



Positron Emission Tomography and Molecular Imaging of Head and Neck Malignancies

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Abstract

Purpose of Review Metabolic reprogramming and avid fluorodeoxyglucose (FDG) uptake in locally advanced head and neck squamous cell carcinomas and other cancers of the upper aerodigestive tract lead to favorable sensitivity and diagnostic accuracy of FDG PET/CT or PET/MR compared to conventional imaging. Meanwhile, the role of non-FDG PET in head and neck malignancies is rapidly expanding.

Recent Findings Accurate staging, identifying a clinically occult primary, or detection of distant metastasis or a synchronous malignancy on FDG PET significantly impacts management. FDG uptake after definitive therapy is an invaluable biomarker for surveillance. Patients with metabolic resolution can be spared from neck dissection, whereas FDG avid refractory disease or distant metastasis could necessitate surgical or systemic therapy. PET tracers targeting amino acid transport or fibroblast activation hold promise for improved specificity and better delineation of tumor prior to radiation therapy given their low physiologic or inflammatory uptake in head and neck compared to FDG. Tracers for hypoxia or cellular proliferation provide complementary information to FDG after radiation therapy for assessment of residual malignant cells that could lead to treatment failure. FDG remains the primary tracer for imaging lymphoma and other pediatric head and neck malignancies. Several other PET tracers such as gallium-

68-labeled somatostatin receptor analogs and fluorodopa are being increasingly used for detection and characterization of head and neck paragangliomas and certain other cancers.

Summary FDG and other PET radiopharmaceuticals are increasingly being exploited in guiding clinical management of various head and neck malignancies and significantly impact patient outcomes.

Keywords Head and neck neoplasms · Positron emission tomography–computed tomography · Squamous cell carcinoma of head and neck · Therapy assessment · ¹⁸FDOPA · ⁶⁸Ga-SSA

Introduction

Head and neck cancers comprise a heterogeneous group of malignancies with distinct histopathology, oncogenesis, clinical behavior, and prognosis. Cancers of the upper aerodigestive tract (nasal cavity and paranasal sinuses, lips and oral cavity, salivary glands, pharynx, and larynx) are significant causes of morbidity and cancer-associated mortality and are by far the most common group of head and neck malignancies referred for imaging. Lymphoma is the most common head and neck malignancy encountered in pediatric imaging centers. Other malignancies with unique characteristics include cancers arising from follicular or para-follicular cells in thyroid gland, paragangliomas, sarcomas, melanoma, and Merkel cell carcinoma, among others. Non-melanomatous skin cancers (basal and squamous cell carcinomas) are often managed with local therapy and not referred for imaging.

Cancers arising from the mucosa of the upper aerodigestive tract are the sixth most common cancer worldwide

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and eighth most common in US men. Most patients (about 60%) present with locally advanced M0 disease (corresponding to stage III or IV). These patients are generally treated with curative-intent chemoradiation. More than half of such patients will develop local recurrence arising from radiation resistant hypoxic residual disease and 20–30% could develop distant metastasis within 2 years from treatment. Squamous cell carcinoma (SCC) is the most common histology, comprising 90–95% of the lesions in the oral cavity and larynx. Other histologies include verrucous carcinoma (a variant of SCC), adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, sinonasal undifferentiated carcinoma, and non-keratinizing nasopharyngeal carcinomas. The latter is seen in 75% of nasopharyngeal carcinomas in the united states and has strong association with Epstein–Barr virus (EBV). Established risk factors for head and neck SCC (HNSCC) include tobacco (smoking or chewing), alcohol, and viruses such as HPV (particularly type 16 in up to 70% of oropharyngeal cancers) or EBV. In some developing countries, chewing betel nut is another significant risk factor.

Tumorigenesis of HNSCC provides insight into factors affecting upregulation of glucose metabolism and potential new molecular imaging strategies. P16 tumor suppressor gene inactivation is frequently found in squamous hyperplasia [1]. Progression to dysplasia and carcinoma in situ is associated with mutations in P53 and other oncogenes [2]. PTEN inactivation is seen in invasive cancers. HNSCCs display significant cellular heterogeneity. Mutations in the catalytic subunit of phosphatidylinositol 3-kinase (PI3KCA), a frequently amplified oncogene in HNSCC, promote epithelial-to-mesenchymal transition [3]. This transition has been linked to development of cancer stem cells within the lesion [4] which play pivotal roles in suppression of immune response, treatment failure, recurrence, and metastasis.

PET: Technical Considerations

PET/CT and PET/MR are hybrid imaging systems that provide inherently coregistered or near-coregistered anatomic and functional information. CT or MR attenuation correction eliminates the need for a separate transmission imaging. For head and neck malignancies, most centers include dedicated imaging of the head and neck performed with arms down to the sides of the patient. Ideally, the protocol would have a small field of view, large matrix size, and minimal spatial smoothing in post-processing. Acquisition time in head and neck stations is increased to improve signal to noise ratio. These optimizations could significantly improve resolution and sensitivity, enabling

detection of small primaries or nodal metastases [5]. Torso imaging (clavicle to mid-thigh, with arms raised above the head) should be performed separately in the same session as standard protocol to evaluate for distant metastasis. Whole body imaging covering torso and extremities through the feet is necessary or advantageous in certain applications including melanoma, Merkel cell carcinoma, cutaneous T-cell lymphoma, and soft tissue and osseous sarcomas.

Oncologic PET/CTs are commonly performed using a low-mA and high-kVp protocol for CT and without the use of intravenous contrast. The CT portion is not optimized for diagnostic interpretation per se and is primarily intended for attenuation correction and localization of PET findings with minimizing radiation exposure in mind [6]. A dedicated contrast-enhanced neck CT can be performed in the same session if recent cross-sectional imaging is not available. Alternatively, the CT portion of the PET–CT can be performed with intravenous contrast with or without adjusting CT acquisition parameters as a compromise between anatomic and morphologic information and ability to characterize lesions by enhancement versus overall radiation exposure from CT and accuracy of attenuation correction. Without iodinated contrast, it may be difficult to evaluate the extent of involvement of adjacent structures or delineate vessels and lymph nodes, particularly in a previously irradiated neck.

PET/MR

With development and adoption of solid-state detectors that are not affected by magnetic fields in the past decade simultaneous acquisition of PET and MR images has become feasible, enabling dynamic registration of functional and anatomic information with high fidelity. Integrated PET/MR systems are not as widely available and there is overall less experience with them compared to PET/CT. MR attenuation correction introduces quantification inaccuracies that are negligible for soft tissue lesions and standardized uptake values (SUV) measured using PET/MR are shown to be reasonably reliable in general clinical applications [7]. Dedicated head and neck MR sequences provide high resolution anatomic and morphologic information helpful in interpretation of PET findings. Diffusion weighted imaging is helpful in areas of high physiologic activity such as lymphoepithelial tissues and may provide complementary information to FDG uptake [8]. Cortical bone erosion is better evaluated on CT than on MR, but MR has better sensitivity for bone marrow involvement. Ability to measure blood flow and volume and derive arterial input function based on MR angiography are useful in investigational settings when kinetic PET analysis is needed.

Clinical evidence so far point to certain applications such as initial staging for which PET/MR has excellent diagnostic performance [9, 10]. In most applications, PET/MR is diagnostically similar if not superior to PET/CT [11, 12]. In nasopharyngeal carcinoma, the superior soft tissue contrast of MRI improves T-staging compared to contrast-enhanced CT [13]. MR can be useful for T-staging and anatomic correlation of oral findings when dental hardware artifact severely degrades CT images. In patients who are unable to receive intravenous contrast PET/MR with T2-weighted imaging can characterize necrotic or cystic lymph node metastasis [11]. Motion artifact could reduce usefulness of non-contrast PET/MR in larynx and hypopharynx. PET/MR can miss some sub centimeter pulmonary nodules that are not FDG avid or are not detected on PET due to small size. However, these nodules are generally clinically insignificant. PET/CT and PET/MR have overall comparable accuracy for evaluation of distant metastases or synchronous cancers [10].

