Update 2018

^{18}F-FDG PET/CT and PET/MRI in Head and Neck Cancer

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Abstract: There are recent advances, namely, a standardized method for reporting therapy response (Hopkins criteria), a multicenter prospective cohort study with excellent negative predictive value of ^{18}F-FDG PET/CT for N0 clinical neck, a phase III multicenter randomized controlled study establishing the value of a negative posttherapy ^{18}F-FDG PET/CT for patient management, a phase II randomized controlled study demonstrating radiation dose reduction strategies for human papilloma virus–related disease, and Food and Drug Administration approval of nivolumab for treatment of recurrent head and neck squamous cell carcinoma.

Key Words: head and neck cancer, PET/CT, PET/MR

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LEARNING OBJECTIVES

After participating in this CME activity, the physician should be better able to:

1. Analyze the most recent advances in PET/CT and PET/MRI in the management of head and neck squamous cell cancer (HNSCC).
2. Interpret the established clinical indications of PET/CT in the management of HNSCC.
3. Compare the pitfalls and challenges of PET/CT.

Head and neck cancer (HNC) refers to a heterogeneous group of malignancies, with an estimated annual incidence over 49,670 and accounts for approximately 9700 deaths in the United States.[1] Approximately 90% are head and neck squamous cell carcinoma (HNSCC), and most arise in the oropharynx or oral cavity. Often, oropharyngeal squamous cell carcinoma (OPSCC) is associated with tobacco and alcohol use. Recently, the incidence of OPSCC has been increasing due to the rise in human papilloma virus (HPV) infection (specifically HPV-16).[2–5] Patients with HPV-related OPSCC tend to be younger and have a better prognosis than HPV-negative disease, regardless of smoking history.[3–6]

There have been several recent advances in therapy for HNSCC. Surgery is the mainstay of treatment for localized disease, and minimally invasive techniques have resulted in good functional outcome with low postoperative morbidity.[7] Radiotherapy with concurrent cisplatin chemotherapy is standard of care for locally advanced disease, and several techniques such as intensity-modulated radiation therapy, proton beam therapy, and image-guided radiation therapy can spare adjacent organ radiation. Intensity-modulated radiation therapy is most commonly used due to its reduced long-term toxicity.[4,6] A phase II trial (ECOG ACRIN E1308) of 80 patients, the majority with stage T1–T3, N0–N2b OPSCC and a history of 10 pack-years or less of cigarette smoking, showed that radiation dose could be reduced in patients with low volume disease and induction chemotherapy.[8] Also, several new approaches to medical management are promising for more advanced disease. For example, a randomized phase III trial (EXTREME study) showed that cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, plus platinum-based chemotherapy resulted in increased overall survival (OS) and progression-free survival (PFS) compared with conventional platinum- and 5-fluorouracil–based chemotherapy.[9] Also, in a phase III clinical trial, nivolumab resulted in longer OS than treatment with standard single-agent therapy in patients with platinum-refractory, recurrent HNSCC (hazards ratio [HR], 0.70; 97.73% confidence interval [CI], 0.51–0.96; $P = 0.01$).[10] The rate of PFS at 6 months with nivolumab was also higher at 19.7% versus 9.9% with standard therapy. The objective response rates by RECIST were 13.3% and 5.8% in the nivolumab and the standard therapy groups, respectively.

IMAGING

(A) Initial Treatment Strategy

Although the etiology, staging, and prognosis across the spectrum of disease that constitute HNC differ, accurate staging is key in all patients to ensure appropriate therapy, and imaging plays an important role.[11] Ultrasound may be helpful to identify cervical lymph nodes and guide biopsy.[12] Contrast-enhanced CT is helpful to identify the primary tumor, local nodal disease, and distant disease such as lung metastases.[13] MRI is helpful for local staging (primary tumor and neck nodal stations), as well as to assess the presence of perineural spread and bone marrow involvement.[14]

In recent years, ^{18}F-FDG PET/CT has become increasingly ubiquitous in the evaluation of HNC. Although precise anatomic definition of the primary disease extent may be difficult on unenhanced CT, the use of contrast-enhanced ^{18}F-FDG PET/CT as well as modern CT scanners with 64 and 128 detector rings have helped to address this issue.[15,16] It is estimated that the overall sensitivity and specificity of ^{18}F-FDG PET/CT for the detection of the primary site of HNSCC is high (over 90% for OPSCC).[17] Small primary tumors may be more easily detected with ^{18}F-FDG PET/CT than with CT or MRI (both of which can be limited by motion

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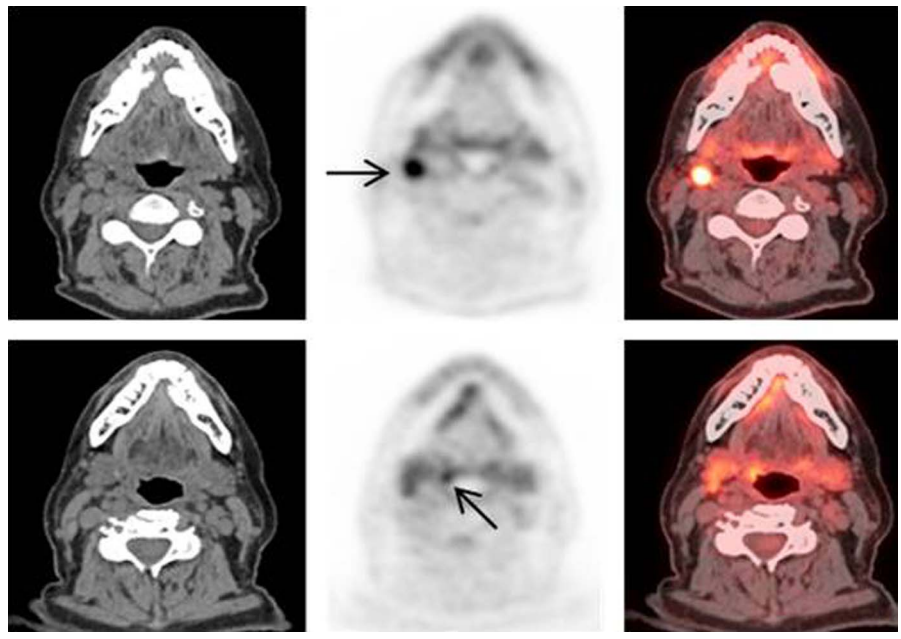

FIGURE 1. Staging–detection of unknown primary. A 67-year-old man, who underwent a thyroid ultrasound demonstrated 1.1 cm right level II lymph node. Fine-needle aspiration results from the right level II node found to be positive for poorly differentiated SCC. ^{18}F-FDG PET/CT scan demonstrates focal FDG uptake at the right glossotonsillar sulcus, proven be a site of primary tumor and FDG-avid right level II metastatic lymph node (cT1 cN1 M0, stage III).

