PET/CT for Head and Neck Squamous Cell Cancer—Uses and Updates for Radiologists

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Abstract Positron emission tomography–computed tomography (PET/CT) is commonly used in the staging and restaging of head and neck squamous cell carcinoma (HNSCC). In this review paper we discuss the scenarios in which PET/CT that can affect the management of HNSCC patients. These include locating a carcinoma of unknown primary, staging the clinically node-negative neck, pre-treatment staging of advanced disease, and post-treatment evaluation. We summarize the evidence for these uses on the basis of recent literature and also discuss emerging applications of PET/CT for HNSCC. These are topics that radiologists commonly encounter in clinical practice and on head and neck tumor boards.

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Introduction

PET/CT (positron emission tomography/computed tomography) is a widely used modality in oncology for a variety of cancers. In the clinic, PET imaging is performed with ^{18}F -fluorodeoxyglucose (FDG), a glucose analog which is taken up by hypermetabolic cancer cells. As a marker of metabolic activity, FDG-PET may detect changes earlier than anatomy-based imaging modalities, for example CT, MRI, or ultrasound. PET/CT can also aid differentiation of residual tumor from post-treatment changes [1, 2]. These advantages have made PET/CT particularly useful in the staging, post-treatment evaluation, and surveillance of patients with head and neck cancer squamous cell cancer (HNSCC).

In this article, we describe common uses of PET/CT for HNSCC and summarize the evidence for these uses on the basis of recent literature. We also discuss emerging applications of PET/CT for HNSCC that may become important in the future. These are topics that radiologists commonly encounter in clinical practice and on head and neck tumor boards.

Clinical Roles of PET/CT—Why do We Need to Know? How Good is PET/CT?

One of the first studies on PET/CT for HNSCC was published in 1992 [3]. Since then, clinical use of PET/CT has expanded, and the number of published papers has multiplied. In the current cost-conscious era of evidence-based medicine, it is important for the radiologist and ordering

Fig. 1 56-year-old man with cervical nodal squamous cell metastases and unknown primary tumor. He presented with an enlarging right neck mass corresponding to level II/III lymph nodes on CT. Biopsy of the lymph nodes revealed squamous cell carcinoma. Initial CT and clinical examination did not identify a primary tumor so PET/CT was performed. Axial CT (a), PET (b) and fused (c) PET/CT images of the neck reveal asymmetric uptake by the palatine tonsils. Right tonsil (arrow) had SUVmax of 10.7 compared with 6.4 for the left tonsil, but was not enlarged. At surgery, a firm, <1 cm friable mass on the right inferior tonsillar pole was seen and biopsied, revealing squamous cell carcinoma

clinician to understand both the strengths and limitations of PET/CT. This section describes four specific scenarios in which PET/CT findings can affect the management of HNSCC patients. For each scenario, we provide an update on the evidence for or against the use of PET/CT.

Carcinoma of Unknown Primary

Carcinoma of unknown primary (CUP) is the clinical situation in which patients present with cervical nodal squamous cell carcinoma metastases without an identifiable primary tumor (Fig. 1). It is important to distinguish CUP, or occult primary cancer, from cases in which the primary is not seen on imaging because the tumor is small, superficial in location, or obscured by a CT or MRI artifact created by dental hardware. Accurate determination of the primary tumor site enables use of more confined radiation fields, minimizing treatment morbidity. Thus, before being labeled as CUP, an extensive diagnostic workup is performed with directed endoscopic biopsies of likely sites of origin and may include tonsillectomy. PET/CT before endoscopy can help detect small primary tumors not

otherwise seen on imaging and thus help to direct biopsies, reduce operative times, and avoid more invasive procedures.

A recent meta-analysis by Zhu et al. evaluated the performance of PET/CT for detection of primary sites among patients with cervical nodal metastases of unknown origin [4•]. They analyzed seven papers which included results for 246 patients and found PET/CT to have excellent diagnostic performance for detection of primary tumors: combined sensitivity was 97 % and specificity was 68 %. Notably, tumor detection was only 44 %, reflecting that many cases were true CUP with no primary tumor found even with extensive workup. This point was also emphasized in the 2013 Guidelines of the Ontario Head and Neck Disease Site Group [5••], who recommended PET/CT for workup of nodal metastases without primary origin, but noted that a primary tumor site may not always be found.

