Advanced HNSCC requires multimodal imaging for appropriate, multidisciplinary treatment planning and follow up.

Multimodal Imaging of Head and Neck Squamous Cell Carcinoma

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Background: The role of imaging in the staging, treatment planning, and ongoing surveillance of patients with head and neck squamous cell carcinoma (HNSCC) continues to evolve. Changes in patient demographics, treatment paradigms, and technology present opportunities and challenges for the management of HNSCC.

Methods: The general indications and usage of standard and multimodal cross-sectional imaging in the evaluation and management of HNSCC are reviewed, with an emphasis on incorporating them into treatment pathways. Emerging imaging technologies and methods with a potential near-term impact on HNSCC are discussed.

Results: In general, the complex, multidisciplinary approach to the treatment of advanced HNSCC requires multimodal imaging for adequate treatment planning and follow up. Early-stage disease can often be managed with clinical and endoscopic examinations and a single, cross-sectional imaging modality (eg, computed tomography, magnetic resonance imaging).

Conclusions: Although generalized treatment pathways and guidelines do exist, the literature is rapidly advancing and new radiotracers and evaluation methods are expected to alter both imaging and treatment recommendations in the years to come.

Background
In the United States, head and neck cancers are expected to account for 3.7% (63,030 new cases) of all cancers diagnosed in 2017.1 In that same year, an estimated 13,360 Americans will die as a result of tumors involving the oral cavity, pharynx, and larynx.1 The worldwide incidence of new cases of head and neck cancers is estimated to be greater by an order of magnitude, with 686,000 new cases diagnosed and 375,000 related deaths.2 Head and neck cancers encompass a broad range of tumor histologies and locations. However, more than 90% of head and neck cancers are squamous cell carcinomas, arising from the upper aerodigestive tract and frequently involving the oral cavity, oropharynx, hypopharynx, and larynx.2 Although the overall rate of new cases of oropharyngeal cancer in the United States has been stable or decreasing, cases linked to human papillomavirus (HPV) continue to rise, altering the demographics and presentation of new cases of head and neck squamous cell carcinoma (HNSCC).3

Because of its low contribution to the overall cancer incidence in the United States, the true impact of HNSCC on public health may be under-represented.1 No widely accepted screening test exists for HNSCC,
and many patients present with advanced-stage disease, requiring disfiguring surgery, chemoradiotherapy, or both. Both timely diagnosis and accurate staging of HNSCC are critical to avoid under- or overtreatment and to minimize mortality and morbidity. Thus, the objective of this review is to summarize the role of imaging in the management of HNSCC throughout the continuum of care while also providing clinical examples highlighting the strengths and weaknesses of each imaging modality (magnetic resonance imaging [MRI], contrast-enhanced computed tomography [CT], and positron emission tomography [PET]/CT).

Role of Imaging
Since the introduction of CT and MRI, the role of imaging in HNSCC has grown. The widespread application of fludeoxyglucose F 18 (18F-FDG) positron emission tomography (PET) in the late 1990s added a functional metabolic component to imaging, with the subsequent fusion of functional (PET) and anatomical (CT) imaging in the combined modality of PET/CT resulting in further improvements in disease management.4 Continued technological progress and the broadening applications further increase the role of diagnostic imaging in the evaluation and management of HNSCC. PET/CT, contrast-enhanced CT, and MRI have well-defined strengths and weaknesses and, therefore, play complementary roles in the evaluation and treatment planning of HNSCC. However, no single imaging modality can accurately diagnose, stage, and provide long-term surveillance of HNSCC.

Initial Staging
Accurate initial staging is critical to the establishment of prognosis, treatment selection, and the management of HNSCC. Guidelines issued by the American Joint Commission on Cancer represent the standard for HNSCC staging and require detection and precise delineation of the patient’s primary tumor (T), cervical nodal involvement (N), and distant metastases (M) for classifying patients, a process known as TNM staging.5 These guidelines provide separate staging criteria based on the mucosal site of origin, separating patients into those with cancers of the lip and oral cavity, pharynx, and larynx.5 The resulting prognostic stage groupings range from stages I to IV and also include substages.5

In general, diagnostic imaging complements the clinical evaluation of the primary tumor and regional cervical lymph nodes and can be used to detect metastases and second primary tumors in patients with HNSCC. Following an initial clinical examination and endoscopy of the upper aerodigestive tract with biopsy, staging is refined with diagnostic imaging and finalized with the pathological evaluation of cervical lymph nodes from nodal dissection, if performed.