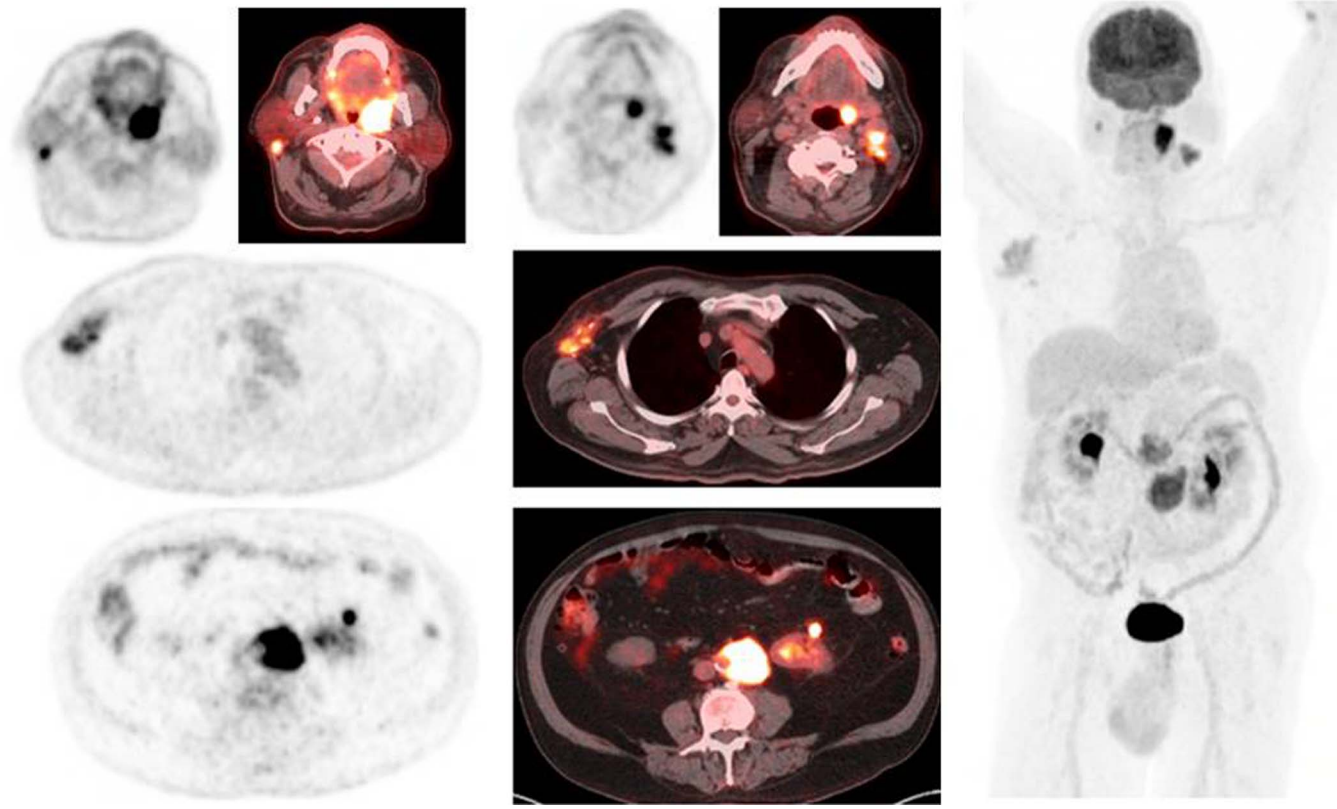

FIGURE 2. Staging–synchronous tumors. A 68-year-old man presented with a right axillary mass and biopsy results showed grade II follicular lymphoma. He underwent an ^{18}F-FDG PET/CT for staging. Images showed intensely hypermetabolic soft tissue mass in left palatine tonsil, hypermetabolic left level II cervical node, right intraparotid node, and confluent nodal mass surrounding abdominal aorta. Further workup of the left cervical level II LN revealed metastatic squamous cell carcinoma, p16 positive.

and metal artifact). However, the spatial resolution of PET and the presence of physiologic FDG uptake in normal tissue, such as in the tonsils or at the base of the tongue, are limiting factors.[18,19] Hence, for accurate primary tumor staging, either a contrast-enhanced ^{18}F-FDG PET/CT or a dedicated contrast-enhanced CT or MRI of the neck is required. The 2017 National Comprehensive Cancer Network (NCCN) guidelines now state that ^{18}F-FDG PET/CT should be considered for the diagnostic workup of stage III to IV disease in oropharyngeal, hypopharyngeal, glottic, supraglottic laryngeal cancers, ethmoid and maxillary sinus tumors, and for nasopharyngeal cancers.[4]

Detecting an Unknown Primary

Detecting the primary site of disease is extremely important for selecting appropriate therapy in patients presenting with nodal neck metastases of unknown primary. The main course of treatment for these patients is neck dissection and adjuvant radiation therapy of the mucosal surface from the skull base to the clavicle.[20] Unknown primary cancer accounts for 1% to 4% of all head and neck tumors (Fig. 1).[21] In a meta-analysis of 7 studies comprising 246 patients, Zhu et al[22] evaluated the diagnostic accuracy of ^{18}F-FDG PET/CT. The authors showed that the primary tumor detection rate varied from 28% to 79% with 97% sensitivity and 68% specificity. Squamous cell carcinoma (SCC) of unknown primary is associated with HPV in the majority of patients.[23] When identified, the primary lesions are most frequently found in the palatine tonsils followed by the base of tongue.[24–26] Human papilloma virus positivity is found in approximately 45% to 75% of all oropharyngeal cancers (OPCs).[27] It is known that biomarkers such as HPV, p16, and Epstein-Barr virus are useful for primary screening and diagnosis. Park et al[28] examined the diagnostic value of these markers compared with ^{18}F-FDG PET/CT in patients with a metastatic cervical lymph node of unknown primary. The authors found that combining imaging and tissue biomarkers will improve the accuracy of localizing the sites of primary HNSCC. As a result, per the 2017 NCCN guidelines, ^{18}F-FDG PET/CT should be considered for the diagnostic workup of metastatic neck lymph nodes from an occult primary tumor.[4]

Detecting Second Primary Malignancy

Patients with HNSCC are at risk for second primary cancers (Fig. 2). Both the sensitivity and specificity of ^{18}F-FDG PET/CT for detecting a second primary malignancy are estimated to be over 95%.[29] Xi et al evaluated the accuracy of ^{18}F-FDG PET/CT for the diagnosis of lung cancer in patients with HNSCC in a meta-analysis of 12 articles where ^{18}F-FDG PET/CT was used for initial staging in 7 studies, and for restaging in 5 studies.[30] The pooled sensitivity, specificity, diagnostic odds ratio, positive likelihood ratio, and negative likelihood ratio for ^{18}F-FDG PET/CT at initial staging were 0.83 (95% CI, 0.67–0.92), 0.98 (95% CI, 0.96–0.99), 297 (95% CI, 96.0–918), 51.0 (95% CI, 20.2–128.3), and 0.17 (95% CI, 0.08–0.36), respectively. Corresponding values for ^{18}F-FDG PET/CT at restaging were 0.96 (95% CI, 0.21–1.00), 0.99 (95% CI, 0.93–1.00), 1571 (95% CI, 13.0–8936), 65.5 (95% CI, 12.8–336.6), and 0.04 (95% CI, 0.01–0.99), respectively.

Staging Cervical Nodal Metastasis

The presence of HNSCC spread to a cervical lymph node is an important prognostic factor. A meta-analysis of 32 studies suggested that the sensitivity and specificity of PET for the detection of cervical lymph node spread from HNSCC was 79% and 86%, respectively, and was superior to CT or MRI (Fig. 3).[31] Of note, in the setting of clinically suspected negative spread to neck lymph nodes (clinical N0 neck), the specificity of ^{18}F-FDG PET/CT is high (76%–93%); however, the sensitivity may be as low as 50% (37%–63%).[32–34] The National Cancer Institute-sponsored prospective multicenter, nonrandomized study (ACRIN 6685) showed a high NPV of ^{18}F-FDG PET/CT in 287 newly diagnosed patients with T2–T4 HNSCC.[35] This may obviate the need for elective neck dissection in cN0 HNSCC patients if the ^{18}F-FDG PET/CT is negative.

