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Molecular Imaging of Head and Neck Cancers

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Abstract: Fluorine-18 (18F)-fluorodeoxyglucose (FDG) positron emission tomography - computed tomography (PET/CT) is an essential tool in the evaluation of head and neck cancers (HNC). 18F-FDG PET/CT can detect the primary site of malignancy in patients with cervical lymph node metastases from an unknown origin and guide treatment. Compared to traditional imaging, 18F-FDG PET/CT has higher sensitivity in detecting distant metastases and potential second primary malignancy, which significantly impacts management. 18F-FDG PET/CT also helps in evaluating recurrent or persistent disease that can be treated with salvage surgery and enables safe avoidance of planned post-radiation neck dissection with a high negative predictive value. For response evaluation, the Hopkins criteria and Neck Imaging Reporting and Data System (NI-RADS) are helpful for a standardized evaluation and recommendation. 18F-FDG PET/CT is also integrated in radiotherapy planning for accurate target delineation. PET/magnetic resonance (PET/MR) is advantageous in HNC because of high soft-tissue resolution of MR imaging and molecular information provided by the PET component. Hypoxia imaging in head and neck cancers has also been evaluated with novel molecular imaging agents. Sentinel lymph node biopsy with SPECT/CT and gamma probe guides early-stage

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HNC surgeries. This chapter highlights the role of molecular imaging in the management of HNC.

Keywords: 18F-FDG PET/CT; head and neck cancer; molecular imaging; PET/MR; sentinel lymph node biopsy

INTRODUCTION

Each year, over 66,000 people in the US and 900,000 people globally are impacted by head and neck squamous cell carcinoma. The most frequent locations for these cancers in clinical practice are the oropharynx (34%), larynx (28%), and oral cavity (18%). Squamous cell carcinoma (SCC) is the most common type of head and neck cancer, accounting for over 90% to 95% of cases (1). The survival for patients with HNC varies based on the stage of the disease, with those having localized disease having a 5-year survival rate of 85.1%, while those with distant metastatic disease having a rate of 40.1%. This significant difference in outcomes highlights the importance of early diagnosis and accurate staging. The primary risk factors for developing squamous cell carcinoma of the head and neck (HNSCC) are tobacco and/or alcohol use. The risk is higher when either of these factors is present alone but increases even more when they are present together. In recent years, human papillomavirus (HPV)-induced oropharyngeal cancers have been rising and HPV-positive head and neck cancers exhibit different tumor biology (2–4).

Various factors, such as the size of the primary tumor, number, and laterality of the affected locoregional lymph nodes, and the presence or absence of distant metastasis determine the TNM staging of HNSCC by the American Joint Committee on Cancer (AJCC). The most recent AJCC revision also includes HPV status in staging oropharyngeal cancers. Depending on the tumor stage, treatment options for HNSCC typically include radiation therapy with or without chemotherapy and surgical resection with lymph node dissection (5).

18F-FDG PET/CT is increasingly used in evaluating head and neck cancers. It has a crucial role in staging, surgical and radiotherapy planning, response assessment, prognostication, detecting second primary, detecting recurrence, and follow-up. This chapter reviews the current role of 18F-FDG PET/CT in the management of head and neck cancers. Further, it discusses the role of PET/MRI, novel molecular imaging agents, sentinel lymph node biopsy and artificial intelligence in head and neck cancers.

ROLE OF 18F-FDG PET/CT IN HEAD AND NECK CANCERS

Computed Tomography (CT) of the soft tissues in the neck or magnetic resonance (MR) imaging of the neck are recommended to outline the primary tumor. If no apparent primary tumor has been identified, it is suggested to perform 18F-FDG PET/CT before conducting further evaluation or biopsy. Moreover, the yield of endoscopy after negative PET may be low (6). For patients with extensive nodal disease or nodal involvement in the lower neck, aggressive

tumor histology, and patients receiving definitive radiation therapy, 18F-FDG PET/CT can help detect additional nodal or distant disease. For surgical planning in tumors that cross or are close to the midline, 18F-FDG PET/CT is recommended for planning surgery in the contralateral neck. 18F-FDG PET/CT is also recommended to evaluate distant metastases in locally advanced HNCs. During early follow-up, 18F-FDG PET/CT can be used instead of or in addition to anatomical imaging to assess recurrent, residual disease, or second primary malignancy for guiding treatment (7, 8).