PET Radiotracers

¹⁸F-Fluorodeoxyglucose (FDG)

FDG is the most common PET tracer in oncologic imaging and in particular for initial workup and assessment of treatment response or surveillance after treatment in HNSCCs (Table 1). FDG uptake is generally amplified in HNSCCs. P53 mutations affect glycolytic metabolism through hypoxia-inducible factor-1 (HIF-1 α) complex binding hypoxia response elements in the promoter region of GLUT1 (glucose transporter 1) and hexokinase II. Overexpression of GLUT1 facilitates FDG uptake which is subsequently phosphorylated by hexokinase II and remains trapped in the cytoplasm. PTEN inactivation also affects glucose metabolism via PI3K/AKT signaling. Fibroblast activation and upregulation of glucose metabolism in tumor stroma [18] as well as tumor associated inflammation play a significant role in overall uptake.

High FDG uptake in primary tumor is suggestive of aggressive malignancy and worse prognosis whereas low uptake is generally seen in neoplasms with more indolent behavior such as low-grade neuroendocrine tumors, differentiated thyroid cancers, or indolent lymphomas.

¹⁸F-Fluorodopa (FDOPA) and Other Amino Acids

Amino acid PET has been extensively studied in neuro-oncology for characterization of indeterminate brain lesions, identification of regions of higher grade histology, differentiating viable tumor versus radiation necrosis and inflammation, delineation of tumor extent before therapy,

and monitoring response to therapy [19]. Sodium-independent large neutral amino acid transport system L (LAT-1 and LAT-2) are implicated in intracellular uptake of ¹⁸F-fluoroethyl tyrosine (FET), fluoro-dihydroxyphenylalanine (FDOPA) and other amino acid PET tracers in CNS tumors. LAT-1 is overexpressed in both primary and metastatic brain lesions. Other transport systems may be additionally involved depending on radiotracer (for example ASCT-2 for fluciclovine), particularly in non-CNS tumors. LAT-1 and ASCT-2 are overexpressed in HNSCC and seem to play a critical role in tumorigenesis [20]. Uptake seems to correlate with glutamine metabolism which provides an alternative energy metabolic pathway to glucose. Uptake of FET and other amino acid PET tracers such as fluoromethyltyrosine (FMT, FAMT) in HNSCC and other malignant lesions is not as intense as with FDG and consequently studies with amino acid PET generally report lower sensitivity than FDG PET [21, 22]. On the other hand, lack of uptake in inflammation relative to malignant lesions [23] leads to potentially better specificity, particularly after radiotherapy, and can inform decisions about observant management in case of a positive FDG PET during treatment evaluation [24]. In areas of high physiologic background FDG uptake (such as skull-base lesion) FET PET has been shown to improve delineation of lesions for treatment planning [25]. In a small study, diagnostic performance of FMT PET in maxillofacial tumors was found to be equal to FDG PET: even though tumors had lower SUV with FMT, the contrast to surrounding normal structures was higher than that of FDG [26]. In 68 patients with oral SCC, FMT and FDG PET had both excellent sensitivity for primary tumor (98 vs. 100%). FMT PET had lower sensitivity (68 vs. 84%) but better specificity (99% vs. 94%) and overall accuracy (97 vs. 94%) for nodal involvement and uptake correlated well with LAT-1 expression and cell proliferation on tumor immunohistochemistry [27].

Fluciclovine is FDA approved and is widely being used for prostate cancer imaging. Its utility in HNSCC is being investigated although data are currently limited to anecdotal evidence and case reports on oropharyngeal SCC incidentally detected on fluciclovine PET [28].

FDOPA has high uptake in neuroendocrine tumors and has high sensitivity for head and neck paragangliomas [29], although the sensitivity is lower than somatostatin receptor PET for malignant or metastatic lesions [30] or hereditary paragangliomas related to succinate dehydrogenase (SDH) mutations [29]. FDOPA PET is superior to MIBG SPECT for paragangliomas as well as both soft tissue and bone or bone marrow metastases in neuroblastoma [31].

Table 1 Some of the PET radiopharmaceuticals clinically used in head and neck malignancies

PET agent	Mechanism of uptake	Applications
^{18}F -FDG	Glucose metabolism (GLUT1, hexokinase II)	HNSCC, lymphoma, melanoma, sarcoma [14] Thyroid cancer (anaplastic or aggressive histology or negative radioiodine scan) [15] Other aggressive head and neck malignancies
^{18}F -FDOPA ^a	Amino acid transporters (LAT-1, LAT-2), amino acid decarboxylase, vesicular monoamine transporters	Paraganglioma [16•], neuroblastoma, neuroendocrine tumors CNS tumors
Amino acid PET (^{11}C -MET, ^{18}F -FET, ^{18}F -FMT, ^{18}F -fluciclovine ^b , etc.)	Amino acid transporters (LAT-1, LAT-2, ASCT-2)	CNS tumors HNSCC (delineation of tumor in therapy planning, differentiation of inflammation from tumor)
^{18}F -FLT	DNA synthesis	HNSCC (early assessment of response to radiation therapy)
^{68}Ga -SSA (^{68}Ga -DOTATATE, ^{68}Ga -DOTATOC, ^{68}Ga -DOTANOC, etc.)	Binding to somatostatin receptors (SSTR2)	Head and neck paragangliomas, paragangliomas associated with succinate dehydrogenase (SDH) mutation [16•] Neuroendocrine tumors (e.g., Merkel cell carcinoma), patient selection prior to PRRT [17]
PSMA PET (^{68}Ga -PSMA-11, ^{18}F -DCFPyL, etc.)	Binding to transmembrane glutamate carboxypeptidase II (PSMA)	Emerging applications (adenoid cystic carcinoma, thyroid cancer)
Integrin $\alpha_v\beta_3$ PET (^{18}F -galacto-RGD, ^{68}Ga -NOTA-RGD, ^{18}F -fluciclatide, ^{18}F -alfatide, ^{18}F -FPPRGD2, etc.)	Binding to integrin $\alpha_v\beta_3$	Imaging tumor angiogenesis Predicting and monitoring treatment response to VEGF tyrosine kinase inhibitor
Hypoxia PET (^{18}F -FMISO, ^{18}F -HX4, ^{18}F -FAZA, ^{18}F -EF5, ^{64}Cu -ATSM, etc.)	Intracellular reduction and trapping under hypoxia	Radiation therapy planning and dose escalation

^aApproved for imaging in Parkinsonian syndromes in the United States

^bApproved for imaging prostate cancer in the United States

Radio Nucleosides

^{18}F -fluorothymidine (FLT) is a thymidine analog used for direct assessment of DNA synthesis and tumor proliferation. Several small-scale studies have shown good sensitivity and specificity for primary head and neck cancers and nodal metastases, with overall comparable tumor to background ratio and diagnostic performance in staging to FDG (e.g., [32]). Like FDG, reactive lymph nodes can have increased FLT uptake due to proliferation of B-cells [33]. High physiologic uptake in bone marrow and liver limits sensitivity for metastases to these organs [34]. FLT, however, has excellent sensitivity for brain metastases and adjacent structures.

FLT uptake decreases quickly after radiation therapy, preceding changes in Ki67 proliferation index and glucose metabolism [35, 36]. Early reduction of FLT uptake during

radiotherapy or chemoradiotherapy is associated with improved long-term outcome [37, 38]. Preliminary data support utility of FLT PET during therapy for assessment of effectiveness and radiation dose escalation planning [39]. However, published evidence suggest that FLT is not superior to FDG after completion of therapy.

Peptides and Large Molecule Imaging Agents

Somatostatin Receptor Analogs (SSA)

Gallium-68 DOTATATE and several other somatostatin receptor (SSTR) targeting PET radiopharmaceuticals are in widespread use for imaging well-differentiated neuroendocrine neoplasms and other neoplasms associated with overexpression of SSTR at the cell membrane. SSTRs

(particularly type 2 receptor, SSTR-2) are highly expressed in neuroendocrine cells. Radiolabeled SSAs have all high affinity to SSTR-2 and some also bind to SSTR-3 and SSTR-5 (e.g., DOTANOC). The physiologic biodistribution and sensitivity and specificity of various gallium-68-labeled SSA PET tracers are overall comparable.