Primary Site
The extent of mucosal involvement by the primary tumor is best documented through clinical and endoscopic examinations, whereas imaging is obtained to evaluate submucosal and deep, soft-tissue extension as well as osseous, cartilaginous, or skull-base involvement.

The location of the primary site of disease can influence the selection of modalities for initial imaging assessment. For example, MRI is often the preferred imaging modality for evaluating the oral cavity, especially the anterior tongue, retromolar trigone, and the floor of the mouth, in which dental hardware and beam-hardening artifact can limit the usefulness of CT (Fig 1).6,7 MRI provides superior soft-tissue contrast and allows the detection of suspicious changes in bone marrow, aiding in the evaluation of the adjacent mandible and other osseous structures when tumor invasion is suspected. MRI is considered the best imaging modality for assessing perineural tumor spread, intracranial and orbital extension (Fig 2), nasopharyngeal carcinoma, and marrow involvement.

However, the superior, soft-tissue contrast provided by MRI of the head and neck is not without its own limitations. The intense inflammatory response surrounding some lesions highlighted with contrast-enhanced MRI can lead to difficulties in determining the true extent of disease, thus complicating treatment approaches and radiation fields (Fig 3). In some cases, the true lesion burden is better delineated with functional techniques such as PET/CT. In addition, the relative scarcity of excitable protons in the osseous matrix results in minimal signal from cortical bone, which may limit the detection

Fig 1A–D.—A man aged 63 years with an infiltrating, destructive mass involving the right mandible from right retromolar trigone squamous cell carcinoma. (A) Axial, contrast-enhanced CT reveals the limited lesion visibility from beam-hardening artifact on CT, even from primarily left-sided dental hardware. (C) Coronal imaging allow improved visualization of the mandibular destruction; however, contrast-enhanced, T1-weighted, fat-suppressed imaging (B and D) provides better representation of the true extent of soft-tissue involvement in this case. CT = computed tomography.
and accurate characterization of osseous destruction on MRI (Fig 4). In these cases, diagnostic CT is often considered the best imaging modality for lesion assessment.

**Locoregional and Nodal Disease**

The most important factor that affects prognosis is cervical nodal status, and an accurate assessment is critical to the treatment plan and choice of therapy. Patients with cervical nodal metastasis, distant metastasis, or both types of metastases have worse prognoses and decreased 5-year survival rates when compared with those without metastatic disease. The importance of nodal status for overall prognosis and management is such that debate remains as to when elective neck dissections or irradiation should be performed, with a 20% or greater risk of occult, microscopic nodal disease often used as a threshold for prophylactic treatment. Imaging detection (or exclusion) of clinically occult nodal metastasis, distant metastasis, or both types of metastases may alter the treatment plan, thus reducing rates of unnecessary surgery and therapy as well as associated morbidity and cost.

Diagnostic imaging adds to the clinical evaluation of cervical nodal involvement by detecting clinically occult nodal metastases and identifying morphological features of clinical importance (Fig 5), such as the presence of extracapsular nodal extension, vascular encase-
ment, and “matted” lymphadenopathy (loss of the fat plane between ≥3 adjacent lymph nodes with extracapsular tissue).9,10 In general, contrast-enhanced CT and MRI are superior for detecting nodal anatomic features and provide an excellent anatomical road map for surgical planning; PET/CT demonstrates excellent overall sensitivity for the presence of nodal metastatic disease.

The detection of small, nonclustering nodal metastases can be challenging when using anatomical imaging approaches such as CT or MRI. Criteria have been established for the assessment of cervical lymph nodes using both modalities; these criteria attempt to balance the sensitivity and specificity of various nodal features, with size being the dominant component.11 Of course, size is not the single imaging feature of interest, and the high spatial resolution and standard use of contrast for both CT and MRI provide improved anatomical definition, which readily reveals suspicious morphological features such as those previously described. The rising prevalence of HPV-positive status in patients with HNSCC has led to an increase in patients presenting with cystic lymph-node metastases, which can be difficult to appreciate on PET/CT due to the minimal metabolic activity in the cystic component but are easily visualized on contrast-enhanced CT and MRI (Fig 6).12

Although PET/CT has superior overall accuracy for the detection of nodal metastases, the absolute physical limitations of the imaging technology can result in false-negative results for nodes measuring less than 1 cm.13 In addition, the nonspecific nature of hypermetabolic activity can confound PET/CT interpretation. Elevated concentrations of 18F-FDG can occur in post-treatment infection and localized inflammation but are also observed during the initial staging process. Oftentimes, PET/CT does not adequately delineate deep soft-tissue extension or osseous involvement, and therefore may not provide an adequate anatomical road map for surgical and treatment planning. High-resolution, cross-sectional imaging with contrast-enhanced CT or MRI provides the anatomical details and soft-tissue contrast necessary for therapy.