Staging

When combined with contrast-enhanced CT, 18F-FDG PET/CT has been shown to have a sensitivity and specificity of over 90% for detecting primary tumors. However, the spatial resolution of PET may not be sufficient to detect very small lesions, especially on the surface of mucous membranes. Furthermore, necrotic primary tumors may not show significant FDG uptake above the normal background level. In such cases, contrast-enhanced PET-CT can be particularly beneficial (9–12).

MR imaging may be better for assessing specific aspects of the primary tumor, such as precise size estimation, small-volume tumors, infiltration of surrounding soft tissues, depth of invasion, perineural spread, or bone marrow involvement. However, a recent prospective study has shown that 18F-FDG PET/CT has a higher sensitivity than MR imaging in the case of small tumors (T1-T2) with good interobserver variability (12, 13). If imaging fails to reveal an obvious primary, NCCN guidelines suggest 18F-FDG PET/CT should be ordered before examination under anesthesia (EUA), biopsies, and tonsillectomy, to help identify potential primary sites before any intervention occurs (8).

For patients with multi-station or lower neck nodal involvement or high-grade tumor histology, NCCN guidelines suggest considering 18F-FDG PET/CT due to its higher sensitivity for nodal and distant metastases (Figure 1) (8). 18F-FDG PET/CT has an added benefit over clinical examination and conventional anatomic imaging in assessing lymph node metastases in HNC. 18F-FDG PET/CT is useful in evaluating clinically negative HNSCC (T2-T4) with high negative predictive value, which may lead to a change in surgical management (14). In addition, 18F-FDG PET/CT can reduce perioperative morbidity, especially since extensive neck dissections and radiation can result in higher morbidity (15). Based on improved outcomes, using 18F-FDG PET/CT is found to be cost-effective per quality-adjusted life-year (16, 17). Recent literature indicates that 18F-FDG PET/CT may have better sensitivity and specificity to detect cervical lymph node involvement than CT and MR imaging (18). Although 18F-FDG PET/CT may be considered to have low sensitivity towards micrometastasis in clinically N0 lymph nodes mostly due to resolution limitations, the results of the large prospective ACRIN 6685 trial revealed a high negative predictive value for N0 disease in T2 to T4 HNSCC (94% with SUV cut-off of 1.8) with change in surgical plans in 22% of patients (13). However, 18F-FDG PET/CT may not be able to detect necrotic cystic lymph nodes, which are more prominently visible on contrast-enhanced CT or MR imaging. In such situations, combining contrast-enhanced CT with PET can be helpful (19–22).

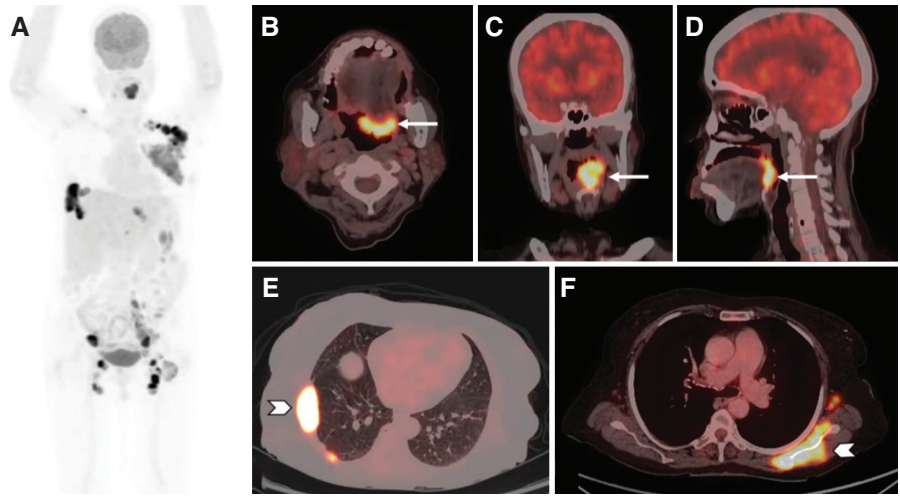

Figure 1. 18F-FDG PET/CT imaging. Baseline whole body 18F-FDG PET/CT imaging in a patient who presented with a mass at the base of tongue. Maximum intensity projection (MIP) image **(A)** and cross-sectional hybrid PET-CT images **(B – F)** reveal a metabolically active primary tumor at the base of tongue (arrows in B, C, D) and metabolically active lesions involving lymph nodes, lungs (arrowhead, E), bones (arrowhead, F), and liver suggestive of widespread metastases.