Gallium-68-labeled SSA are the preferred PET tracers for localization of sporadic head and neck paragangliomas and paragangliomas associated with succinate dehydrogenase (SDH) mutation with better diagnostic performance compared to cross-sectional imaging, scintigraphy, or FDG PET [16, 40]. FDOPA is superior to SSTR imaging for other hereditary paraganglioma–pheochromocytoma syndromes.

SSA PET is useful in other neoplasms with neuroendocrine origin involving head and neck such as medullary thyroid carcinoma or Merkel cell carcinoma and may help in patient selection for peptide receptor radionuclide therapy [41, 42]. High uptake observed in a subset of undifferentiated nasopharyngeal carcinomas and contrast with low activity in the background is helpful for tumor volume delineation prior to radiation therapy particularly in tumors infiltrating skull base although SSTR overexpression can be lost in recurrent disease [43, 44].

PSMA-Targeted Agents

Despite its name, prostate specific membrane antigen (PSMA) is a transmembrane enzyme that is overexpressed in a variety of malignant and non-malignant cells and tumor neovasculature. As with SSAs, PSMA radioligands can be used as diagnostic and therapeutic pairs. Current data on the utility of PSMA imaging in HNSCC beside case reports [45] are limited. However, there is emerging data suggesting high expression of PSMA and diagnostic utility of PSMA PET in certain other head and neck malignancies such as differentiated thyroid cancer and adenoid cystic carcinoma [46]. High physiologic uptake in salivary glands and PSMA avidity reportedly in 40% of salivary duct carcinomas [47] are factor affecting sensitivity and specificity of PSMA PET in head and neck cancers.

Radiolabeled Antibodies

Monoclonal antibodies or antibody fragments targeting cell surface protein such as EGFR, VEGF, HER2, and PD1 are increasingly used in treatment of patients with HNSCC and other malignancies. Epidermal growth factor receptor is commonly overexpressed in HNSCC. Cetuximab, an EGFR monoclonal antibody, is useful in systemic therapy of HNSCC. Combination of cetuximab and radiation

therapy is more effective than radiation therapy alone in locally advanced disease.

Feasibility of several radioisotope-antibody conjugates for imaging and/or radionuclide therapy has been demonstrated in preclinical studies. A recently published phase-I clinical trial with zirconium 89-labeled anti-CD8 antibody in patients with head and neck cancers and other malignancies [48] show uptake in most lesions by 24 h and as early as 2 h reflecting infiltrating CD8+ T-cells. Radiolabeled antibodies generally require prolonged interval between injection and imaging to achieve desired biodistribution, necessitating positron emitting radiometals such as Zr-89 (half-life of 3.3 days) with significantly slower decay than F-18, Ga-68, or even Cu-64. Delayed imaging is particularly important for antibodies known to have prolonged circulation time such as cetuximab and 6–7 days may be needed to improve tumor to background ratio before imaging head and neck malignancies [49]. Two-step pretargeting methods (for example using Diels–Alder reaction) are alternatively being investigated which allow for administration of antibody conjugated with a ligand followed by delayed administration of a small molecule PET tracer that selectively reacts with the ligand [50]. Unfortunately, while radiolabeled cetuximab was promising in preclinical studies [51], human studies have not yet established a strong correlation between uptake on ⁸⁹Zr-cetuximab PET and outcome of cetuximab therapy [52]. More promising results exist for other investigational immuno-PET tracers such as ⁸⁹Zr-atezolizumab (a PD-L1 antibody) which have been shown to predict response to corresponding therapies [53].

Integrins ($\alpha_v\beta_3$ and $\alpha_v\beta_6$)

Integrins are heterodimeric transmembrane extracellular matrix adhesion receptors that mediate critical signaling pathways in development, immune response, and cancer. Integrins can recognize the arginine-glycine-aspartic acid (RGD) motives in extracellular matrix proteins, and small conformational changes can highly modulate their binding affinity [54]. Consequently, different integrins bind selectively to certain peptides or matrix proteins but not others [55].

The integrin $\alpha_v\beta_3$ plays a significant role in regulating angiogenesis via interaction with vascular endothelial growth factor receptor (VEGFR) and blocking integrin $\alpha_v\beta_3$ with RGD cyclic peptides has been shown to inhibit neovascularization [56]. PET radiopharmaceuticals targeting integrin $\alpha_v\beta_3$ can help in patient selection and evaluation of response to anti-angiogenesis therapy in vascular cancers such as HNSCCs. Several RGD PET tracers are known to provide sufficient tumor to background contrast in HNSCCs although the degree of uptake is low and more

heterogenous compared to FDG [57, 58], reflecting variability in tumor microvascular density and activated endothelial cells [59]. ^{18}F -labeled dimeric RGD peptides such as FPPRGD2 have advantageous biodistribution characteristics [60] and may be diagnostically superior to first-generation tracers such as ^{18}F -galacto-RGD and ^{18}F -fluciclatide for imaging head and neck cancers [61]. VEGFR is a key molecular target for therapy in various malignancies and RGD PET may be helpful for predicting and monitoring treatment response to VEGF tyrosine kinase inhibitors such as pazopanib [62].

The integrin $\alpha_v\beta_6$ is overexpressed in epithelial dysplasias and multiple carcinomas including HNSCCs and plays a role in epithelial–mesenchymal transition and invasion [63]. $\alpha_v\beta_6$ binds to fibronectin and is involved in transformation growth factor- β activation. Since $\alpha_v\beta_6$ is not expressed by healthy epithelial cells, it seems to be an excellent target for diagnostic imaging and anticancer therapies. Our group and other have engineered several cystine knot and RGD peptides that bind preferentially with high affinity to $\alpha_v\beta_6$, have developed ^{64}Cu -DOTA, ^{68}Ga -NODAGA and ^{18}F -FP conjugates for PET, and have evaluated their ability to detect cancer in living systems [64, 65]. Preliminary results with ^{68}Ga -DOTA-SFLAP3 show high affinity to $\alpha_v\beta_6$ followed by rapid internalization in multiple HNSCC cell lines and moderate uptake on PET was demonstrated in a patient with HNSCC 60 min after administration in both primary lesion and nodal metastasis [66].

Fibroblast Activation Protein Inhibitors (FAPI) PET

Fibroblast activation protein (FAP) is overexpressed in cancer-associated fibroblasts of several tumor entities, including head and neck cancers [67]. In contrast to ^{18}F -FDG, no diet or fasting in preparation for the examination is necessary, and image acquisition can potentially be started a few minutes after tracer injection. Due to low physiologic uptake in oral and pharyngeal mucosa FAPI PET tracers can provide excellent tumor to background contrast [68•] and can help delineate gross tumor volumes and detect areas of involvement missed on contrast-enhanced CT for radiation therapy planning [67].

Hypoxia PET

Tumor hypoxia, a common feature of HNSCC, is a negative prognostic factor as it reduces radiation induced DNA damage and increases rate of chemoradiation therapy failure [69] but can increase efficacy of other treatments such as anti-EGFR [70] or hypoxia-activated prodrugs [71]. Nitroimidazoles such as fluoromisonidazole (FMISO)

has been extensively studied for hypoxia imaging. FMISO is a first-generation tracer which has high initial non-specific uptake due to lipophilicity followed by slow washout, requiring 2–4 h between tracer injection and scanning for adequate contrast. Dynamic PET and pharmacokinetic modeling can be used to derive a hypoxia metric that correlates better than other PET measures (e.g., SUV) with response to radiotherapy [72]. Second and third generation tracers such as ^{18}F -HX4 or FAZA offer faster clearance. ATSM compounds with copper radioisotopes (particularly Cu-64) have been shown to rapidly delineate areas of hypoxia with high specificity and have superior washout characteristics compared to nitroimidazole-based tracers such as FMISO, with no significant difference in image quality at 1 versus 16 h after injection [73] and can potentially enable development of diagnostic-therapeutic pairs [74].

