks of imaging too early versus too late. Accuracy is generally greater for scans performed more than 12 wk after radiation, likely because of a reduction in radiation-induced inflammation (62). Recently, we reported that the percentage of $^{18}$F-FDG PET/CT studies that are indeterminate because of possible treatment-related inflammation stabilizes between 4 and 24 mo after treatment and that the most appropriate timing for posttherapy PET/CT is between 3 and 4 mo (63).
dissections. Moeller et al. (18) conducted a prospective study of 98 patients with HPV-positive OPSCC who underwent contrast-enhanced PET/CT after radiotherapy as the primary treatment. The authors showed that enhanced PET/CT has a better negative predictive value than either enhanced CT or nonenhanced PET/CT alone in patients with HPV-positive OPSCC. Furthermore, they concluded that PET/CT with an SUV\textsubscript{max} threshold of 2 in patients with HPV-positive OPSCC offers a high negative predictive value (100%) that may obviate unnecessary neck dissections.

Studies demonstrating the value of PET/CT in management of the neck after radiotherapy with or without chemotherapy in HPV-positive OPSCC patients are limited and evolving (Table 1). Chan et al. (66) studied 77 patients with HPV-positive OPSCC who underwent contrast-enhanced PET/CT after radiotherapy as the primary treatment. The authors showed that enhanced PET/CT has a better negative predictive value than either enhanced CT or nonenhanced PET/CT alone in patients with HPV-positive OPSCC. Furthermore, they concluded that PET/CT with an SUV\textsubscript{max} threshold of 2 in patients with HPV-positive OPSCC offers a high negative predictive value (100%) that may obviate unnecessary neck dissections. Moeller et al. (67) conducted a prospective study of 98 patients with HNSCC for posttherapy assessment. Only 1 of 3 patients had a known HPV status. The authors concluded that 18F-FDG PET/CT SUV\textsubscript{max} provides little value over CT alone in radiation response assessment for unselected patients with locally advanced HNSCC. However, 18F-FDG PET/CT SUV\textsubscript{max} improved assessment of treatment response in high-risk patients, such as those with HPV-negative and nonoropharyngeal disease, and unlike the CT reads, the PET/CT reads were not dichotomized into positive and negative for residual tumor based on qualitative assessment. As the HPV-positive OPSCC clinical paradigms evolve, future studies are warranted to fully establish the value of 18F-FDG PET/CT in assessing therapy for these patients.

**SUMMARY**

HPV-positive OPSCC represents an emerging disease that differs from HPV-negative OPSCC in natural history and prognosis. Contrast-enhanced PET/CT is essential to accurately stage the primary site when there are smaller tumors and to detect locoregional nodal metastases when there is a higher proportion of cystic nodal metastases and distant metastases manifesting in unusual sites with a disseminating phenotype. In addition, 18F-FDG MTV is emerging as a prognostic parameter for outcome in HPV-positive OPSCC patients.

For these HPV-positive OPSCC patients, individualizing patient management is a real possibility, with reduction of radiotherapy dose to reduce treatment-related morbidities. 18F-FDG PET/CT has proven to be useful in assessing therapy for HNSCC, and early studies have shown similar efficacy for HPV-positive OPSCC. 18F-FDG PET/CT will also play a role in the therapy assessment of HPV-positive OPSCC patients in the setting of dose reduction, initially to prove these dose-reduction strategies are efficacious without compromising patient outcome. The better prognosis and outcome of HPV-positive patients would likely warrant less intense imaging follow-up during the 5-y follow-up period after treatment. However, the manifestation of distant metastases later in the disease course and at unusual sites with a disseminating phenotype would require a longer follow-up with PET/CT. At this stage, it is unclear whether identifying distant metastases earlier during follow-up would improve patient outcome.

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