Pretreatment Staging for Clinical N0 Disease

Patients with clinical N0 disease are those with known primary HNSCC, but no clinically detectable nodal

Fig. 2 69-year-old man with a large base of tongue squamous cell carcinoma and clinical N0 disease. He presented with increasing tongue pain, dysphagia, and odynophagia, and had no palpable nodes on neck examination. Neck CT revealed bilateral base of tongue mass

but no suspicious lymph nodes. A PET/CT was performed to identify occult nodal metastases. (a) and (b) Fused PET/CT images show the base of tongue mass and two hypermetabolic right level IIA nodes (arrows) indicative of metastatic disease

metastases (Fig. 2). These patients have a better prognosis than those with nodal disease. However, early nodal metastases may be occult—not clinically palpable or observed on CT or MRI. The risk of harboring nodal disease is based on such clinical factors as tumor stage, tumor location, histologic characteristics, and historical data from the surgical literature. Traditionally, patients with at least an estimated 15–20 % risk of occult metastases undergo some form of elective neck treatment [6].

These percentages suggest that most clinical N0 patients undergo potentially unnecessary therapy, with the accompanying healthcare costs and treatment morbidity. It is well accepted that a pre-treatment PET/CT that positively identifies previously occult lymph nodes confirms the need for targeted therapy to the neck (Fig. 2). However, it is more controversial whether a negative PET/CT precludes the need for elective nodal dissection or radiotherapy.

The best evidence to date addressing whether PET/CT can effectively exclude occult disease and prevent elective nodal treatment comes from a meta-analysis of 32 studies (1235 HNSCC patients) assessing the diagnostic accuracy of PET for detection of nodal metastases [6]. Kyzas et al. performed a subgroup analysis for clinical N0 disease and found the specificity of PET was 87 %, but with sensitivity of only 50 %. A more recent meta-analysis by Liao et al. [7•] compared the performance of PET with that of other modalities without functional imaging (ultrasound, CT, or MRI) for clinical N0 disease. From 11 studies with 587 patients, combined specificity for PET was 87 % and sensitivity was 66 %, which was not significantly different from those for ultrasound, CT, and MRI.

A multicenter clinical trial led by the American College of Radiology Imaging Network (ACRIN) is currently

evaluating this question prospectively. Their objective is to determine the negative predictive value of PET for patients with clinically N0 neck. Until these results are available, the current literature suggest PET/CT is suboptimum for deciding whether to avoid elective nodal therapy for patients with clinical N0 disease: there is no evidence that PET/CT is better than anatomical imaging alone and PET/CT will still miss up to half of patients with clinically occult metastases.

Pretreatment Staging in Advanced Disease

Accurate nodal staging is also important for patients with clinically detectable nodal metastases. A difficult scenario is when a patient has unilateral metastatic cervical nodes, but has high risk of clinically occult contralateral node involvement. Such patients include those with tumors centered at the midline or which invade the midline, or simply patients with a large burden of ipsilateral nodal disease (Fig. 3). These patients may have elective bilateral nodal treatment despite a clinically negative contralateral neck. As with the scenario for clinical N0 disease, some propose that a negative PET/CT may help with the decision to limit treatment to the ipsilateral neck or selective nodal treatment.

For nodal staging in general, individual studies show that PET/CT is better than CT and/or MRI alone in the strict sense of finding more malignant nodes. A study by Nguyen of 71 patients found 94 % sensitivity for PET/CT versus 79 % for MR or CT alone [8]. However, in studies that focus on the ipsilateral and contralateral cervical nodes, the performance of PET is lower for contralateral nodes. Kim et al. [9] compared PET/CT with MR or CT for

Fig. 3 63-year-old man with a soft-palate squamous cell carcinoma and occult contralateral nodal metastasis. **(a)** Axial CT image shows a left level IIA node to be mildly enlarged and enhancing (arrow). There were no suspicious right-sided lymph nodes. Despite the right neck being normal on clinical examination and CT, a PET/CT was performed because the tumor was midline which is associated with an increased risk of bilateral metastases. **(b)** PET and **(c)** fused PET/CT images show both level IIA nodes (arrows) have increased FDG uptake (arrows). The stage of the patient's disease increased from N1 (one node <3 cm) to N2c (bilateral nodal disease)

determination of the laterality of nodal disease for 114 patients. For ipsilateral metastases, they reported higher sensitivities of 88 % for PET versus 70 % for CT/MRI. For contralateral disease, the sensitivity of PET and CT/MRI was 52 and 36 %, respectively. A more recent study of PET/CT among 61 patients found similar sensitivities of 80 % for ipsilateral disease and 65 % for contralateral disease [10]. Both studies concluded that PET/CT could not be used to avoid contralateral neck surgery or radiotherapy for high-risk patients. Interestingly, the sensitivity of PET for contralateral nodal disease is similar to the sensitivity for occult metastases when there is clinically N0 disease, which emphasizes the limitation of PET in detecting small metastatic nodal deposits.