**Distant Metastatic Disease**

Distant metastases are estimated to be extant in 10% to 15% of patients at the time of HNSCC presentation and can profoundly alter treatment.14 In such cases, localized surgery and radiotherapy with curative intent are abandoned and management directed toward a palliative, systemic approach.

Screening for metastatic disease at the time of the initial diagnosis is a generally well accepted use of PET/CT for the initial evaluation of advanced head and neck cancers, with PET/CT demonstrating superior sensitivity for the detection of distant metastases as well as second primary cancers.15 In patients for whom PET/CT is unavailable or not clearly indicated, those with HNSCC and higher-stage lesions will still often receive imaging beyond the anatomical limitations of the head and neck. In general, head and neck cancers tend to have distant metastases to the lungs, with nasopharyngeal carcinoma proving to be the exception with osseous metastases.16 In these instances, patients will often undergo dedicated, contrast-enhanced CT of the chest due to the increased risk of metastatic disease.14

**Challenges**

Despite the approaches for initial TNM staging, several questions remain as to the most appropriate approach for evaluating patients with less-common clinical presentations such as occult primary lesions and those presenting without palpable cervical adenopathy.

**Cancer of Unknown Primary:** Patients with HNSCC can present with cervical adenopathy from an occult primary lesion despite thorough clinical or endoscopic evaluation, a situation termed carcinoma of unknown primary (CUP).17 Historically, CUP was a rare presentation of patients with HNSCC, especially as the use of multimodal imaging became widespread.18 However, the increasing prevalence of HPV-positive disease has led to an increase in CUP, possibly due to the tendency of these tumors to have increased nodal disease burden with small or occult primary lesions.12,19

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*Fig 6A–D. — (A) Axial and (C) coronal, contrast-enhanced CT imaging of the skull base and neck reveal faintly enhancing, primary oropharyngeal squamous cell carcinoma (HPV/p16 positive) at the right tongue base (arrowhead) with a cystic, right, level 2A metastatic lymph node (red arrow) in a man aged 59 years. (B, D) Fluodeoxyglucose F 18 PET/CT imaging shows intense uptake in the primary lesion, but significantly less uptake in the cystic node when compared with an adjacent subcentimeter, tumor-containing level 2 node (yellow arrow). HPV-positive nodes may become cystic and have low-level, nonspecific metabolic activity on PET/CT.

CT = computed tomography, HPV = human papillomavirus, PET = positron emission tomography.*
PET/CT has been shown to have superior sensitivity compared with contrast-enhanced CT and combined CT/MRI for the detection of occult primary lesions, with the added advantage of its ability to detect distant metastatic disease and synchronous second malignancies (Fig 7). In addition, PET/CT can locate infraclavicular sites of primary disease when primary head and neck cancer is not the source of adenopathy, and it has been recommended for the workup of patients when standard clinical and imaging approaches are unable to identify a primary site of disease.21,22

Management of “true” CUP remains challenging, with panendoscopy, tonsillectomy, and “blind” biopsies of lymphoid tissue advocated as possible approaches to identify occult primary lesions when diagnostic imaging is unable to provide a potential target.23,24

**Clinically Negative Neck:** Patients can present with symptomatic primary lesions without palpable nodal metastatic disease, a situation termed clinically negative neck (staged cN0 in the TNM staging system). These cases are diagnostically challenging because the nodal status of the patient is of primary importance for disease prognosis and management.