In addition to the advantages of 18F-FDG PET/CT for the locoregional disease assessment, it is also valuable to identify metastatic disease that can be often missed on traditional workup. The most common sites of metastases in head and neck cancers are the lungs, bones, and liver. The likelihood of distant metastases is associated with nodal status, advanced T-stage, poorly differentiated tumors, and older age. Additionally, HPV-negative oropharyngeal cancers are more likely to have distant metastases than HPV-positive tumors. The highest incidence of distant metastases during initial evaluation is noted in nasopharyngeal cancers (9%), followed by hypopharyngeal (7%), oropharyngeal (4%), laryngeal (3%), and oral cavity cancers (2%). In non-nasopharyngeal cancers, the overall incidence of distant metastases is about 3% (23–27). 18F-FDG PET/CT is reported to have a high sensitivity (98%) and specificity (95%) in detecting distant metastatic disease, with a low false-negative rate (3%) and a higher sensitivity than whole body 3T MR imaging (28, 29). Compared to CT alone, 18F-FDG PET/CT is more accurate in detecting unexpected metastases, especially subtle bone metastases. Incorporating 18F-FDG PET/CT into the initial assessment results in a change in the staging of the disease and therapy planning by upstaging or downstaging, leading to significant modification of treatment plans in up to 13% of patients (30–32).

For patients with locoregionally advanced cancer (e.g., T3–T4 primary or ≥N1 nodal staging), NCCN guidelines recommend 18F-FDG PET/CT to evaluate for distant disease and thoracic metastases. However, additional contrast-enhanced brain MRI may be obtained to rule out brain metastasis for cancers where this is a concern (8).

Surgical planning

For patients under consideration for a surgical primary approach, the NCCN guidelines recommend 18F-FDG PET/CT for tumors approaching the midline to determine the surgical approach to the contralateral neck (8). 18F-FDG PET/CT can assist with surgical planning in patients with head and neck squamous cell carcinoma with a known primary site. 18F-FDG PET/CT has demonstrated higher accuracy than MRI in determining tumor size and staging in patients with oral cavity SCC and dental artifacts on MRI. 18F-FDG PET/CT is also helpful in detecting mandibular invasion, with high sensitivity and specificity. It can also aid in evaluating the extent of osseous involvement, which is crucial in determining the appropriate surgical approach and reconstructive options (33).

MRI or CT may demonstrate false-negative results in patients with occult neck disease (clinically N0). Elective neck dissection is often recommended for HNSCC patients with a risk of occult metastases in their lymph node basins that is greater than 20%. Neck dissection is associated with a risk of a range of complications, such as cranial nerve damage, sensory dysfunction, shoulder dysfunction, and cervical scars (34). The potential of 18F-FDG PET/CT in clinically N0 necks as a substitute for elective neck dissection has been explored. It has shown high negative predictive value leading to a change in the surgical management plan and higher sensitivity and specificity than conventional imaging (13, 35–37).

Identifying occult lymph nodes on 18F-FDG PET/CT also results in changes to surgical planning, such as finding a suspicious lymph node on the contralateral side of the primary lesion in oral cavity SCC cases, which would mandate a bilateral neck dissection. Although a previous meta-analysis from 2012 had suggested that CT, MRI, PET, and ultrasound had the same diagnostic accuracy for detecting clinically N0 disease, recent literature suggests that 18F-FDG PET/CT is significantly more sensitive and accurate than CT/MRI imaging for detecting metastatic disease in the contralateral neck (38, 39).

18F-FDG PET/CT has also proven helpful in detecting occult retropharyngeal nodes in individuals with HPV-related oropharyngeal cancer. These nodes are typically not discovered through conventional neck dissection performed on this population, and they may lead to further treatment by radiation or chemoradiation over surgery as the primary therapy (40, 41).

The NCCN guidelines recommend that patients with stage III/IV HNSCC receive 18F-FDG PET/CT as part of their initial diagnostic workup. For patients with locally advanced disease, surgical treatment of the primary site can be extensive and require significant reconstruction. Thus, detecting distant metastases in this patient population is essential to prevent unnecessary aggressive surgical treatment (7, 42).

Second primary cancers may occur in 5% to 10% of cases of HNSCC, especially in smokers or those with HPV-negative disease (43). These secondary cancers are frequently found in the head and neck (field cancerization), esophagus, and lungs (similar risk factors). Identifying a second primary cancer is crucial for treatment planning. Before the wide availability and use of 18F-FDG PET/CT, pan-endoscopy was routinely used in newly diagnosed patients with head and neck cancer to detect second primary tumors in the head and neck region. 18F-FDG PET/CT can be used as an accurate method of screening for second primary tumors and may be able to replace the need for pan-endoscopy. In these cases, 18F-FDG PET/CT

carries a high negative predictive value and can also identify second primary cancers beyond the scope of pan-endoscopy (43, 44).