Hypoxic tumor volume on pre-therapy PET is strongly associated with treatment resistance in HNSCC [75]. Nodal uptake correlates with uptake in the primary tumor and can be combined together to improve prognostication [76, 77]. Hypoxic tumor volume is associated with modulation of expression of multiple hypoxia genes in oropharyngeal SCC implicated in cell proliferation, migration, and inhibition of apoptosis [78]. Dose escalation in patients with hypoxic tumors can improve outcome without increasing toxicity [79]. PET during therapy can detect residual tumor hypoxia which is biomarker predicting emergence of resistance to radiotherapy [80].

HNSCC and Other Malignancies Arising from the Aerodigestive Tract Mucosa

Initial Workup

Staging

The tumor, node, metastasis (TNM) staging system is the basis for assessment of disease status, prognosis, and management of head and neck malignancies. Clinical staging is based on available history, physical examination, and whatever imaging is performed. Pathological TNM (pTNM) applies only if the patient undergoes surgery. Advanced imaging including PET is not mandatory and may not be ubiquitously available particularly in developing countries. However, PET should be considered in initial workup particularly in patients who present with nodal involvement, but no clinically obvious primary, patients under consideration for a surgical primary approach with tumors that approach midline, or prior to definitive radiation therapy [81].

Definitions of T and N stages vary depending on the primary site. The latest AJCC staging manual (8th edition) introduces significant modifications from 7th edition [82]. Depth of invasion which is difficult to assess on PET is now included in T-staging of oral cavity and skin cancers. T4 indicates advanced local disease and upgrades the overall staging to stage 4 except in HPV-mediated (P16+) oropharynx carcinomas. Separate staging system for P16+ cancers reflect their overall better prognosis than P16– malignancies. PET/MR or PET/CT with intravenous administration of iodinated contrast helps in evaluation for specific sites of disease involvement which might upstage a tumor.

Nodal staging is a significant prognostic factor in head and neck cancers which particularly benefits from high sensitivity of FDG PET. In the Memorial Sloan Kettering Cancer-Princess Margaret Hospital (MSKCC-PMH) institutional dataset the 5-year survival in HNSCC decreases by 20% for N1 and more than 50% for N2 disease compared to patients without nodal involvement [83]. The clinical N-category is determined based on number, size, and laterality of nodal metastases. In cancers of sinonasal or oral cavity, salivary glands, larynx, and P16(–) oropharynx or hypopharynx cancers the N-category is affected by presence of overt extra-nodal extension. Radiographic evidence can support extra-nodal extension although per se it is not sufficient to change the N-category.

Clinically N0 cancers are associated with 20–25% chance of occult lymph node metastasis in patients with de novo head and neck cancers [84, 85]. In one study, more than 20% of patients who underwent neck dissection were found to have occult contralateral nodal metastases [86]. Patient who undergo selective neck dissection for staging may require removal of a large number of nodes to yield adequate sampling [87]. PET/CT and PET/MR have excellent sensitivity compared to other imaging modalities for nodal involvement and can identify metastatic involvement in lymph nodes that are not enlarged by size criteria even though necrotic nodes and micrometastasis can lead to false negative results. Still, the recently published results of ACRIN 6685 trials confirmed the high negative predictive value of FDG PET in nodal assessment (NPV = 87%). The results of PET impacted surgical management in one in five patients [88••].

Distant metastatic involvement or a second unrelated primary malignancy are reportedly present in about 10% of HNSCC patients at initial presentation and can significantly affect management and survival [89]. Lung and bone are frequent sites of metastases and are more common than brain and liver involvement. Advanced nodal disease or recurrent HNSCC are associated with a high risk of distant metastasis [90]. FDG PET/CT is superior to other imaging strategies for detection of distant or synchronous

malignancies [89, 91] and is the preferred modality for evaluation of distant metastases in locoregionally advanced head and neck cancers (i.e., T3 or higher or nodal involvement) [81]. PET/CT and brain MRI (or alternatively PET/MR with optional chest CT) should be considered if there is concern for brain involvement (such as in neuroendocrine carcinoma, high-grade adenocarcinoma, or mucosal melanoma).

Workup of Carcinoma of Unknown Primary

The majority (90%) of cancers presenting without a clear primary site on initial workup has viral association. P16+ SCCs are staged as HPV-mediated oropharyngeal cancer, whereas EBER (Epstein–Barr encoding region)-positive cancers are staged as nasopharyngeal cancer. Lymphoma and certain other malignancies such as thyroid or salivary gland origin can also be identified based on histology. Depending on the site of primary lesion, head and neck cancers tend to involve certain nodal stations. This knowledge is helpful in guiding assessment of patients who present with lymphadenopathy without a clear primary lesion on initial physical examination. PET/CT in staging has similar or higher sensitivity compared to CT or MRI for identification of the primary tumor. The overall detection rate for PET is 25–37% which compares favorably to conventional imaging (9–23% detection rate) [92]. False negatives occur in small tumors (generally corresponding to T1 category) and PET has lower sensitivity in structures with high background physiologic activity. Dental artifact is less problematic compared to CT or MRI. However, the diagnostic utility of FDG PET falls short of the value of a positive biomarker (HPV, p16 and EBV) in FNA of metastatic lymph nodes for prognostication and guiding definitive treatment [93]. When neither imaging nor these biomarkers detect the primary malignancy, patients are considered stage III (for N1M0) or IVA–C (N2M0, N3M0, or M1).

Prognostication

Several studies have examined if pre-treatment FDG PET or interim PET during treatment could provide prognostic information in HNSCC. High uptake in lesions (SUV_{max}), volume of metabolically activity tissue (metabolic tumor volume, MTV), or a combination of the degree of uptake and tumor volume (total lesion glycolysis, TLG), and tumor heterogeneity on pre-therapy PET all negatively correlate with the outcome of patients with nasopharyngeal carcinoma although the magnitude of these effects is variable between studies [94, 95]. In locally advanced oropharyngeal cancer patients treated with definitive chemoradiation, MTV of primary tumor and lymph nodes

were found to independently predict overall survival [96]. FDG PET seems to be more prognostically informative in patient with HPV negative HNSCCs [97], although even in low-risk HPV-related oropharyngeal cancers volumetric parameters has been reported to predict the risk of locoregional failure and overall survival after definitive chemoradiation [98].

Although MTV has emerged as the most clinically relevant PET prognostic parameters in multiple studies, a standardized methodology for measuring MTV has not yet been established and validated, and its impact on management of patients remains unclear [99].

FDG and other PET tracers such as FLT have been used as early predictors of response to concurrent chemoradiation therapy. Persistent or increased FDG uptake as early as two weeks after starting induction chemotherapy indicates a high risk of failure [100, 101]. A reduction of uptake by 50% or more from baseline FDG PET appears to suggest improved progression free survival. The exact criteria for assessment of early response and incorporating early assessment in management decisions has not been established yet [102]. Preliminary results suggest that patients identified as responders on PET benefit from conservative management aimed to preserve function and can avoid extensive surgeries with adequate long-term disease control [103].

Assessment of Response to Therapy and Surveillance

FDG PET/CT is the preferred imaging modality for evaluation of patients with advanced HNSCC who undergo definitive radiation or chemoradiation therapy and is recommended to document response and assess for residual disease. Locoregional recurrence is a major factor contributing to mortality after definitive chemoradiation therapy particularly in patients with HPV-negative HNSCC. Residual cancer stem cells in hypoxic niches can lead to treatment failure, tumor recurrence, or metastases even when the tumor bulk shrinks in responds to therapy [104].

FDG PET has high sensitivity and negative predictive value for residual/refractory disease. In patients without any clinical evidence of residual disease PET should be performed 12 or more weeks (but less than 6 months) after completion of therapy to reduce uptake associated with post-radiation inflammation although it may be considered earlier if there is clinical suspicion for refractory disease, or in patients treated surgically who have not yet received radiation therapy [105]. Scans performed within 7 weeks of radiation therapy are shown to have low accuracy [106].