Use of PET/CT for the evaluation of the clinically negative neck is controversial, especially for early-stage disease: Historical studies have been unable to discern a significant advantage of PET or PET/CT over more traditional, cross-sectional imaging such as contrast-enhanced CT and MRI.25-28 One meta-analysis found similar diagnostic accuracy rates between MRI, CT, PET, and ultrasonography for the detection of occult disease in the setting of a clinically negative neck.29 However, data from Roh et al,30 who conducted a prospective clinical trial, found PET/CT to have superior sensitivity for the detection of clinically occult, cervical metastatic disease compared with CT/MRI (71% vs 50%), a finding that highlights the importance of the improved anatomical localization seen in the combined PET/CT approach.4,31 Although it is an active area of research, PET/CT may be reaching the point where certain neck dissections may be avoided or — at the very least — minimized, thus resulting in decreased associated costs and morbidity.30

**Second Primary Malignancies:** Patients with HNSCC are at significant risk of second (synchronous) or metachronous primary malignancies, which can present at the initial diagnosis, during treatment, and at follow-up visits; these malignancies are estimated to occur in approximately 12% of cases. Presumably, these tumors are multifactorial in origin, with environmental factors (eg, use of tobacco, alcohol), infectious agents (eg, Epstein–Barr virus, HPV), and location of the primary lesion potentially playing a role in determining where and how frequently these lesion occur.32 The impact of second primary malignancies on overall patient survival is significant.32 Approximately 75% of patients with HNSCC and second primary cancers will have those second primary cancers outside of the head and neck region, primarily involving the lungs. Therefore, it is imperative that infraclavicular imaging (contrast-enhanced CT of the chest, whole-body PET/CT, or whole-body MRI) be pursued for select patients.

Whole-body imaging is the standard approach for PET/CT in patients with HNSCC, unlike the limited field of view used for MRI and CT imaging. The extended anatomical field of PET/CT provides an advantage for detecting both distant metastatic disease and second primary malignancies outside of the head and neck, with pooled sensitivity and specificity rates estimated to be 88.8% and 95.1%, respectively.6 Whole-body MRI offers the potential to detect metastatic disease and second primary malignancies without the need for ionizing radiation; however, comparative studies in the pretreatment setting found no statistical difference between PET/CT and whole-body MRI.33

**Residual or Recurrent Disease**

Patients with HNSCC who receive treatment may be cured of disease, harbor residual neoplasms at treatment sites, experience locally recurrent disease, or develop distant metastatic disease or new second primary malignancies (local or distant). Evaluation of these patients requires an approach that accounts for the sta-
tistical likelihood of local and distant disease and appropriately leverages imaging.

Detection of malignant disease (residual, recurrent, or second primary malignancies) in the treated head and neck can be challenging. Soft-tissue changes and anatomical disfigurement seen after surgery, chemotherapy, radiotherapy, or all 3 courses of management can distort the intricate anatomy of the head and neck, thereby limiting sensitivity for detecting residual or recurrent disease. PET/CT has been suggested as the best modality for assessment of the post-treatment or altered neck, although appropriate timing of follow-up PET/CT imaging (generally 12 weeks after treatment) is required to minimize false-positive findings from residual, treatment-related hypermetabolic activity (Fig 8).34 PET/CT with iodinated intravenous contrast has several diagnostic advantages but is not routinely used at most institutions.35

In addition to the challenge of detecting locoregional failure on follow-up examination, patients with HNSCC may be at significant risk for distant metastatic disease and remote primary cancers, especially patients with higher-stage malignancies.14 PET/CT was found to have high sensitivity and specificity rates (92% and 95%, respectively) for detecting distant metastatic disease in patients suspected of having recurrent HNSCC (Fig 9).36 Protocols for whole-body MRI have also been used and compared with PET/CT for the evaluation of HNSCC in the post-treatment setting; however, superiority was not demonstrated of either modality, although a trend was observed toward greater diagnostic accuracy with PET/CT.37

Emerging Applications
Prognostic Evaluation With Functional Imaging

Several efforts have been published regarding the use of quantitative 18F-FDG PET/CT measures as prognostic factors for head and neck cancers.38 These quantitative measures include the mean, max, and peak of the standardized uptake value, total glycolytic volume, mean glycolytic volume, and many others.39

Despite the search to associate individual quantitative, continuous variables with clinically significant prognostic outcomes, studies have indicated that there is value in more qualitative assessments such as the visual pattern of metabolic activity.38,40,41 For example, qualitative metrics by Koyasu et al38 characterized lesions as having ring-shaped (ie, central decreased activity) vs sphere-shaped distributions of 18F-FDG and demonstrated a robust prediction of outcomes in their cohort. Mathematically characterizing these qualitative measures is the focus of the field of radiomics, an area of study that has had some success in head and neck

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Fig 8A–C. — Imaging in a man aged 52 years with head and neck squamous cell carcinoma negative for human papillomavirus. (A) Beam-hardening effect from dental hardware limits evaluation of the oropharynx and adjacent structures on contrast-enhanced CT. (B) Combined PET/CT is less affected by beam hardening and reveals nonspecific, diffuse activity post partial glossectomy. (C) Repeat imaging several months later reveals more focal, intense, radiotracer accumulation in the posterior and anterior tongue and floor of the mouth, subsequently determined to be recurrent disease. CT = computed tomography, PET = positron emission tomography.