If feasible, salvage surgery is offered to patients who develop a relapse or second primary disease. However, salvage surgery may be most effective for patients with limited locoregional spread or those who can achieve negative surgical margins. Imaging is crucial in determining the extent of the disease and whether the suggested salvage surgery is feasible or appropriate. This imaging is especially important for patients who have undergone prior neck radiation or surgery, as these can complicate traditional imaging findings due to anatomical changes or chronic inflammation caused by previous treatments (44).

Detection of metastatic sites by 18F-FDG PET/CT in a patient suspected of having a recurrence or secondary malignancy renders salvage surgery unnecessary. 18F-FDG PET/CT is valuable in decision-making, and the necessity of salvage neck dissection to treat persistent disease after chemoradiation and 18F-FDG PET/CT surveillance reduces the need for salvage neck surgery without compromising survival. For detecting nodal disease within six months of treatment for head and neck cancer, 18F-FDG PET/CT has overall high sensitivity (85%) and specificity (95%) for detecting recurrent or persistent disease but relatively lower sensitivity (75%) and specificity (87%) in patients with HPV-related tumors. (45–47).

Radiotherapy planning

Using 18F-FDG PET/CT in image-guided radiation therapy ensures optimal tumor control and treatment response and minimizes radiation exposure to nearby normal tissues, especially in the neck region where vital structures like cranial nerves, blood vessels, salivary glands, and spinal cord are present. The results of 18F-FDG PET/CT can affect the size of the primary tumor and nodal disease volumes in up to 10% of patients, as well as detect additional metastatic disease or synchronous malignancies, leading to modifications in radiation treatment planning. Using 18F-FDG PET/CT for estimating nodal disease volume is more effective in achieving regional disease control and improving patient outcomes than CT nodal volume. 18F-FDG PET/CT-based intensity-modulated arc therapy has shown improved treatment efficacy, shorter delivery time, and better dose control to the surrounding normal tissues at risk compared to the more commonly used static intensity-modulated radiation therapy dose-based painting by numbers. The use of 18F-FDG PET/CT to compare images of radiation treatment planning before treatment and during follow-up is suggested to increase the accuracy of diagnosing disease recurrence versus inflammation post-radiation. The UPGRADE-RT trial is currently underway to assess the use of 18F-FDG PET/CT to guide the reduction of radiation therapy dose to small lymph nodes that do not meet size criteria assessed by 18F-FDG PET/CT in HNC patients. The aim is to evaluate the risk of disease recurrence and improve the quality of life of patients by reducing complications related to radiation on vital structures in the head and neck (30–32, 48).

A single-scan PET/CT simulator method is widely used in the United States, in which radiotherapy planning CT scan and the PET scan are acquired simultaneously while the patient is in the treatment position on a flat couch. The fusion between the CT and PET images is automatically performed based on their shared

coordinate system. This approach offers benefits such as reducing the number of patient visits and minimizing variations between the PET and radiotherapy planning CT. The use of a flat couch on PET/CT simulators is advantageous because radiotherapy is traditionally planned and delivered on a flat couch. In contrast, diagnostic PET/CT scanners usually have non-flat couches, which may pose limitations while attempting to register diagnostic PET/CT scans with radiotherapy planning CTs. Furthermore, a dedicated PET/CT simulator allows for the implementation of motion management techniques like respiratory gating during PET acquisition, enabling accurate targeting and registration in areas affected by motion. This approach allows for both PET scanning and simulation alignment, ensuring that the patient's position in the PET/CT scanner aligns with the treatment unit consistently. This integrated approach streamlines the process by conducting the CT scan and minimizing head movement during the two scans (48).

NCCN guidelines recommend 18F-FDG PET/CT for patients scheduled for a definitive radiotherapy approach due to the higher sensitivity of 18F-FDG PET/CT for identifying involved lymph nodes (8).