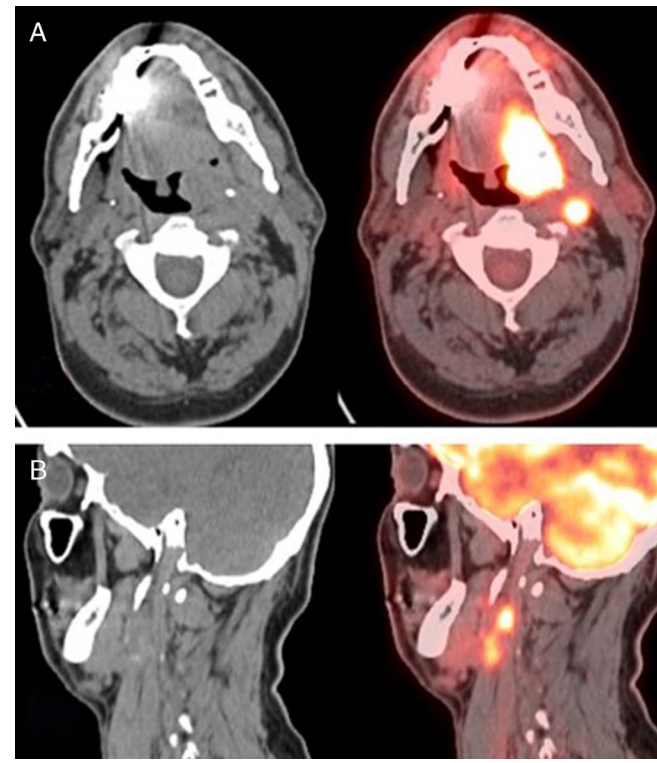

FIGURE 3. Staging neck nodal metastasis. A 52-year-old man with squamous cell carcinoma of the left tonsil (primary T4). Axial CT and PET/CT fused images (**A**) demonstrated highly FDG-avid primary tumor and subcentimetric metastatic lymph node at level II. Sagittal CT and PET/CT fused images (**B**) showed subcentimetric metastatic lymph node at level II and III (T4N1M0).

Staging Distant Metastasis

The presence of distant metastases is an important prognostic factor in patients with HNSCC (Fig. 4). Metastases to the lungs are the most common, and chest CT is valuable in this setting, with a reported sensitivity and specificity of 73% and 80%, respectively.[36] ^{18}F-FDG PET/CT is recommended as first-line imaging for detecting distant metastases and may be superior to whole-body (WB) MRI.[37,38] Chan et al[37] compared the diagnostic value of ^{18}F-FDG PET/CT and WB-MRI for the assessment of distant metastases and second primary cancer in patients with oropharyngeal or hypopharyngeal squamous cell carcinoma. Among 103 patients in the study, the authors found that the sensitivity of WB-MRI was lower than that of ^{18}F-FDG PET/CT (66.7% vs 83.3%) on a patient-based analysis. MRI and ^{18}F-FDG PET/CT had high NPV (93.2% vs 96.4%), but only moderate positive predictive value (PPV) (80.0% vs 78.9%). Yi et al[39] showed in a recent meta-analysis including 1291 patients that detection of bone metastases with ^{18}F-FDG PET/CT had 89% sensitivity and 99% specificity; which was better than the results obtained by skeletal scintigraphy. Therefore,

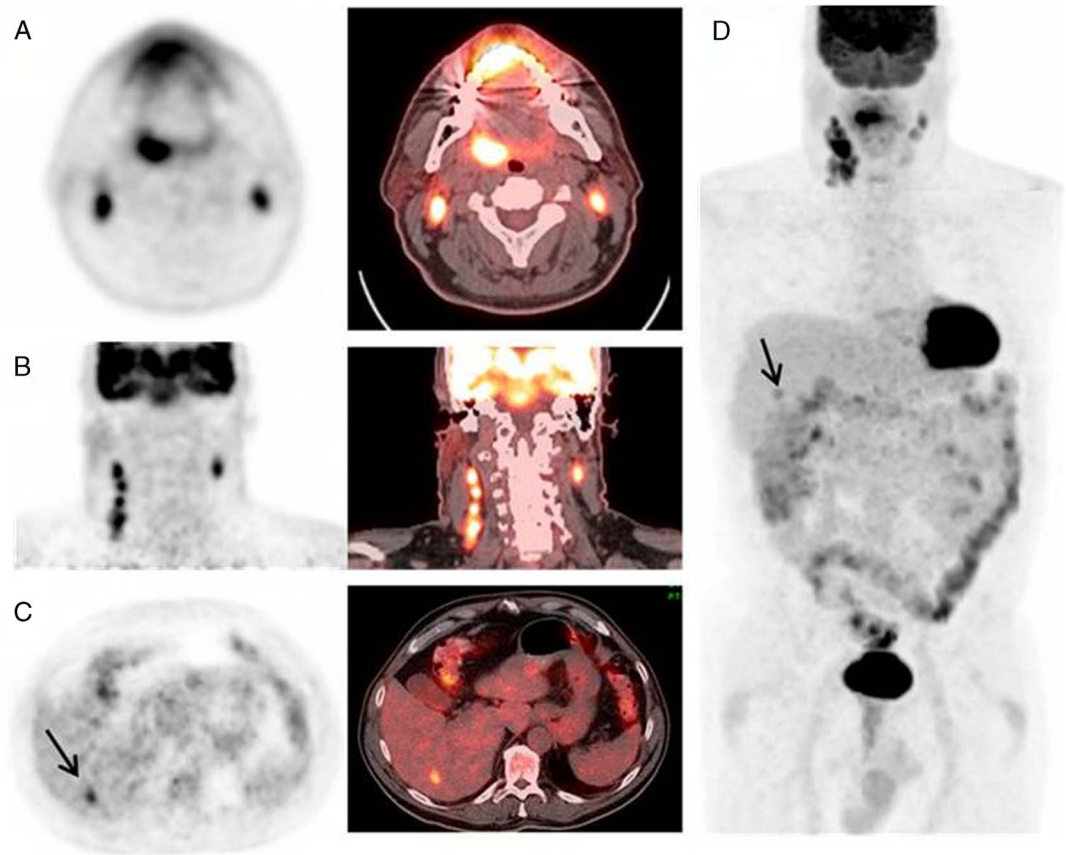

FIGURE 4. Staging distant metastasis. A 64-year-old man with moderately differentiated, p16 positive, squamous cell carcinoma of the right tonsil. Axial PET and PET/CT fused images (**A**) showed FDG-avid primary tumor at right tonsil and bilateral level II lymph nodes, coronal PET, and PET/CT fused images (**B**) showed bilateral multiple metastatic lymph nodes. ^{18}F-FDG PET/CT demonstrated an 11-mm right hepatic FDG-avid lesion (**C**). MIP images (**D**) showed primary tumor with regional metastatic lymph nodes and distant liver metastasis (T2N2bM1).