A recently published multicenter phase-III clinical trial has demonstrated that patients with advanced nodal disease (N2 and N3) who undergo PET-CT surveillance after

definitive radiation have similar survival but require fewer surgeries compared to patients who undergo planned neck dissection [107••]. Limiting neck dissection to PET-positive patients is highly cost-effective [108]. In another multicenter clinical trial, patient with resolution of metabolically active disease on PET 12 weeks after completion of treatment had a low likelihood of having a positive PET at 1 year or a need for therapy within 2 years after chemoradiation [109]. If there is no visually detectable residual uptake at prior tumor location above background the risk of local recurrence is very low [110]. The sensitivity of PET for subclinical residual sites of disease after chemoradiation which may harbor cancer stem cells is considerably higher than other modalities such as MRI (97% vs. 69%) although the specificity is lower (46% vs. 77%) [111].

Several visual interpretation criteria for assessment of response based on FDG uptake on post-therapy PET (Table 2) have so far been proposed, with overall similar prognostic performance [112]. Focal uptake greater than that of normal liver parenchyma is generally considered to be abnormal and suggestive of residual or recurrent malignancy [113], particularly if it corresponds to a discrete lymph node or structural abnormality [114]. Diffuse mucosal uptake or uptake in muscles is, however, a relatively common finding after radiation therapy due to inflammatory processes (Fig. 1). A few studies have reported quantitative measures to be superior to visual interpretation [109], although the difference in diagnostic performance is small and some of the measures used have not been widely available or validated outside of investigational settings and may have poor reproducibility [115].

The Neck Imaging Reporting and Data System (NI-RADS) published by the American College of Radiology is primarily a standardized radiologic reporting system developed for contrast-enhanced CT surveillance with or without FDG PET [116]. A standardized reporting system facilitates communication between radiologists and referring physicians. NI-RADS additionally incorporates specific management recommendations based on imaging finding. Assessment of FDG uptake in NI-RADS is subjective and is not covered by the standard itself. Even though this could potentially lead to confusion between of NI-RADS 2 (low suspicion) versus 3 (high suspicion), the overall score reproducibility and inter-reader agreement has been shown to be acceptable [117]. Combination of metabolic features and morphologic and structural information from contrast-enhanced CT improves accuracy and confidence in interpreting. The negative predictive values of NI-RADS 1 and 2 based on first post-therapy PET and contrast-enhanced CT are > 90% and 80–90%, respectively. In contrast, 40–60% of NI-RADS 3 patients will have recurrent disease [118–120].

Table 2 Commonly used response assessment criteria using FDG PET

Score: category	FDG uptake
Porceddu et al. [114]	
Negative	No residual FDG activity above background or diffuse uptake in the absence of a corresponding suspicious structural abnormality
Equivocal	FDG activity greater than adjacent normal tissues but below background liver activity
Positive	Focal uptake corresponding to a structural abnormality of greater intensity than background liver
Hopkins criteria [113]	
1: Complete metabolic response (CMR)	Uptake less than internal jugular vein (IJV)
2: Likely CMR	Mild uptake (> IJV but < liver)
3: Likely post-radiation inflammation	Diffuse uptake greater than IJV or liver
4: Probably persistent tumor	Moderate focal uptake (> liver)
5: Persistent tumor	Intense focal uptake (> liver)
5-Point scale (lymphoma) [121]	
1: CMR	No uptake
2: CMR	Uptake \leq mediastinal blood pool
3: Probably CMR	Uptake > mediastinal blood pool but \leq liver
4: Probably persistent disease	Moderately increased uptake compared with liver
5: Persistent disease	Intense focal uptake (> 2 \times liver) or new lesions
NI-RADS [116]	
0: Incomplete imaging	
1: No recurrence	No abnormal FDG uptake/diffuse linear mucosal enhancement after radiation
2: Low suspicion	Focal mucosal enhancement, mild to moderate mucosal FDG uptake
3: High suspicion	New or enlarging primary mass or lymph node or intense focal uptake
4: Definite recurrence	Pathologically proven or definite radiological and clinic progression

Response to Immunotherapy

PD1/PD-L1 inhibitors such as pembrolizumab or nivolumab have been shown to improve survival in patients with refractory head and neck cancers. Overexpression of PD-L1 in tumor is associated with higher likelihood of response to PD1/PD-L1 inhibitors, although PD-L1-negative patients have also been shown to respond. Immunotherapy may lose effectiveness during treatment requiring dynamic monitoring of response to therapy. Some patients experience an acceleration of tumor growth kinetics (hyperprogression) [122]. Imaging is important for monitoring therapy as well as for assessment of immune-related side effects such as pneumonitis, pancreatitis, or enterocolitis [123].

FDG PET can detect tumor response before morphological changes manifest and has high sensitivity for immune-related side effects. However, response assessment during immunotherapy can be challenging since inflammatory reaction within the lesion during the treatment can affect FDG uptake and even mimic disease progression. Pseudoprogression in HNSCC treated with

immune check point inhibitors is, however, uncommon and an increase in tumor burden on the interim PETs is associated with poor survival [124]. Patients with low disease burden on initial PET are most likely to benefit from immunotherapy.

Other Head and Neck Malignancies

Head and Neck Paragangliomas

Head and neck paragangliomas arise from the parasympathetic nervous system and chemoreceptors such as carotid body in characteristic locations including the jugular foramen, along the course of the vagus nerve, and medial aspect of the carotid bifurcation. Head and neck paragangliomas are neuroendocrine neoplasms with low malignant potential and unlike pheochromocytoma and sympathetic paragangliomas, are rarely functional. They are often discovered incidentally or due to symptoms related to mass effect, pulsatile tinnitus (glomus jugulare), or symptoms caused by involvement of cranial nerves and adjacent

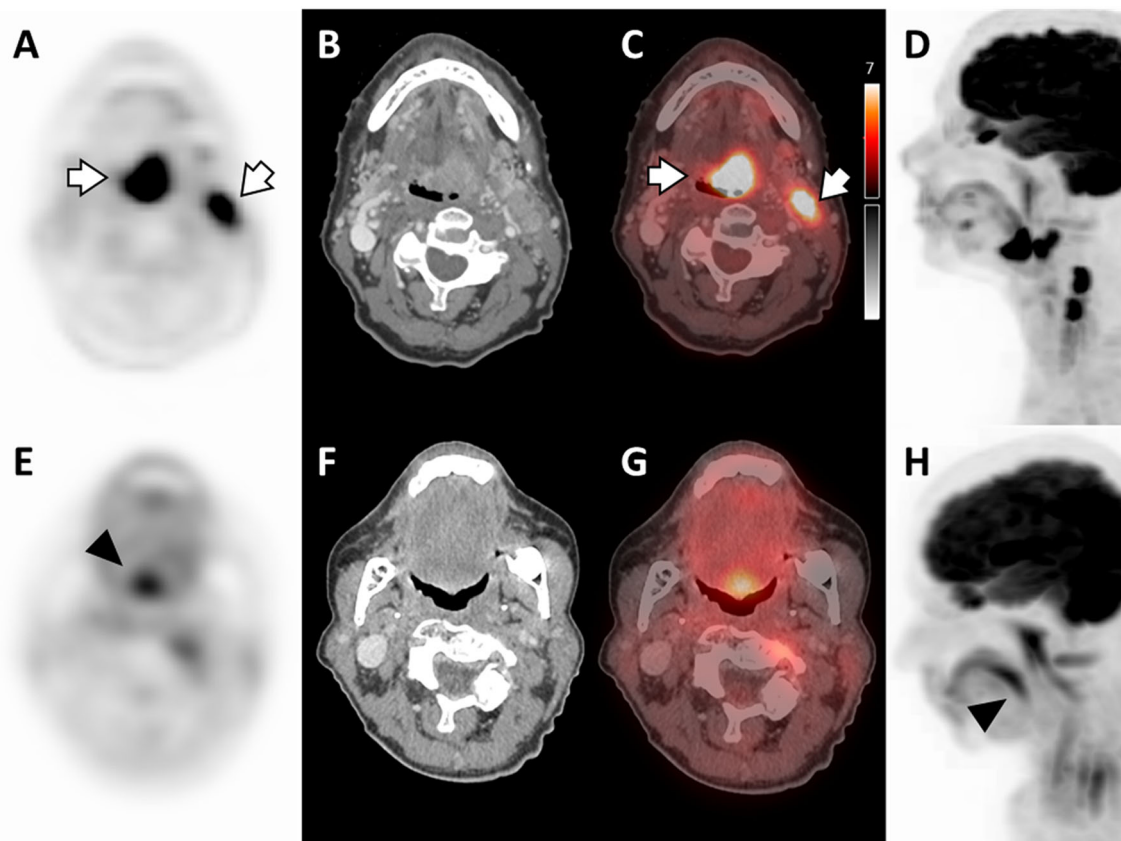


Fig. 1 Pre- and post-treatment FDG PET in a 73 years of age female with squamous cell carcinoma of the base of the tongue (clinical stage cT2N2bM0) undergoing cetuximab-based chemoradiation therapy. **a–d** Radiation therapy planning PET (**a**), CT with intravenous contrast (**b**), fused (**c**), and lateral PET maximum intensity projection (**d**). Intense uptake (arrows) is seen in left base of tongue-enhancing mass (SUV_{max} 13.9 g/mL) and multiple enlarged left upper and mid-