Treatment response assessment

Several criteria have been proposed to evaluate treatment response in patients with head and neck cancer, including NI-RADS, Hopkins, Porceddu, and Deauville. According to Hopkins criteria, scores of 1, 2, and 3 indicate no residual disease, while scores of 4 and 5 indicate its presence (Table 1). Because of its high negative predictive value, this system could help evaluate treatment response and avoid unnecessary invasive procedures. In a multicenter study called the ECLYPS study, the Hopkins criteria were used to assess treatment response in HNSCC patients who underwent primary chemoradiation. The results showed a high negative predictive value (92%), specificity (91%), and accuracy (86%). The authors also noted that the ability to detect recurrent disease decreased over time, with optimal performance at around 12 weeks after treatment completion (49). In a recent study comparing the four qualitative assessment criteria mentioned above, all had similar diagnostic performance in detecting recurrent disease in HNSCC patients treated with chemoradiation or radiation therapy alone in the primary tumor and nodal disease site. All four criteria were associated with a significant difference in progression-free and overall survival. The NI-RADS had the highest number of overall indeterminate scores, while the Hopkins criteria had the least, likely due to the more subjective nature of the NI-RADS criteria. The Deauville and Porceddu criteria showed a marginal improvement in negative predictive value while keeping the number of indeterminate scores low (48–51). We recommend modifying the Hopkins Criteria similar to NCCN modification of Deauville score (for Lymphoma) to incorporate new metastatic lesions (not previously present) and new foci not deemed to be cancer-related on response assessment scans (52). Furthermore, our group is evaluating an integrated modified Hopkins-NIRADS response assessment system to include CECT assessments when available.

18F-FDG PET/CT is important for assessing the treatment response within 6 months after completing therapy, particularly in patients treated with systemic therapy with or without radiation therapy while preserving the

TABLE 1 Hopkins criteria and NI-RADS (PET/CECT)

Hopkins Criteria	NI-RADS
5-point scoring (1-5) using 18F-FDG PET/CT	4-tier classification using cross-sectional imaging (CT or MRI) ± 18F-FDG-PET/CT
Score 1: FDG uptake Less than Internal jugular vein (IJV) blood pool *(Complete metabolic response)*	**PET/CECT surveillance**
Score 2: FDG uptake Focal uptake greater than IJV but less than liver *(Likely complete metabolic response)*	**Primary**
Score 3: Diffuse uptake greater than IJV or liver *(Likely inflammation)*	1: No evidence of recurrence: routine surveillance, CECT
Score 4: Focal uptake greater than liver *(Likely residual tumor)*	2: Questionable recurrence (ill-defined)
Score 5: Focal and intense uptake *(Residual tumor)*	a) Superficial abnormality (skin, mucosal surface, etc): direct visual inspection
	b) Deep abnormality < 1 cm with mild/intermediate FDG: short interval follow-up PET/CECT
	c) Deep abnormality > 1 cm with mild/intermediate FDG: short interval follow-up or biopsy if clinically indicated
	3: High suspicion (new discrete nodule or mass, FDG avid): biopsy if clinically needed
	4: Known recurrence- biopsy proven
	Nodes
	1: No evidence of nodal disease recurrence- routine surveillance
	2: Questionable nodal recurrence or residual nodal disease
	a) < 1.5 cm with mild/ intermediate FDG: surveillance
	b) > 1.5 cm with mild/intermediate FDG: biopsy or short interval f/u
	3: High suspicion (new, enlarging, FDG avid): biopsy if clinically needed
	4: Known recurrence: biopsy proven

affected organ. Patients who undergo surgery or chemoradiation benefit most from 18F-FDG PET/CT due to its high negative predictive value (100% for surgery and 97% for chemoradiation), which has a significant effect on clinical evaluations and can reduce the number of unnecessary diagnostic or therapeutic interventions. However, the positive predictive value and specificity are lower in patients receiving chemoradiation, possibly due to inflammation after treatment. There is higher likelihood of residual disease in more intense and focal lesions whereas diffuse and/or less intense foci tend to be inflammatory related to post therapy changes (53–55). PET-NECK was a randomized controlled trial that found that 18F-FDG PET/CT surveillance after primary chemoradiation therapy in HNSCC patients with N2 or N3 disease was associated with a reduction in neck dissections, leading to fewer surgical complications and lower treatment costs. The HPV status of the tumors did not have a significant impact on the results (45).

Occult primary detection

A precise, evidence-based algorithm is necessary to diagnose and manage occult primary cancers. These patients often undergo a range of tests, including clinical evaluation, imaging, panendoscopy, and tonsillectomy, to improve the detection rate and prognosis. The most common location of the unknown primary tumor is in the oropharynx, specifically the palatine tonsil, followed by the base of the tongue, nasopharynx, and hypopharynx (56, 57).

18F-FDG PET/CT has the added advantage of detecting occult primary tumors with a high degree of diagnostic accuracy (~89%). 18F-FDG PET/CT can identify primary tumors in about 40% of patients (54–60). Since the palatine tonsil is the most common site of occult head and neck tumors, it is crucial to assess metabolic activity in this region carefully. A cutoff ratio of 1.5 of the maximum standardized uptake value (SUVmax) between the two tonsils may detect cancers with 100% sensitivity and specificity as reported in a retrospective study with a small sample size (58–61).