^{18}F-FDG PET/CT is more accurate than skeletal scintigraphy for osseous metastases. A recent prospective study of 307 patients compared chest radiographs plus head and neck MRI versus chest CT plus head and neck MRI versus ^{18}F-FDG PET/CT to determine the detection rate of distant metastasis and synchronous HNSCC.[40] ^{18}F-FDG PET/CT correctly detected 25 (8%) synchronous cancers, which was significantly more than other methods (chest radiographs plus MRI [3 patients, 1%] and chest CT plus MRI [6 patients, 2%]). The true detection rate of distant metastasis and/or synchronous cancer with ^{18}F-FDG PET/CT was 13% (40 patients), which was significantly higher than the other methods (2% [6 patients] for chest x-ray plus MRI and 6% [17 patients] for chest CT plus MRI).

Therapy Planning

It has been suggested that ^{18}F-FDG PET/CT improves therapy planning, not only due to improved staging but also through the ability to provide information on tumor biology and gross tumor volume.[41] PET/CT-based contouring is more accurate than CT-based volume in terms of gross tumor volume including identifying involved nodal levels as well as improved interreliability for radiotherapy (RT) contouring.[38] Several ways of using PET segmentation to delineate tumor volume have been described, with highly operator-dependent manual segmentation as the most commonly used method. Therefore, more objective methods have been proposed such as isocontouring, based on an SUV threshold definition in primary tumor and metastatic lymph nodes. Berthon et al[42] used the novel Automatic Decision Tree–Based Learning Algorithm for Advanced Segmentation (ATLAAS) model in 20 HNSCC patients who were candidates for radical chemoradiotherapy (CRT). The authors reported that this model allows a consistent, operator-independent approach. Schinagl et al[43] studied validated FDG PET segmentation tools for volume assessment of lymph node metastases. Nodal volumes were compared with the true volume as determined by pathological examination in HNSCC patients. The authors showed that FDG PET accurately estimated metastatic lymph node volume. Authors recommended an automated segmentation method for the purposes of reproducibility and interinstitutional comparison. In addition, Sridhar et al[44] evaluated the primary tumor MTV that was segmented using 2 methods such as gradient and 30%, 40%, and 50% SUV_{max} threshold in 52 patients diagnosed with head and neck, lung, and colorectal cancers. They found that, the intraclass correlation coefficients among the pathologic volume and the gradient-based and 30%, 40%, and 50% SUV_{max} threshold MTVs were 0.95, 0.85, 0.80, and 0.76, respectively. Thus, this study has shown that there is a fair to excellent correlations between the PET-based MTV and pathologic volume.

Predicting Patient Outcomes

Many prognostic factors affect treatment outcome and treatment strategy can be changed if the prognostic factors are known

before the treatment. The SUV_{max} is the most commonly used semiquantitative PET parameter that measures glucose metabolism. The tumor SUV_{max} is predictive of local control and survival in HNSCC.[45] Difference in SUV_{max} values from early and late images can be more relevant prognostic indicators for recurrence-free survival.[46] MTV and total lesion glycolysis (TLG) are the other parameters reflecting the metabolic activity of tumors.[47] Briefly, MTV is a volumetric measurement of the tumor cells with increased FDG uptake. Meanwhile, TLG represents glycolytic activity, which is the product of the mean SUV and tumor volume. It is suggested that these parameters might be used as prognostic tools for prediction of prognosis of the disease and response to existing therapies. In a meta-analysis, the prognostic value of MTV and TLG were evaluated in 13 studies including 1180 HNSCC patients by determining the HR of event-free survival (EFS) and OS.[48] It was shown that patients with a high MTV in comparison with patients with a low MTV showed 3.06-fold and 3.51-fold higher risks for adverse events or risk of death, respectively. Meanwhile, patients with a high TLG had a 3.10-fold higher risk of events or a 3.14-fold higher risk of death than patients with low TLG. Huang et al[49] demonstrated in their meta-analysis with 14 studies and 1134 nasopharyngeal carcinoma patients that SUV_{max}, MTV, and TLG, with a fixed SUV of 2.5, of primary tumors before treatment initiation may be independent prognostic factors. Hazards ratios of SUV_{max} of primary tumor, MTV of primary tumor, and TLG of primary tumor for EFS were 1.31 (95% CI, 1.11–1.55; $P = 0.001$), 2.38 (95% CI, 1.53–3.70; $P < 0.001$), and 1.65 (95% CI, 0.76–3.59; $P = 0.21$), respectively. Cacicedo et al[50] found that pretreatment nodal SUV_{max} value in patients with locally advanced HNSCC is prognostic for distant metastasis-free survival. Authors also showed that patients with neck nodal metastasis and higher than SUV_{max} of 5.4, associated with an increased risk of distant metastases (HR, 3.3; 95% CI, 1.17–9.25; $P = 0.023$).

(B) Subsequent Treatment Strategy

^{18}F-FDG PET/CT is useful to evaluate therapy response and for detection of recurrent disease.[51] In a landmark prospective, randomized, controlled trial of 564 patients with advanced HNC (no metastatic disease), Mehanna et al[52] showed that ^{18}F-FDG PET/CT performed at 12 weeks after completion of CRT could direct neck dissection (Fig. 5). Specifically, neck dissection performed only if ^{18}F-FDG PET/CT posttherapy showed incomplete or equivocal response (Fig. 6) resulted in similar patient quality of life and survival at lower cost than when neck dissection was planned because of stage N2 or N3 disease. The authors recommended that the patients with equivocal FDG uptake and HPV-negative disease should proceed to neck dissection. However, patients with HPV-positive disease having enlarged nodes with no FDG uptake after CRT may be closely followed up with serial CT or PET/CT. This strategy of avoiding surgical complications may be more cost-effective than neck dissection.

Standardized Therapy Assessment Method–Hopkins Criteria

One of the limitations in evaluating ^{18}F-FDG PET/CT effectiveness posttherapy for patients with HNSCC is the lack of a universal scoring system for result classification. To address this, a 5-point qualitative posttherapy assessment scoring system (Hopkins criteria) has been proposed for HNC using ^{18}F-FDG PET/CT (Table 1). The Hopkins criteria[53] has strong interreader agreement, excellent NPV, and is predictive of both PFS and OS. In the cited study, the overall agreement between readers was 86%, the NPV was 91%, and using a Kaplan-Meier survival analysis, the PFS and OS between patients classified as negative for residual tumor by the 5-point scale compared with those classified as positive was statistically significant. The HR was 0.05 (95% CI, 0.02–0.11) for PFS and 0.046 (95% CI, 0.018–0.120) for OS. Hopkins criteria have been validated externally. Kendi et al[54] reported an external validation study of Hopkins criteria, including 69 HNSCC patients who underwent posttherapy PET/CT between 5 and 24 weeks after completion of therapy. Percentage of the agreement between the readers were found for overall, right neck, left neck, and primary tumor site were 91.3%, 97.6%, 97.6%, and 91.3%, respectively. This