jugular lymph nodes (SUV_{max} 12.2 g/mL). **e–h** FDG PET 3 months after completion of therapy shows resolution of uptake in the primary lesion and lymph nodes. Moderate uptake (SUV_{max} 6.8 g/mL) is seen in the posterior tongue at midline (solid arrowhead) which appears focal on axial view, but linear on lateral maximal intensity projection (**h**). The patient remained disease free during follow-up of more than 5 years

structures. Metastases are uncommon and are typically limited to the regional lymph nodes.

Paragangliomas are highly vascular and avidly enhance on CECT or MR. Flow voids are commonly seen on T2-weighted images. Erosion of the bony cortex surrounding the jugular foramen and extension into the tympanic cavity (glomus jugulotympanicum) can be best seen on CT [125]. Most head and neck paragangliomas are not MIBG avid. In contrast, FDOPA and ⁶⁸Ga-SSA PET have both excellent sensitivity and specificity for head and neck paragangliomas (Fig. 2). FDOPA can be used as a first-line imaging tool [16•]. The combination of FDOPA and MR can be used to delineate tumors prior to treatment and results in larger gross tumor volumes compared to MR alone [126]. FDOPA PET/CT is also superior to CT or MRI in evaluation for recurrence after treatment [127].

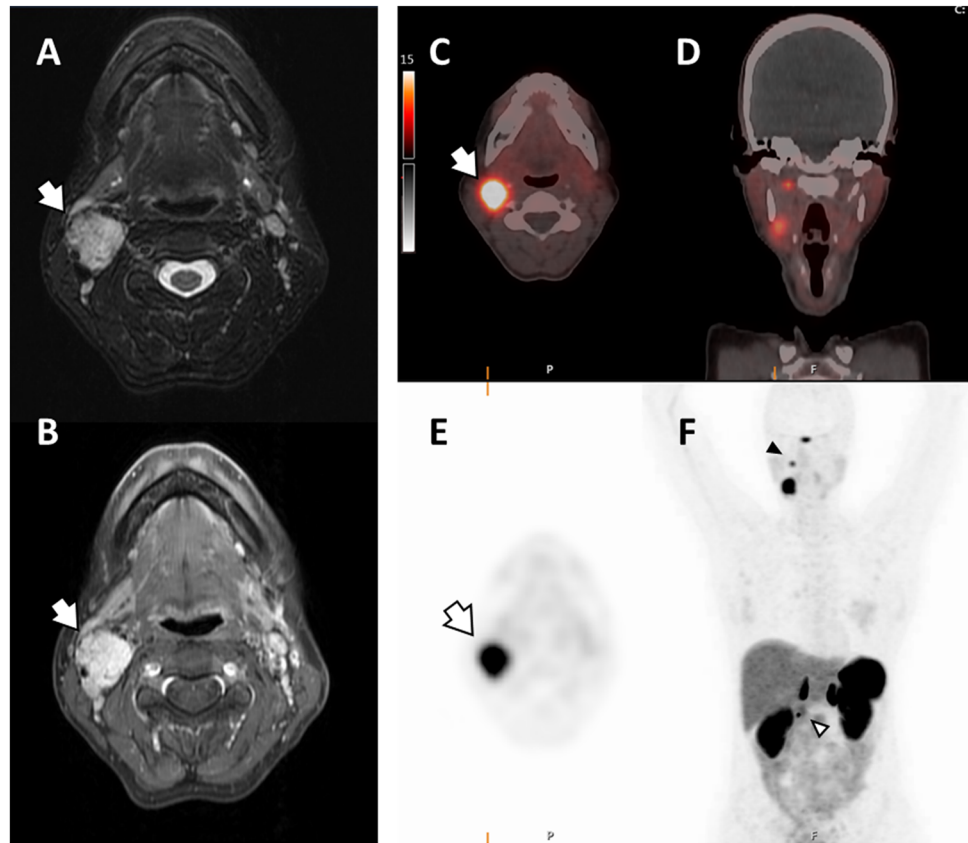
Hereditary head and neck paragangliomas are most associated with germline mutations in one of the SDH subunit genes. ⁶⁸Ga-SSA is superior to other imaging modalities for paragangliomas associated with SDH

mutation and can detect smaller lesions than FDOPA. FDG PET also has high sensitivity and can be complementary to FDOPA or CT/MRI in the localization of primary and metastatic paragangliomas associated with SDH mutation [128, 129]. Its sensitivity in areas of high physiologic uptake, however, is reduced. Of note, sporadic head and neck paragangliomas are typically not FDG avid.

Thyroid Cancer

FDG PET is useful in evaluation of non-iodine avid and aggressive histologies such as tall cell, Hurthle cell, poorly differentiated, and anaplastic thyroid carcinomas [130], as well as biochemically recurrent differentiated thyroid carcinoma with negative or equivocal radioiodine imaging [15]. FDG PET/CT is recommended for initial staging of patients with anaplastic thyroid carcinomas as well as for assessment of treatment response 3–6 months after initial therapy.

Fig. 2 A 46 years of age female with history of right carotid body tumor and family history of paraganglioma. **a** T2 and **b** Gd contrast-enhanced MRI show characteristic appearance of the right carotid body tumor. A small structure with similar signal characteristics seen anterior to the left carotid bifurcation was felt to represent a level 2A lymph node. **c–f** Ga⁶⁸-DOTATATE PET shows two SSA avid lesions in the right neck corresponding to right carotid body tumor and a smaller glomus jugulare (**f** maximum intensity projection, black arrowhead), as well as a small paraganglioma adjacent to the upper pole of the right kidney (white arrowhead). No focal uptake in the left neck is seen on PET



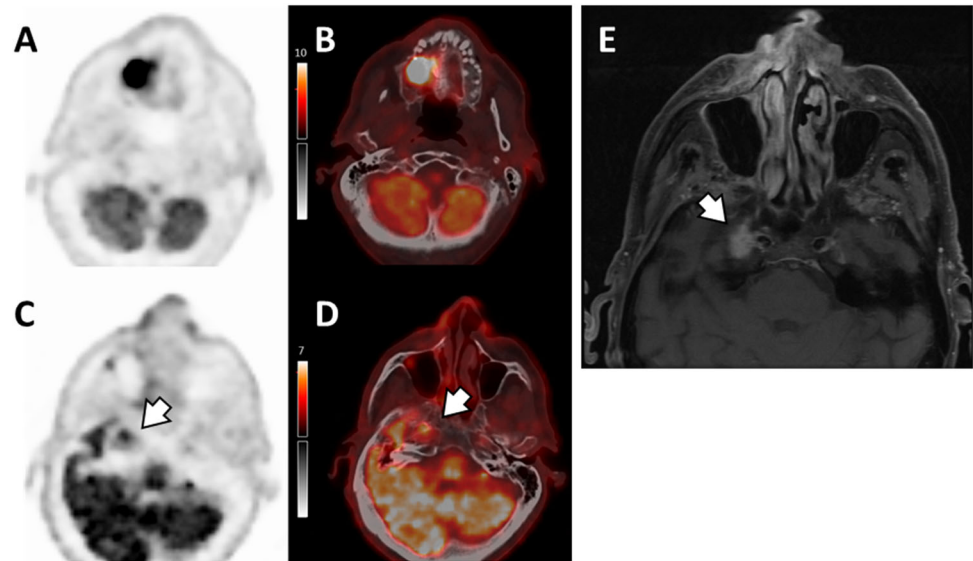
In patients with isolated increased thyroglobulin antibody levels FDG PET had high sensitivity and specificity for evaluation of recurrence [131]. Approximately one third of patients with recurrent or metastatic differentiated thyroid carcinoma develop radioiodine refractory disease. In patients with stimulated thyroglobulin levels > 10 ng/mL but negative I-123 or I-131 whole body scan, a negative FDG PET or low FDG uptake in lesions could identify patients who will likely remain responsive to radioiodine therapy and demonstrate uptake on post-therapy scans [132]. FDG PET can localize radioiodine refractory sites that are amenable to surgical management. The sensitivity of FDG PET does not appear to depend on elevated thyroid stimulating hormone. Stimulated I-124 PET is more sensitive than I-123 or I-131 scintigraphy for detection and localization of radioiodine sensitive lesions and combined with FDG PET has reported to inform and modify management in two thirds of patients with elevated thyroglobulin levels and negative whole body imaging [133]. Other imaging PET tracers for imaging differentiated thyroid carcinomas include PSMA ligands with early results suggestive of favorable diagnostic accuracy compared to FDG [134] and potential for use as theragnostic pair [135].