Second primary malignancy detection

A study involving 248 HNC patients revealed that a second primary malignancy was detected in around 7% of cases (62). A meta-analysis of 12 studies reported a pooled sensitivity of 88% and specificity of 95% for identifying distant metastases and second primary malignancies using 18F-FDG PET/CT (63). Careful evaluation of sites with normal physiologic or benign inflammatory metabolic activity is crucial. Compared to traditional methods, 18F-FDG PET/CT also aids in reducing false-positive diagnoses. Common locations of second primary malignancies include the esophagus, stomach, thyroid, lung, colon, and breast. A second primary malignancy diagnosis is linked to poor overall survival and progression-free survival (62, 63).

Disease recurrence detection and follow-up

Most recurrences of head and neck cancer tend to occur within the first two years following the treatment. A study by Beswick and colleagues showed that 45% of asymptomatic recurrences of HNSCC were detected within the first 6 months after treatment, with 79% detected within the first year, 95% within 2 years, and all detected within 4 years. Therefore, additional imaging is more likely to yield results if conducted earlier in the post-therapy period (64).

When staging recurrent disease, before any therapy of relapsed/refractory disease for exploring distant disease or second primaries, NCCN guidelines suggest that 18F-FDG PET/CT may complement or replace other imaging modalities, which may significantly impact the choice of therapy (8).

While the initial baseline 18F-FDG PET/CT performed between 3 to 6 months after therapy is valuable, it is uncertain whether additional routine imaging benefits asymptomatic patients with negative scans. It also remains unclear whether detecting asymptomatic recurrence through routine surveillance 18F-FDG PET/CT impacts survival (65).

According to the NCCN guidelines, routine imaging is not recommended for patients with a negative 18F-FDG PET/CT at 3 months post-therapy and negative clinical examination. However, additional imaging should be

conducted for those with worrisome or ambiguous signs and symptoms. The NCCN guidelines also suggest that routine surveillance imaging may be helpful to visualize areas that are inaccessible during clinical examination, such as deep-seated or obscured anatomic locations caused by treatment-related changes. Overall, routine post-therapy surveillance imaging should be tailored to individual patients and consider factors such as tumor type, stage, prognostic factors, symptoms, and clinical assessment. Based on current evidence, NCCN guidelines have laid out post-treatment follow-up guidelines for using 18F-FDG PET/CT. It is recommended to perform 18F-FDG PET/CT within 3–6 months of definitive radiation or systemic therapy to assess response to treatment and identify residual tumor, if any. Also, early 18F-FDG PET/CT scans before 12 weeks should be avoided in the absence of signs of recurrence or progression, due to significant false-positive rates. The optimal timing of 18F-FDG PET/CT after radiotherapy appears to be at the 3- to 6-month window. A negative PET at this time point predicts improved overall survival at 2 years (8).

The NCCN guidelines for post-therapy imaging of head and neck cancers do not differentiate between HPV-positive and HPV-negative disease. 18F-FDG PET/CT surveillance at 12 weeks post-therapy has been as effective as planned neck dissection for HPV-positive and HPV-negative advanced HNSCC. However, 18F-FDG PET/CT may not perform as well in HPV-positive disease and often has inconclusive results, with several studies showing low positive predictive values (PPVs) for the baseline post-therapy 18F-FDG PET/CT in HPV-positive patients (8, 65).

Timely detection of disease recurrence is crucial for these patients and can significantly impact their outcome and survival. As previously mentioned, using 18F-FDG PET/CT can help evaluate treatment response early on during follow-up. After primary radiation therapy, the positive and negative predictive values for detecting recurrent disease are high, especially one year after treatment (100% for both). Six months after treatment, these values are slightly lower but still good (ranging from 71% to 100% and 93% to 100%, respectively). Regarding identifying primary tumor recurrence, 18F-FDG PET/CT has a similar diagnostic performance to MR imaging and is superior in detecting nodal disease recurrence. Combining 18F-FDG PET/CT and MR imaging has the best overall detection rates for locoregional disease recurrence (66).