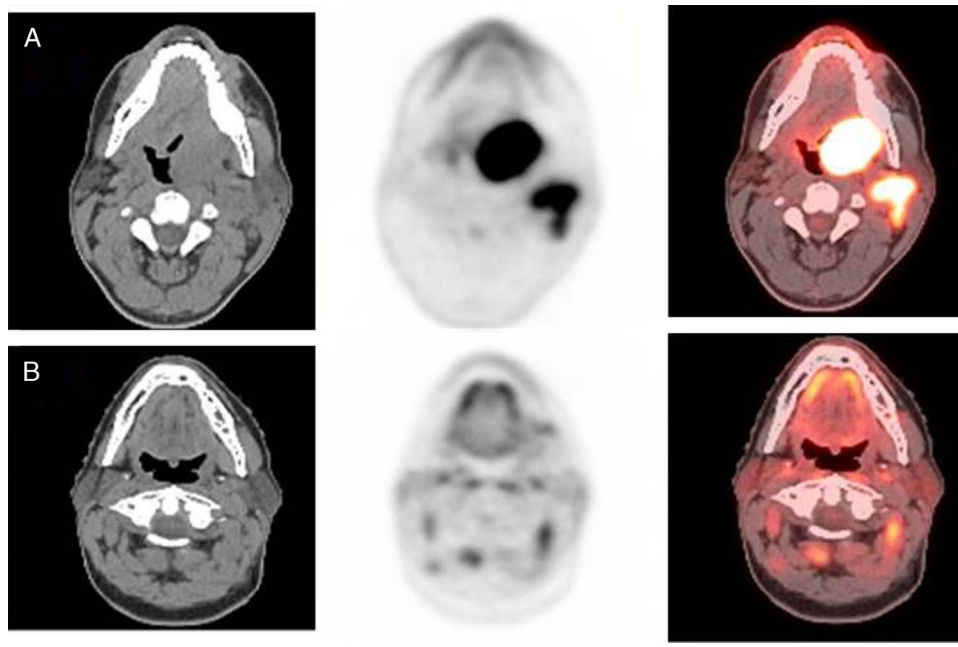

FIGURE 5. Therapy response–complete metabolic response. A 56-year-old man, T2N1M0 left tonsil tumor with metastatic level II lymph nodes. Axial CT, PET, and fused images showed primary tumor and metastatic lymph nodes (**A**). He received concurrent CRT and 3 months posttherapy ^{18}F-FDG PET/CT demonstrated complete response (**B**).

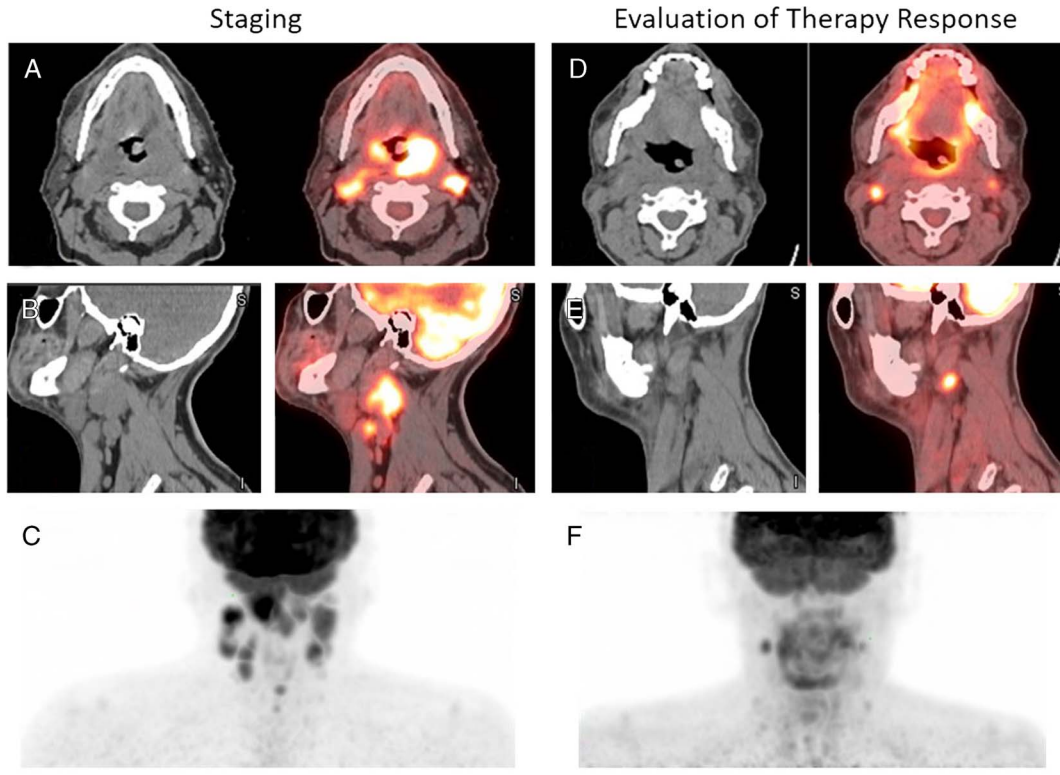

FIGURE 6. Therapy response–partial metabolic response. A 54-year-old man with a diagnosis of stage T3N2cM0, p16 + poorly differentiated left tonsillar SCC, treated with CRT (A dose of 70 Gy was delivered in 35 fractions of 2 Gy each with concomitant weekly cisplatin). Axial CT and PET/CT fused images (**A**) showed a large FDG-avid left tonsillar primary tumor (SUV_{max}, 14.6) and bilateral FDG-avid level II lymph nodes; sagittal CT and PET/CT fused images (**B**) showed level II and III intensely FDG-avid lymph nodes. MIP images (**C**) showed primary tumor with regional metastatic lymph nodes. Therapy response was evaluated with FDG PET/CT, 3 months after completing CRT. There is resolution of previously seen FDG-avid left tonsillar mass in axial CT and PET/CT fused images (**D**) and persistent bilateral level II lymph nodes in axial (**D**) and sagittal CT and PET/CT fused images (**E**). MIP images (**F**) showed persistent bilateral level II lymph nodes after CRT. The patient underwent bilateral neck dissection, 1 lymph node (white arrow) that left level II lymph node was found metastatic out of 32 lymph nodes.

study showed a PPV of 30% (range, 25%–33%) and NPV of 94.9% (range, 89.5%–96.5%) for primary tumor. The Hopkins criteria demonstrated that interreader agreement has a moderate to almost perfect agreement with a very high NPV in this external validation study.

Accuracy of PET/CT as Therapy Assessment Imaging Modality

In a meta-analysis of 51 studies comprising 2335 patients, Gupta and colleagues[55] evaluated the diagnostic performance of the posttreatment FDG PET/CT scan. The impact of timing of posttreatment FDG PET/CT was also assessed before and after 12 weeks. The pooled sensitivity (79.9% and 72.7%), specificity (87.5% and 87.6%), NPV (95.1% and 94.5%), and PPV (58.6% and 52.1%) of FDG PET/CT were reported for the primary site and the neck nodes, respectively. Sensitivity was higher in both primary tumor (91.9% vs 73.6%, $P = 0.12$) and neck nodes (90.4% vs 62.5%, $P < 0.001$) in scans performed greater than or equal to 12 weeks compared those less than 12 weeks. Similarly, Isles and colleagues[56] performed a meta-analysis of 27 studies to evaluate the effectiveness of PET in detection of recurrence or residual HNSCC after CRT. They reported pooled sensitivity, specificity, PPV, and NPV of 94%, 82%, 75%, and 95%, respectively. Considering the effect of the timing of scans,

TABLE 1. Five-Point Qualitative Posttherapy Assessment Scoring System (Hopkins Criteria) for Head and Neck Squamous Cell Carcinoma PET/CT

Score	^{18}F-FDG Uptake Pattern	Response Category
1	^{18}F-FDG uptake at the primary site and nodes less than IJV	Complete metabolic response
2	Focal ^{18}F-FDG uptake at the primary site and nodes greater than IJV but less than liver	Likely complete metabolic response
3	Diffuse ^{18}F-FDG uptake at the primary site or nodes is greater than IJV or liver	Likely postradiation inflammation
4	Focal ^{18}F-FDG uptake at the primary site or nodes greater than liver	Likely residual tumor
5	Focal and intense ^{18}F-FDG uptake at the primary site or nodes	Residual tumor

Scores 1, 2, and 3, which represent complete metabolic response, likely complete metabolic response, and likely postradiation inflammation, respectively, were considered negative for tumor. Scores 4 and 5, which represent likely residual tumor and residual tumor, respectively, were considered positive for tumor. New lesion would be considered as progressive disease.

authors indicated that the sensitivity is significantly higher for scans performed greater than 10 weeks after CRT compared with those performed less than 10 weeks ($P = 0.002$).