Focal FDG uptake within the thyroid gland is a common incidental finding and is present in 1–2% of PET studies performed for reasons unrelated to thyroid.

Hypermetabolic thyroid nodules have a high probability of malignancy: More than one third of sonographically confirmed 1 cm or larger FDG avid nodules are malignant. In patients whose prognosis or management is likely to be affected by a diagnosis of thyroid cancer or metastatic involvement of thyroid gland FNA should be considered. Active surveillance is recommended if no or subcm sonographic correlate is identified.

Medullary thyroid carcinoma arises from para-follicular thyroid C cells and can be sporadic or be a part of hereditary syndromes such as type 2 multiple endocrine neoplasia (MEN2). In MEN2, medullary thyroid cancer is often multicentric. Nodal involvement is common at presentation, particularly in advanced T-stage. The role of PET in medullary thyroid cancer is evolving [136]. FDOPA, FDG, and Ga-68-labeled SSA PET all could be useful for localization and staging and are superior to conventional imaging and scintigraphy. False negatives can occur for small lesions or in areas of high physiologic activity. NaF PET or bone scintigraphy can improve detection of osseous metastases. FDOPA has overall better accuracy and diagnostic performance compared to FDG or SSA PET [137]. FDG uptake is generally low in differentiated medullary thyroid cancer. High FDG uptake is associated with worse prognosis and may reveal dedifferentiated cancers that have low FDOPA uptake and SSTR

Fig. 3 A 79 years of age male with a history of right-sided maxillary mass was referred for further evaluation. **a** Axial PET and **b** fused images demonstrate intense uptake in a mass arising from the inferior right maxillary sinus. **c** and **d** Focal uptake can be seen in the skull base more superiorly (arrow). **e** Post-contrast T1-weighted axial MRI demonstrates perineural invasion. The pathology was consistent with diffuse large B cell lymphoma



expression. In post-operative patients the sensitivity of PET for recurrent or metastatic disease increases with elevated serum calcitonin levels (and carcinoembryonic antigen levels for FDG, 28646462, 30684230). SSA imaging is particularly useful if peptide receptor radionuclide therapy (PRRT) such as Lu177-DOTATATE is being considered [138].

Salivary Gland Neoplasms

Salivary gland neoplasms include numerous distinct histopathologic entities with widely different behavior and malignant potential. Most of the salivary gland neoplasm arise in the parotid gland. Most parotid gland neoplasms are benign, with pleomorphic adenoma being the most common neoplasm. Malignant transformation (carcinoma ex pleomorphic adenoma) is rare in parotid gland although it has been reported in a quarter of cases in minor salivary glands [139]. Papillary lymphomatous cystadenoma (Warthin's tumor) is the second most common intraparotid neoplasm, and is associated with smoking, male gender, and bilateral lesions. Both pleomorphic adenoma and Warthin's tumor can have intense FDG uptake (particularly the latter). The degree of FDG uptake does not reliably differentiate between benign versus malignant salivary gland tumors [140]. Although incidental focal uptake in the parotid gland on PET is often due to a benign etiology, in patients with head and neck malignancies or lymphoma further evaluation may be necessary to rule out intraparotid lymph node involvement.

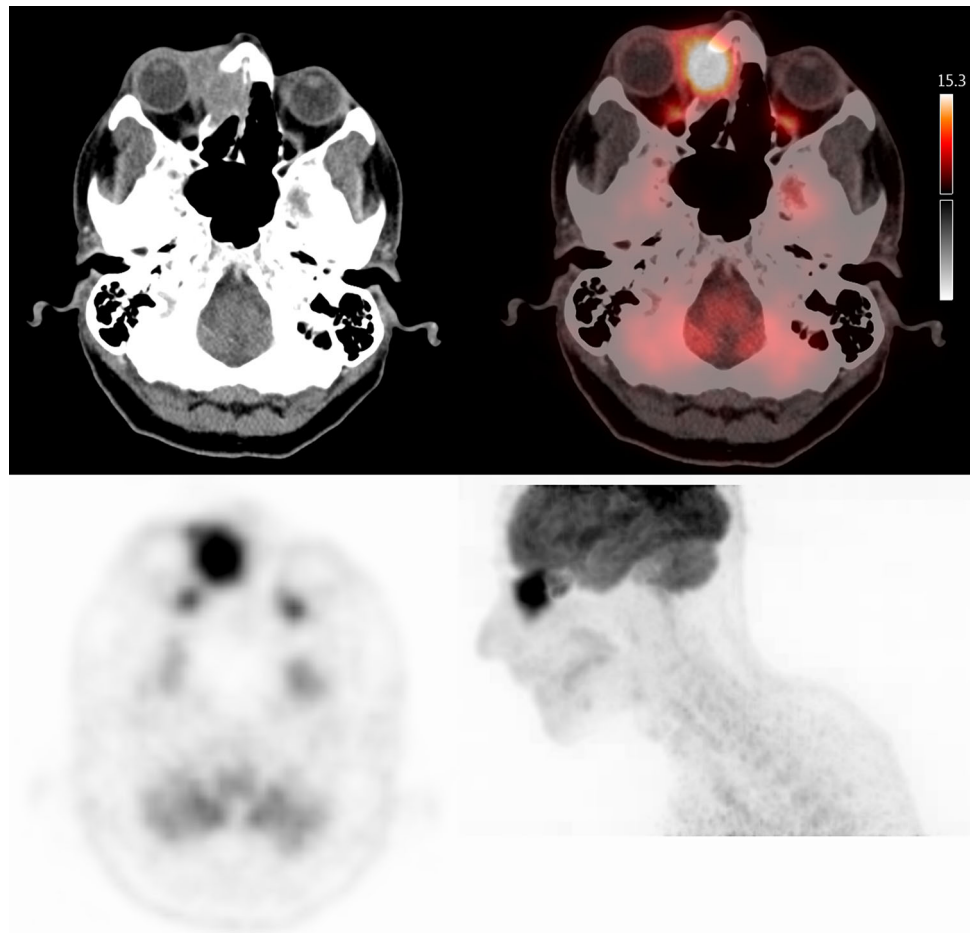
Malignant epithelial salivary gland tumors include mucoepidermoid carcinoma, adenoid cystic carcinomas, and numerous other less common histopathologic subtypes [141]. High-grade mucoepidermoid carcinomas are less

common than low-grade cancers but are associated with significantly worse prognosis. Adenoid cystic carcinomas accounts for one in three to four salivary gland malignancy, commonly arising in the minor salivary glands. They are generally more indolent than other salivary gland carcinomas but tend to have perineural invasion or hematological spread early in the course of the disease. Other epithelial cancers vary significantly in terms of behavior and aggressiveness. Oncocytic carcinoma and salivary duct carcinoma are associated with higher grade and worse prognosis than other varieties.