Detecting disease recurrence in patients with HNC is crucial for planning appropriate management and improving patient outcomes. Among the various quantitative PET parameters, metabolic tumor volume (MTV) is the most informative for predicting disease progression and post-radiation locoregional disease control. 18F-FDG PET/CT can also predict disease recurrence or progression during pretreatment evaluation, aiding in treatment planning. Studies have demonstrated that MTV and total lesion glycolysis (TLG) can predict disease progression after primary surgical treatment (67, 68). In patients suspected of having recurrent disease, 18F-FDG PET/CT can detect distant disease in about 30% of patients, with the lungs and bones being the most common sites. Patients without extensive recurrent disease or distant metastases who undergo salvage surgical management have better survival outcomes than those without, underscoring the importance of accurately detecting disease recurrence and appropriate management in these patients (67, 68).

Prognosis prediction

18F-FDG PET/CT staging is more effective than traditional imaging techniques and can classify tumors as local, locally advanced, locoregional, or distant metastatic. This staging system is particularly useful for predicting disease-specific survival in HNSCC patients with recurrent cancer. In HNC, quantitative PET parameters such as MTV and TLG of the primary tumor and lymph nodes with metastases predict the prognosis. These parameters can also identify patients who may need further treatment strategies to improve outcomes and predict progressive disease in patients who underwent primary surgical management. Volumetric parameters are superior in outcome predictions than the most clinically estimated SUVmax. Patients with HNSCC who have the recurrent disease may have a lower overall survival if the recurrent tumor has intense FDG uptake (69–71).

After undergoing primary surgical management, those with persistent FDG uptake have an unfavorable prognosis. Recently, 18F-FDG PET/CT imaging of tumors has focused on tumor radiomics, particularly tumor heterogeneity and texture analysis. Texture analysis has been shown to predict treatment response in patients undergoing primary chemoradiation. In addition, preliminary findings suggest that tumors that are less heterogeneous and have focal FDG uptake are more likely to have localized disease and a better prognosis compared to those with extensive and heterogeneous disease (48, 72–74).

18F-FDG PET/CT interpretation: Pearls and pitfalls

The complex structure and functions of the head and neck make it difficult to interpret 18F-FDG PET/CT studies accurately. Additionally, there are areas in the head and neck that normally show prominent but physiologic FDG uptake. Symmetric FDG accumulation in lymphoid tissue (Waldeyer's ring) is a normal finding in younger patients. It can also be due to benign conditions such as infections and inflammation, which may be seen as focal FDG uptake and false positive interpretation. SUVmax ratio is more robust than differences in absolute SUVmax values, in a patient with biopsy proven neck nodal metastasis but unknown primary, asymmetry ratio of 1.6 is highly suspicious for malignancy (75).

Increased metabolic activity in brown adipose tissue (BAT) is seen as bilateral FDG uptake in various areas of the body, making it difficult to differentiate between physiological and pathological FDG uptake in patients with primary tumors of the head and neck or lymphoma, but CT images can aid in differentiation. Propranolol and benzodiazepines can decrease the uptake of FDG in brown adipose tissue (BAT) (75).

Talking and snoring can result in increased uptake in muscles of phonation and vocal cords. Similarly, excessive eye movements during the FDG uptake phase can increase extraocular muscle uptake. These findings may mimic malignancy but can be easily clarified on corresponding non-contrast CT images (75).

Puffed-cheek technique involves puffing the cheeks to fill the oral vestibule with air, creating negative contrast and separating the buccal and labial mucosa from the gingival mucosa, allowing for separate assessment of both mucosal surfaces. The technique provides better visualization of the buccinator muscles, pterygomandibular raphe, and retromolar trigone. The puffed-cheek technique is recommended when a tumor in the oral cavity cannot be accurately located, or its

extent demonstrated due to the apposition of the buccal and gingival mucosal surfaces or when the mucosal surfaces of the tongue and gingiva are closely apposed (76).

In open-mouth technique, the patient is instructed to open their mouth, and a device (such as a 50-mL syringe) is inserted between the teeth to ensure proper immobilization. The open-mouth technique is recommended when dental amalgam artifacts obscure a tumor in the oral cavity and oropharynx. Dental amalgam attenuates an X-ray beam, similar to lead filtration. According to the findings, an open-mouth 18F-FDG PET/CT scan may provide superior results in detecting and localizing oral cavity carcinomas compared to a conventional 18F-FDG PET/CT scan. This technique can also help evaluate the tumor's extent and detect its involvement with adjacent structures (77).