Timing of Therapy Assessment PET/CT

FDG PET/CT findings in posttherapy assessment are time and therapy dependent. An increase in FDG uptake occurs in recently radiated tissues, which may last for 12 to 16 weeks (Fig. 7). To ensure a balance between the disadvantages of early and late imaging, the first posttreatment FDG PET/CT scan to assess therapy response is recommended at least 12 weeks postradiation therapy, to minimize radiation-related inflammatory uptake and at least 3 weeks after completion of chemotherapy (ideally just before the next cycle). Performing the ^{18}F-FDG PET/CT sooner may be associated with lower sensitivity and specificity.

FDG PET/CT is increasingly used in the therapy assessment of neoadjuvant chemotherapy before definitive therapy.[57] Wong et al[58] showed through a prospective study of 20 patients with advanced HNSCC that ^{18}F-FDG PET/CT done 2 weeks after the first cycle of induction chemotherapy was an early predictive biomarker for chemotherapy response.

Detecting Recurrences in Follow-up

The incidence of locoregional recurrent disease posttherapy is high (25%–50%), and the majority recur within 2 to 3 years of therapy.[59–61] The NCCN guidelines suggest clinical surveillance every 1 to 3 months for the first year after therapy, every 2 to 4 months for the second year after therapy, and every 4 to 6 months for the subsequent 3 years.[11] Imaging of the primary site of disease is recommended within 6 months of therapy.[62] CT and MRI are commonly the imaging modalities chosen; however, interpretation may be limited by changes from therapy.[63,64] There have been several studies suggesting ^{18}F-FDG PET/CT is valuable for assessing patients with HNSCC posttherapy (Fig. 8). Meta-analyses have suggested a high sensitivity and specificity of ^{18}F-FDG PET/CT for detecting residual or recurrent HNC posttherapy (80%–94% and 80%–95%, respectively).[60,61,65–67] When compared with WB-MRI in patients with a history of oropharyngeal and hypopharyngeal squamous cell carcinoma, ^{18}F-FDG PET/CT was found to be more accurate for the detection of disease recurrence.[68]

Also, the use of contrast-enhanced ^{18}F-FDG PET/CT with an additional head and neck acquisition may improve the specificity of locoregional recurrence.[69] When imaging is performed 12 months after therapy for detection of recurrences, the sensitivity of ^{18}F-FDG PET/CT for the detection of recurrent disease has been reported to be as high as 100%.[70]

^{18}F-FDG PET/CT posttherapy can predict survival in patients with HNSCC. In a retrospective study of 134 patients with HNSCC, patients with ^{18}F-FDG PET/CT positive disease after therapy had a significantly shorter OS compared with those who were ^{18}F-FDG PET/CT negative.[71] In addition, Paidpally et al[72] showed in their retrospective study that total MTV with gradient-based segmentation and clinical HPV status are potential markers for OS in patients with recurrent advanced HNSCC treated with CRT.

The disease recurrence is less common in HPV-positive oropharyngeal SCC, up to 36% of patients experience treatment failure within 8 years. There is controversy over the pattern and timing of

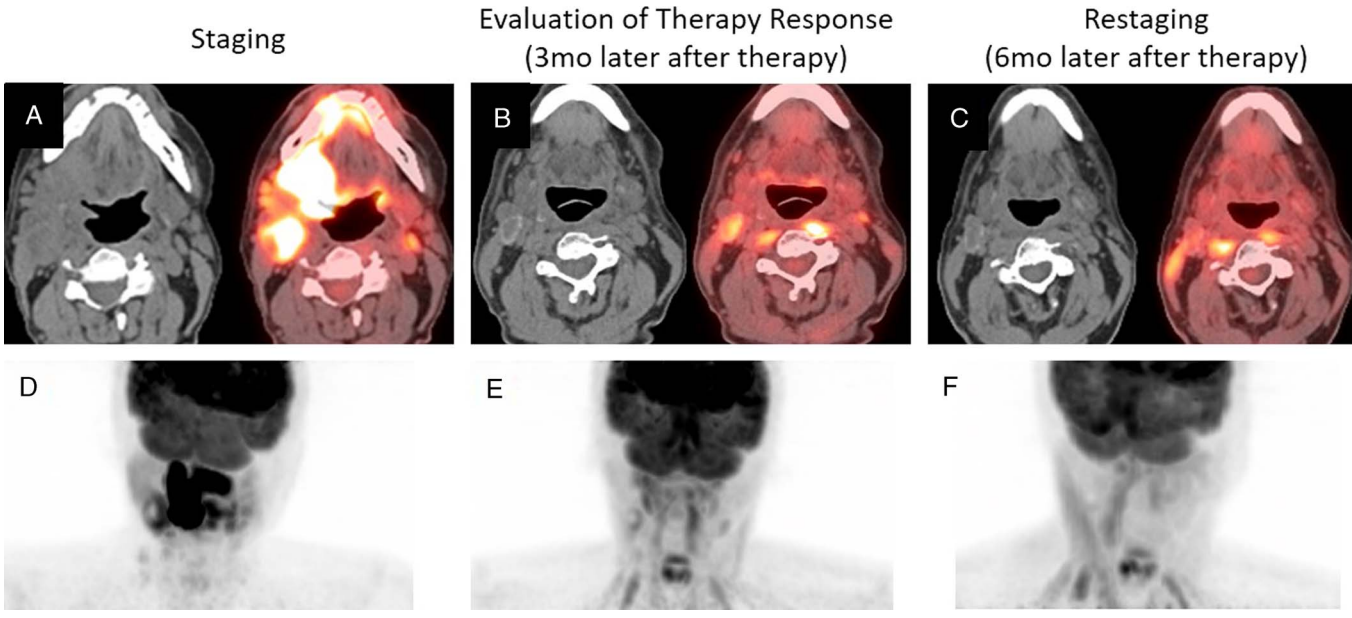

FIGURE 7. Therapy response–inflammatory uptake. A 61-year-old man presented with p16-negative, squamous cell carcinoma of right tonsil, T4bN2bM0. Axial CT and PET/CT fused images (**A**) showed FDG-avid left tonsillar primary tumor and bilateral FDG-avid level II lymph nodes. Axial CT and PET/CT fused images (**B**) showed complete therapy response in the primary tumor with FDG PET/CT, 3 months after finishing CRT. Low-level residual FDG uptake seen within a necrotic right level II node and a small left level II node suggesting residual metabolic uptake, likely posttherapy inflammation. The patient underwent restaging images 6 months after completing the therapy. Axial CT and PET/CT fused images (**C**) demonstrated decrease in size and FDG uptake of the necrotic right level II lymph node without any therapy. MIP images (**D**) showed primary tumor with regional metastatic lymph nodes in staging images and complete response of primary tumor and low level residual FDG uptake in bilateral level II lymph nodes after CRT (**E**) and complete response of primary tumor and bilateral level II lymph nodes in restaging images (**F**).