Post-Treatment Evaluation for Residual Disease

One of the most important and well-established uses of PET/CT in HNSCC is post-treatment evaluation after curative-intent chemoradiation (Fig. 4). After chemoradiation therapy, the two potential outcomes are complete response or residual disease. Patients with complete

response will receive no further treatment whereas patients with residual disease require salvage surgery at the sub-optimally treated tumor sites. One of the challenges after treatment is differentiating between residual tumor and post-treatment changes on CT or MRI, because some patients with complete response may still have residual nodal tissue with no viable tumor (Fig. 4). For these patients a negative PET/CT may support the decision to closely observe the patient rather than perform unnecessary surgery.

The largest meta-analysis evaluating the diagnostic performance of post-treatment PET/CT in HNSCC was that by Gupta et al. [11•] which included 51 prospective and retrospective studies of 2,335 patients. The combined specificity (88 %) and negative predictive value (95 %) were excellent and the same for both primary tumor and nodal metastases. These results support the practice at many institutions that a negative PET scan could be used to avoid salvage surgery. However, a limitation of PET/CT for post-treatment evaluation is seen in the setting of a positive PET scan. Gupta et al. [11•] found low positive predictive values for the primary tumor (59 %) and nodal

Fig. 4 48-year-old man with residual disease after curative-intent chemoradiation for T4N2bM0 left palatine tonsil squamous cell carcinoma. **(a)** Pretreatment fused PET/CT image shows a large left tonsillar mass extending into the base of the tongue and oral tongue (*arrowheads*), and an enlarged metabolically active left level IIA node (*arrow*). He had persistent left tongue pain and trismus 11 weeks after completion of chemoradiation. A PET/CT scan performed shortly afterward. **(b)** Post-treatment fused PET/CT image shows a persistent mass with metabolic activity in the left tonsil and tongue base (*arrowheads*). This is highly suggestive of residual disease at the primary site and was confirmed by biopsy. **(c)** Post-treatment fused PET/CT image shows no metabolic activity in the remaining left level IIA node lymph node (*arrow*). This is consistent with the response for the nodal metastasis

disease (52 %), which indicate the tracer, FDG, is not tumor-specific. Metabolic uptake can indicate tumor, but can also be found with treatment change or inflammation.

The timing of PET/CT can help to reduce false-positive results; Gupta et al. obtained fewer false-positive results for nodes in studies timed at or greater than 12 weeks (5.7 %) after completion of chemoradiation compared with before 12 weeks (14.9 %). A recent single-center study reported similar results. For 311 patients, the accuracy for scans performed within two months after the completion of treatment was 69 % as opposed to 93 % for scans after 2 months [12].

Some centers also advocate performing a second post-treatment PET/CT scan within six months of chemoradiation. A large retrospective study of 512 patients examined the value of one negative PET/CT compared with two negative PET/CT scans. After a minimum 12-month follow-up period, they found one negative PET/CT had 91 % negative predictive value (NPV) for malignancy, but two negative PET/CTs performed within six months of each other had 98 % NPV [1•]. The implication is that a single

post-treatment PET/CT may not be adequate to eliminate the need for further radiological surveillance, but clinicians could rely on clinical surveillance after a second PET/CT.

Future Directions—Trends and Developments

Evaluating Early Treatment Response

One topic of active interest is evaluation of response to therapy by using PET/CT *during* treatment. This may entail imaging within the first few weeks of an eight-week course of concurrent chemoradiation or during induction chemotherapy which is performed before chemoradiation. Early evaluation with PET/CT at these times could enable detection of favorable or unfavorable metabolic changes before anatomic changes are evident and, thus, early identification of non-responders who may be candidates for adaptive treatment strategies, new molecularly-targeted therapy, or primary surgery.

The results of the studies are mixed for imaging with PET/CT during the first few weeks of chemoradiation

(intra-treatment imaging). Hentschel et al. [13] performed PET scans for 37 patients several times during radiation for HNSCC and found imaging at 1–2 weeks to be the best time for identifying patients with response, as indicated by a rapid drop in FDG uptake. Castaldi et al. [14] performed imaging at two weeks and found poor correlation between early PET changes and clinical outcome. Other studies have imaged later during radiotherapy (four weeks) and found intra-treatment PET to be useful if there was dramatic response (high specificity), but persistent metabolic activity on the intra-treatment PET did not identify patients that would have residual disease or poorer prognosis (low sensitivity) [15].

Induction (or neoadjuvant) chemotherapy is used in some centers for patients with inoperable locally advanced tumors. In the last decade several studies have shown that PET/CT can be used to identify patients who are more likely to respond to concurrent chemoradiation after induction chemotherapy [16, 17]. In the most recent study, Abgral et al. [18] performed PET/CT twice during three cycles of induction chemotherapy for 15 patients with HNSCC and reported significantly better event-free survival for patients for whom reduction in SUVmax was greater than 15–25 %.

One issue in evaluation of early treatment response is the feasibility of distinguishing small changes in metabolic activity reflecting tumor response from baseline variation in tumor metabolic activity. Hoang et al. quantified the baseline variability and compared the changes in SUVmax with intra-treatment change. They found that baseline variability in SUVmax in nodal metastases could vary by

as much as 10 % even if the imaging was performed on the same scanner, but the variability was still less than intra-treatment change at 1–2 weeks [19].