FDG PET is useful in staging or restaging salivary gland malignancies and has high impact on management of these cancers, although it has not yet been explicitly included in oncology guidelines [81, 142]. The incidence of occult lymph node metastasis in salivary gland carcinomas is lower than HNSCCs, and the role neck dissection is less well established. Nonetheless, in high-grade salivary gland malignancies FDG PET/CT has been shown to be more accurate than contrast-enhanced CT or MRI for evaluation of extent of disease and nodal and distant metastatic involvement [143–145]. High uptake in primary tumor and heterogeneity of uptake are reported to correlate inversely with prognosis and survival [146].

Emerging results with PSMA PET suggest high sensitivity for detection of primary and metastatic adenoid cystic carcinomas [46]. PSMA is overexpressed in more than 90% of primary tumors with uptake greater than liver considered a positive study [47].

Fig. 4 70-year-old male with a trans-spatial mass with intense uptake involving the ethmoid sinus and medial right orbit. Biopsy of the mass was consistent with NUT carcinoma



Sinonasal Tumors and Poorly Differentiated Malignancies

Various neoplasms arise from the sinonasal mucosa with somewhat characteristic degrees of uptake on FDG PET [147]. Both adenocarcinoma and undifferentiated carcinoma are associated with intense uptake [148]. Sinonasal undifferentiated carcinoma has been reported to have several folds higher uptake than olfactory neuroblastoma [149]. Uptake associated with sinonasal neuroendocrine carcinoma is typically lower than other primary sinonasal malignancies [148]. Pattern of invasion and uptake may help differentiate sinonasal small round blue cell tumors when the histopathologic diagnosis is inconclusive [150]. Perineural spread is a common feature in sinonasal adenoid cystic carcinoma although it can be seen in other malignancies (Fig. 3).

Esthesioneuroblastoma is a rare neuroectodermal tumor that can arise in adults or children. FDG PET is more sensitive than other imaging modalities for assessment of nodal involvement and has been reported to affect management of 40% of patients [151]. Nodal metastasis is associated with poor survival. Nuclear protein in testis

(NUT) is a rare aggressive squamous cell epithelial cancer that usually arises in the midline of the body (Fig. 4). NUT carcinoma typically presents in adolescence or early adulthood but can be seen later in life and is in the differential diagnosis of poorly differentiated tumor that shows abrupt areas of keratinization [152]. FDG PET has been shown to be useful for assessment of therapy [153].

Pediatric Head and Neck Malignancies

Lymphoma is the most common head and neck malignancy in children. Other commonly seen malignancies include rhabdomyosarcoma, neural tumors including primitive neuroectodermal tumors, thyroid malignancies, soft tissue sarcomas such as rhabdomyosarcoma, and nasopharyngeal carcinoma [154, 155]. Other epithelial malignancies are rare in children and much less common than salivary gland and skeletal malignancies and metastatic disease such as neuroblastomas [156].

PET/CT or PET/MR are essential in evaluation of aggressive lymphomas and can be useful for staging and monitoring therapy in other pediatric head and neck sarcomas and other malignancies [157]. With simultaneous

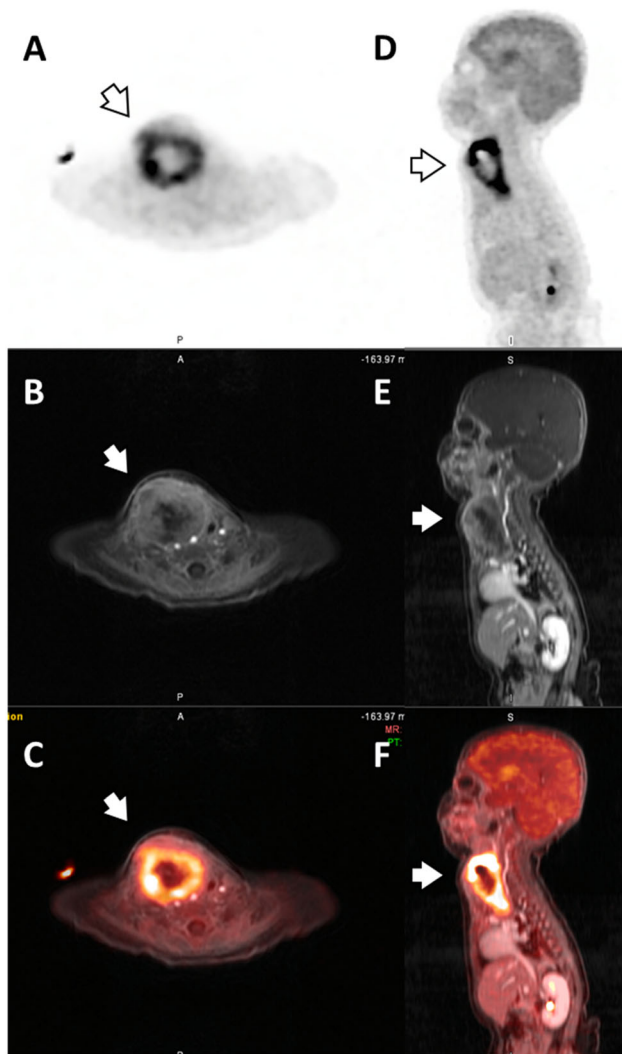


Fig. 5 A 6-month-old boy was referred for evaluation of a large neck mass. **a** FDG PET, **b** post-contrast T1-weighted axial MR, **c** fused PET/MR in axial plane show a large centrally necrotic right neck mass with intense uptake. The biopsy of the mass showed a malignant rhabdoid tumor. **d–f** Sagittal reformats

PET and MR acquisition long scan times per bed position necessary to accommodate diagnostic MRI sequences enable significant dose reduction while preserving high diagnostic PET quality (Fig. 5).

As in adults, most oncologic PETs in children are with FDG. The biodistribution of FDG in children can be different from adults. High uptake in metabolically active brown adipose tissue is more commonly than in adults, and some centers pretreat with benzodiazepines to reduce it. Intense symmetric uptake in the Waldeyer's ring and soft palate can be a normal finding. Physiologic activity in pharyngeal lymphoid tissue peaks at 6–8 years of age and diminishes during adulthood. As in adult head and neck malignancies, the degree of uptake correlates with aggressiveness and can be helpful in assessment for high-

grade transformation or for targeting biopsy in tumors with heterogenous histology such as malignant peripheral nerve sheath tumors or sarcomas. For sarcomas, we typically perform whole body PET (vertex to toes). In pediatric lymphomas, however, a skull to thigh protocol may be sufficient [158].

Neuroblastoma can arise as a neck mass in children although primary head and neck neuroblastoma is less common than metastatic craniofacial involvement [159]. While FDG PET has limited sensitivity for neuroblastoma, it provides complementary information to MIBG scintigraphy which can impact management. FDOPA and ^{68}Ga -SSAs are other PET tracers useful in evaluation of patients with neuroblastoma.

Summary

The role of PET and molecular imaging in head and neck malignancies has evolved significantly over the past decade. FDG PET/CT has since emerged as the preferred imaging modality for initial evaluation and monitoring treatment response in locally advanced or metastatic HNSCCs and other malignancies of the upper aerodigestive tract. PET/MR systems hold promise for further improving diagnostic performance in head and neck cancers and reduce radiation exposure particularly in pediatric patients. The arsenal of PET tracers for staging and delineation of tumor prior to therapy is expanding as FAPI and other radiolabeled small or large molecule tracers are being introduced. There is now extensive experience in assessment of treatment response using FDG PET with established visual interpretation criteria and inclusion of PET findings in NI-RADS. Several other PET tracers may offer better specificity in irradiated neck particularly if observant management is considered. The utility of ^{68}Ga -SSA and FDOPA in imaging paraganglioma and tumors of neuroectodermal origin has now been well recognized. Usefulness of new or other existing PET tracers such as PSMA-targeted agents in various other head and neck malignancies including thyroid and salivary gland cancers is increasingly explored and holds promise for improving diagnostic accuracy of imaging and/or providing novel radionuclide therapies for these malignancies in the upcoming years.

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Compliance with Ethical Guidelines

Conflict of interest None.

Ethical Approval Not applicable.

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- Of importance
- Of major importance

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