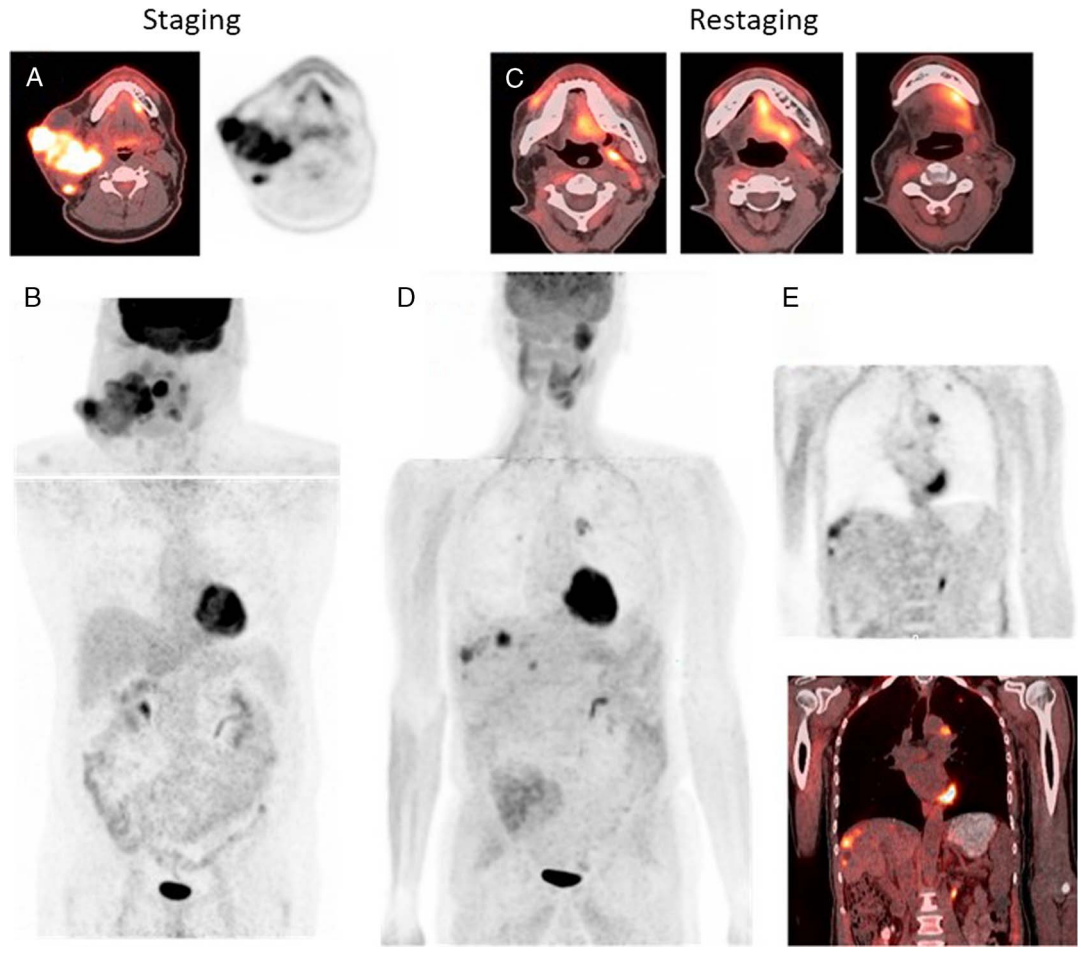

FIGURE 8. Detection of metastasis. A 59-year-old man who presented T1N3M0 (IVB) HPV-negative poorly differentiated squamous cell carcinoma of the right tonsil, treated with CRT and neck dissection. Liver metastases, pulmonary, mediastinal, and right hilar metastases detected after 9 months from the end of therapy. Axial PET/CT fused and PET images (**A**) showed intensely FDG uptake in primary tumor site. MIP images (**B**) showed primary tumor without distant metastasis 9 months after finishing CRT and neck dissection, complete therapy response at primary tumor site in FDG PET/CT images (**C**). MIP images (**D**) showed metabolically active metastatic disease in the liver, left lung, and mediastinal, right hilar lymph nodes. Coronal PET/CT fused and PET images (**E**) showed liver, left lung, mediastinal lymph nodes.

recurrence in HPV-positive versus HPV-negative cohorts. The pattern and timing of recurrences and distant metastases may be different in patients with HPV-positive disease with late metastases (after 2 years of completion of therapy) and "disseminated type" seen in many solid organs and skeleton.[73,74] However, the secondary analysis of RTOG 0129 and RTOG 0522 found that 41% of HPV-positive and 38% of HPV-negative OPC displayed isolated distant metastatic disease at first progression.[75] Median time to distant metastasis did not differ based on p16 status (11.9 vs 12.4 months). OPCs that were p16-positive or p16-negative were found to have similar anatomic distribution of distant metastasis (lung, 73% vs 70%; bone, 14.6% vs 15.2%; liver, 8.3% vs 15.2%; other, 16.7% vs 12.1%). Despite these similarities, patients with HPV-positive disease showed significantly improved OS relative to those with HPV-negative disease (2.6 vs 0.8 years, respectively). There is also evidence that HPV-positive patients with negative PET/CT within 6 to 12 months of completion of therapy have a median 28 months of PFS.[76] These observations suggest that the frequency of follow-up PET/CT (or any imaging) can be reduced in patients with HPV-positive oropharyngeal SCC patients.

RECENT ADVANCES

In recent years, integrated PET/MRI systems have become available in the clinical setting. Schaarschmidt et al[77] evaluated the accuracy of integrated ^{18}F-FDG PET/MR, ^{18}F-FDG PET/CT, and MRI in initial tumor diagnosis and recurrence in 25 patients with histopathologically confirmed HNSCC. They found no significant differences in T and N staging and cancer recurrence among the 3 modalities ($P > 0.017$). Although ^{18}F-FDG PET/MR had higher sensitivity than MR in tumor recurrence, the accuracy was found to be equivalent to FDG PET/CT. However, it should be noted that PET/MRI provides unique opportunities for multiparametric imaging such as interrogating a lesion with FDG metabolism (SUV_{max}) and apparent diffusion coefficient.[78] As Rasmussen et al[79] and Lambrecht et al[80] have reported that high SUV_{max} and low apparent diffusion coefficient values correlate with poor patient clinical outcomes, PET/MR could improve upon current methods for determining prognosis.

Recent studies demonstrate that FDG PET has the potential to predict the tumor heterogeneity defined as differences between

tumors of the same type in different patients. Tumor heterogeneity can be intertumoral and/or intratumoral and has the potential to predict the patient's prognosis. Heterogeneity varies even for the same stage because there are differences in such properties as the growth rate, vascularity, and necrosis.[81,82] Intratumoral heterogeneity mechanism remains unclear; however, some authors reported that increased glucose transporter and hexokinase expression and also decreased expression of glucose 6-phosphatase by immunohistochemistry was shown to be involved in heterogeneous glucose uptake in HNSCC.[83,84] Kwon et al[81] indicated that the intratumoral heterogeneity of ^{18}F-FDG uptake is an important prognostic factor for OS as well as demonstrating that SUV_{max}, MTV, TLG, and heterogeneity factor of the primary tumor were significant prognostic factors in oral cavity cancer. Mena et al investigated 105 HPV-positive OPSCC patients retrospectively. They demonstrated that intratumoral metabolic heterogeneity using ^{18}F-FDG PET/CT was a prognostic factor for EFS with primary HPV-positive OPSCC.[85] Oh et al[86] showed the same in a small group of patients with hypopharyngeal squamous cell cancer (HPSCC) who underwent cisplatin-based induction chemotherapy followed by definitive CRT. The authors showed that textural features–derived baseline ^{18}F-FDG PET images may be predictive of response to CRT and survival in HPSCC and intratumoral heterogeneity may identify patients at risk for low response rates and poor DFS and OS outcomes. Accordingly, the abnormal textural feature of tumor coarseness may be useful for predicting response and survival after CRT in HPSCC patients.