Novel PET Radiopharmaceuticals

PET is often seen as being synonymous with ^{18}F -FDG, but a variety of other radiopharmaceuticals have been evaluated for imaging HNSCC. Although these novel PET tracers target tumor more specifically than does FDG, they currently have a number of disadvantages that have limited clinical adoption (Table 1).

The most promising alternative tracer is ^{18}F -fluoromisonidazole (FMISO), which is a molecular agent for tumor hypoxia. Because hypoxic cells are more resistant to the cytotoxic effects of radiation, hypoxia is associated with poor outcome in HNSCC [20]. Current obstacles to clinical use are long examination protocols (4 h post-injection) and a “ceiling effect” in which hypoxia is underestimated below a threshold [21, 22]. However, it has been shown to have some promise in evaluation of intra-treatment and post-treatment response and has been used to help target dose painting and dose escalation procedures for radiotherapy [23–32].

^{18}F -fluoroazomycin arabinoside (FAZA), another hypoxic agent, has recently been evaluated in a study with pretreatment and intra-treatment time points. The investigators observed significantly lower disease-free survival among patients with hypoxic tumors [33•]. There has also been interest in ^{18}F -fluorothymidine (FLT) for intra-treatment imaging. This is a DNA analog which tracks cell

Table 1 Novel tracers for head and neck squamous cell cancer

Tracer	Pathway	Uses/advantages	Disadvantages compared with FDG PET
^{18}F -F-MISO	Hypoxia	Detect hypoxia during radiotherapy [32] Radiation planning [27, 29]	Long imaging procedure [21]
^{18}F -HX ₄ , ^{18}F -FAZA	Hypoxia	May be faster than F-MISO [33•, 37]	Still experimental
^{18}F -fluorothymidine (FLT)	DNA synthesis (thymidine analog)	More specific for cancer than FDG [38•] Possible uses in post-treatment assessment (detects change earlier) [34] and as a prognostic indicator [39]	Less sensitive than FDG [38•] Higher background uptake in the liver and bone marrow [38•]
^{18}F -fluoroethyltyrosine (^{18}F -FET)	Protein synthesis (amino acid analog)	More specific for cancer than FDG [40]	Less sensitive than FDG [40]
^{11}C -methionine (^{11}C -MET)	Protein synthesis (amino acid analog)	Has been used to predict effectiveness of carbon-ion radiotherapy [41, 42]	Short half-life Other applications not yet validated
Choline (^{18}F or ^{11}C)	Cell proliferation (membrane synthesis)	Similar to FDG; may be more useful in skull base tumors [43]	Not otherwise superior to FDG [43], slightly less effective for recurrence [43, 44]
^{18}F -galacto-RGD	Angiogenesis ($\alpha\text{v}\beta 3$ receptor)	Demonstrates receptor expression [45]	Little validation for humans with head and neck PET

proliferation. Hoshikawa et al. [34] observed earlier and greater reductions in SUV on FLT imaging than FDG in the intra-treatment period.

Obstacles to use include lack of access to tracers and reimbursement. Insurance companies do not currently reimburse for use of tracers other than FDG. In addition, even for research purposes, many of the tracers may be difficult to obtain, and tracers using radionuclides other than F-18 require use of an on-site cyclotron, because other commonly used radionuclides, for example C-11, have very short half-lives.

PET/MRI

A technological advance causing substantial excitement is PET/MRI, in which a PET and an MRI scan are acquired together, either simultaneously or sequentially. MRI has advantages over CT in having greater contrast resolution, which is especially advantageous for evaluation of mucosal lesions and perineural disease. Although studies have shown combined PET and MRI to be superior to evaluation with MRI only, there are no proven differences between PET/CT and the more costly PET/MRI for HNSCC [35]. In a prospective study comparing PET/CT with PET/MRI for 17 patients with HNSCC, diagnostic capability was not significantly different [36].

Conclusion

In summary, PET has many useful applications in the diagnosis and treatment of HNSCC. Literature supports its utility for evaluation of carcinoma with unknown primaries and for post-treatment assessment of residual disease, but it currently still seems to be limited for detection of clinically occult nodal metastases. For determining early response during treatment, it remains more specific than sensitive, which is problematic because it is more important to identify non-responders to therapy. Because FDG is not tumor-specific, active research is being conducted to evaluate new PET tracers for early treatment response.

Compliance with Ethics Guidelines

Conflict of Interest JD Oldan declares no conflicts of interest. DS Yoo received payment from Oakstone for development of educational materials. WT Lee declares no conflicts of interest. JK Hoang declares no conflicts of interest.

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- Of major importance

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