Fig 9A–D. — A woman aged 55 years with recurrent squamous cell carcinoma of the right maxillary sinus, negative for human papillomavirus and Epstein–Barr virus (same patient seen in Fig 3), now involving the pterygoids and mandible. (A) Maximum intensity projection, (B) CT, (C) 18F-FDG PET, and (D) 18F-FDG PET/CT imaging reveal evidence of numerous, distant pulmonary metastases. 18F-FDG = fludeoxyglucose F 18, CT = computed tomography, PET = positron emission tomography.
cancers and can potentially offer a more generalizable, systematic approach.\textsuperscript{40,41}

**New Radiotracers**

Use of \textit{PET/CT} has traditionally focused on 18F-FDG, a positron-emitting radiotracer that follows the initial steps of glucose metabolism and takes advantage of the propensity of malignant cells to preferentially utilize aerobic glycolysis as an energy source, the so-called Warburg effect.\textsuperscript{42} There is an increasing assortment of radiotracers targeting alternate pathways (fluorothymidine F 18, cellular proliferation), receptor targets, and tumor environmental conditions (fluoromisonidazole F 18, tumor hypoxia) that may prove useful for further characterizing HNSCC in patients.\textsuperscript{43-45}

**Discussion**

The medical literature outlines well-defined roles for the various imaging modalities for the evaluation, management, and surveillance of HNSCC. Although these roles are generally accepted by multidisciplinary clinical services, variability exists between institutions regarding which imaging modality or modalities are useful for specific clinical situations. Surgeon and radiologist preference, availability, cost, health insurance coverage, and the patient’s clinical condition will impact imaging choices and utilization.

Treatment pathways developed at Moffitt Cancer Center and elsewhere provide guidance regarding the timing, frequency, and recommended protocols for the various imaging modalities used for the management of HNSCC.\textsuperscript{46} At Moffitt Cancer Center, we utilize contrast-enhanced CT as the mainstay of our cross-sectional imaging in patients with HNSCC and utilize MRI as a “problem solver” or in specific clinical situations such as perineural tumor spread or intracranial or orbital extension, as well as for the evaluation of postoperative patients with abnormal findings on PET/CT and a normal clinical examination. The utilization of MRI and contrast-enhanced CT is determined by patient-specific clinical concerns and questions that need to be answered by imaging. PET/CT is initially used in patients with higher T-staged disease at Moffitt Cancer Center to identify second primary malignancies and distant metastases, as well as in the post-treatment and surveillance settings to detect treatment failure and recurrence. Patient and disease-specific factors often lead to the adjustment of pathway recommendations, which are usually addressed on a case-by-case basis during multidisciplinary tumor boards.

**Conclusions**

The functional and physiological advantages of positron emission tomography (PET)/computed tomography (CT) combined with the cross-sectional anatomical details, superior soft-tissue contrast, and osseous evaluation provided by magnetic resonance imaging (MRI) or contrast-enhanced CT result in the most comprehensive imaging evaluation of head and neck squamous cell carcinoma (HNSCC). The complete evaluation provided by combined modalities (PET/CT with or without contrast-enhanced CT or MRI) is often needed for the management of advanced (stage III/IV) HNSCC, which generally requires multidisciplinary treatment encompassing surgery, radiotherapy, and chemotherapy. Fluodeoxyglucose F 18 PET/CT has become the imaging cornerstone for evaluating these patients, with the decision being whether to utilize contrast-enhanced CT or MRI for anatomical details. Early-stage cancers, on the other hand, are often adequately imaged and staged with a single modality, usually contrast-enhanced CT. Established imaging guidelines are in constant flux as new imaging paradigms, radiotracers, and therapies are introduced and evaluated, and it is expected that quantitative imaging approaches will begin to play a more important role in the management of HNSCC.

**References**