Moreover, increasing evidence suggests that textural features on pretreatment ^{18}F-FDG PET images are associated with response and survival in solid tumors. Chen et al[87] evaluated comprehensive textural indices in HNSCCs to understand their correlation with endogenous markers with immunohistochemical data from pretreatment biopsy specimens (Glut1, CAIX, VEGF, HIF-1α, epidermal growth factor receptor, Ki-67, Bcl-2, CLAUDIN-4, YAP-1, c-Met, and p16) and their role in predicting RT or CRT outcomes. They showed that receiving definitive RT or CRT in pharyngeal cancer patients and determining the texture heterogeneity can provide valuable prognostic information beyond traditional PET-related parameters. The treatment outcome can be stratified by textural features, T stage, VEGF, and HIF-1α. Consequently, the authors suggest that high-risk patients should be aggressively or alternatively treated, or a novel therapeutic strategy should be used for their treatment. Similarly, Choi et al[88] evaluated the association between the tumor stroma ratio and intratumoral heterogeneity measured ^{18}F-FDG and MRI, and further investigated the prognostic significance of imaging biomarkers in HNSCC. In their study, heterogeneity imaging parameters were found significantly associated with the tumor stroma ratio, and this may help to facilitate the risk stratification for tumor recurrence in HNSCC. The heterogeneity of tumors evaluated by ^{18}F-FDG PET for predicting therapy response is a promising new area of research, driving precision medicine.

CONCLUSIONS

^{18}F-FDG PET/CT is standard of care for patients with unknown head and neck primary tumor to localize the site of primary disease, for baseline staging of stage III to IV HNSCC, assessing therapy response when patients have undergone CRT, and restaging HNSCC when clinical suspicion suggest recurrence.

Recent advances include a standardized method for reporting therapy response (Hopkins criteria), evidence of excellent NPV of FDG PET/CT for cN0 neck for nodal metastasis, the value of a negative posttherapy FDG PET/CT for patient management, successful demonstration of radiation dose reduction strategies for HPV-positive disease in multicenter clinical trials, and the recent Food and Drug Administration approval of nivolumab for treatment of recurrent HNSCC will have significant impact on clinical practice. The potential role of tumor heterogeneity in predicting therapy response and outcome, elucidating textural features for analysis using FDG PET, and the evolving role of PET/MRI in patients with HNC will be key areas of development in the future.

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SA-CME Examination

SA-CME Learning Objectives:

After participating in this CME activity, the physician should be better able to:

1. Analyze the most recent advances in PET/CT and PET/MRI in the management of head and neck squamous cell cancer (HNSCC).
2. Interpret the established clinical indications of PET/CT in the management of HNSCC.
3. Compare the pitfalls and challenges of interpreting head and neck PET/CT.

Question 1: What is the most common head and neck cancer cell type?

A. Squamous cell carcinoma
B. Adenoid cystic carcinoma
C. Mucoepidermoid carcinoma
D. Basal cell carcinoma

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Question 2: Where are head and neck squamous cell cancers most commonly located?

A. The nasopharynx or nasal cavity
B. The oropharynx or oral cavity
C. The glottis or epiglottis
D. The larynx

References:

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69–90.
2. Subramaniam RM, Alluri KC, Tahari AK, et al. PET/CT imaging and human papilloma virus-positive oropharyngeal squamous cell cancer: evolving clinical imaging paradigm. *J Nucl Med*. 2014;55:431–438.

Question 3: Oropharyngeal squamous cell carcinoma is most commonly associated with which virus?

A. HSV
B. VZV
C. H3N2
D. HPV

Reference:

2. Subramaniam RM, Alluri KC, Tahari AK, et al. PET/CT imaging and human papilloma virus-positive oropharyngeal squamous cell cancer: evolving clinical imaging paradigm. *J Nucl Med*. 2014;55:431–438.

Question 4: How are localized head and neck squamous cell cancers most commonly treated?
A. Surgery
B. Radiation
C. Chemotherapy
D. Radiation and chemotherapy.

Reference:
7. Murer K, Huber GF, Haile SR, et al. Comparison of morbidity between sentinel node biopsy and elective neck dissection for treatment of the n0 neck in patients with oral squamous cell carcinoma. *Head Neck*. 2011;33: 1260–1264.

Question 5: Which imaging examination is most useful for localizing the site of primary disease in head and neck malignancy of unknown origin?
A. CT
B. ^{18}F-FDG PET/CT
C. MRI
D. Ultrasound

Reference:
4. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Head and Neck Cancers. Version 2. May 8, 2017. Available at: https://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf.

Question 6: When identified on a subsequent investigation, where is the primary lesion most commonly located in patients with squamous cell carcinoma of unknown primary?
A. Fossa of Rosenmüller
B. Base of tongue
C. Palatine tonsils
D. Larynx

References:
24. Motz K, Qualliotine JR, Rettig E, et al. Changes in unknown primary squamous cell carcinoma of the head and neck at initial presentation in the era of human papillomavirus. *JAMA Otolaryngol Head Neck Surg*. 2016;142: 223–228.
25. Upile NS, Shaw RJ, Jones TM, et al. Squamous cell carcinoma of the head and neck outside the oropharynx is rarely human papillomavirus related. *Laryngoscope*. 2014;124:2739–2744.

Question 7: What is the most common site of distant metastases in patients with head and neck squamous cell carcinoma?
A. Brain
B. Bone
C. Liver
D. Lungs

Reference:
36. Xu GZ, Guan DJ, He ZY. (18)FDG-PET/CT for detecting distant metastases and second primary cancers in patients with head and neck cancer. A metaanalysis. *Oral Oncol*. 2011;47:560–565.

Question 8: What is the minimal recommended delay before the performance of ^{18}F-FDG PET/CT be following completion of radiotherapy?
A. 8 weeks
B. 10 weeks
C. 12 weeks
D. 14 weeks

Reference:
56. Isles MG, McConkey C, Mehanna HM. A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy. *Clin Otolaryngol*. 2008;33:210–222.

Question 9: The NCCN guidelines suggest continued follow-up of locoregional recurrent head and neck cancer posttherapy for how long?
A. 5 years after therapy
B. 7 years after therapy
C. 10 years after therapy
D. 15 years after therapy

References:
4. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Head and Neck Cancers. Version 2. May 8, 2017. Available at: https://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf.

Question 10: What is the Hopkins criteria for ^{18}F-FDG uptake at the primary site and nodes for a score of 1? [IVJ indicates internal jugular vein].
A. Less than IJV
B. The same as the IJV
C. More than the IJV but less than liver
D. More than liver

References:
53. Marcus C, Ciarallo A, Tahari A, et al. Head and neck PET/CT: therapy response interpretation criteria (Hopkins Criteria)- interreader reliability, accuracy, and survival outcomes. *J Nucl Med*. 2014;55:1411–1416.
54. Kendi AT, Brandon D, Switchenko J, et al. Head and neck PET/CT therapy response interpretation criteria (Hopkins criteria)—external validation study. *Am J Nucl Med Mol Imaging*. 2017;7:174–180.