Modified Valsalva maneuver technique involves exhaling against the resistance of pursed lips or a pursed nose rather than a closed glottis. To ensure accurate results, the patient should be able to hold their breath for at least 10 seconds and receive prior training. The modified Valsalva maneuver has two main effects: opening the glottis and expanding the laryngeal vestibule and piriform sinuses. The modified Valsalva maneuver is recommended when a hypopharyngeal tumor is not accurately located or evaluated due to the mucosal surfaces being in contact during a quiet respiration exam. It may also be beneficial for examining the nasopharynx in cases where the pharyngeal recesses are compressed. (77, 78)

In Phonation, the patient is instructed to say the sound "e" uniformly for at least 10 seconds and hold their breath for the same amount of time. It is recommended that the patient undergo training prior to the examination. The scan range should be from the hyoid bone to the trachea, with a 1-mm section thickness for better spatial resolution, and acquisition should take no longer than 10 seconds to prevent motion artifacts. Phonation is used when a clear view of the true and false vocal cords is not available, and the exact location of a laryngeal tumor is unknown after a quiet respiration examination. During apnea, the true vocal cords could be pressed together and indistinguishable. However, they might be spread apart and not visible during a quiet respiration examination (78).

The modified Valsalva and phonation maneuvers are primarily employed during CT scanning. However, incorporating these techniques during hybrid PET/CT imaging is challenging since a PET scan requires at least 2 to 3 minutes for one field of view, making it extremely difficult to sustain the modified Valsalva or phonation maneuver for that duration. Consequently, motion artifacts and difficulties in aligning CT and PET images may exist. Nonetheless, when an abnormal uptake focus is detected in the hypopharynx or larynx during standard PET/CT imaging, an additional CT scan utilizing these techniques could be conducted and reviewed along with the regular whole-body 18F-FDG PET/CT scan (75, 78).

NOVEL PET MOLECULAR IMAGING AGENTS IN HEAD AND NECK CANCERS

PET molecular imaging agents other than FDG are used to evaluate tumor characteristics such as hypoxia, amino acid metabolism, and tumor proliferation,

which are different from glucose uptake and metabolism assessed by 18F-FDG. Among these, the most extensively studied agents are those specific to tumor hypoxia, such as 18F-fluoromisonidazole, 18F-fluoroazomycin arabinoside, 18F-flortanidazole, and [64Cu][Cu-diacetyl-bis(N(4)-methylthiosemicarbazone)] ([64Cu][Cu(ATSM)]). These are useful in treatment planning, as hypoxic cells are known to be radiation-resistant and are often associated with disease recurrence (79, 80). Identifying tumor foci noninvasively with these molecular imaging agents can aid in optimizing radiation treatment, leading to better tumor control and treatment response. Additionally, molecular imaging agents such as 11C-methionine and radiolabeled tyrosine have shown uptake in tumors with minimal to no uptake in inflammatory cells and normal brain tissue, making them helpful in differentiating disease recurrence from inflammation (48, 81). Agents that reflect tumor proliferation, such as 18F-fluorothymidine, can help monitor treatment response or plan optimal radiation treatment in areas of high tumor proliferation. High radiotracer uptake is generally associated with poor prognosis, which can help clinicians change treatment approaches to improve outcomes in these patients (48, 82).

PET/MR IMAGING IN HEAD AND NECK CANCER

As stated earlier, MR imaging and CT are the most commonly used head and neck imaging modalities. However, the major limitations of these techniques include accurate detection of suspected recurrence and lymph node metastases. 18F-FDG PET/CT can increase tumor recurrence detection. PET/MR imaging has the potential to provide a desired combination of molecular information and high soft tissue contrast, making it a promising modality for oncologic imaging. Literature suggests PET/MR is comparable to 18F-FDG PET/CT in its overall performance for staging and restaging head and neck cancer and in radiation therapy planning. PET/MR has benefits in the characterization and prognosis of head and neck malignancies through multiparametric imaging. Most clinical PET/MR studies currently focus on FDG imaging of squamous cell carcinoma originating from various locations in the upper aerodigestive tract. However, it is desirable to have PET/MR studies that specifically examine certain histopathological tumor types, non-epithelial malignancies (such as major salivary gland tumors), squamous cell carcinomas that arise in specific locations, and malignancies that are imaged using non-FDG molecular imaging agents. However, due to the relatively high costs of PET/MR scanners, the facility requirements, and the fact that multidisciplinary head and neck cancer treatment is mostly concentrated at academic centers, the widespread use of this imaging method beyond major hospitals is currently limited (83, 84).

For the T-staging, hybrid 18F-FDG PET/MR imaging has superior diagnostic accuracy, and for nodal (N) and metastatic (M) staging of HNC, its diagnostic accuracy is at least comparable to that of 18F-FDG PET/CT or MR imaging (85–87). In addition, the use of 18F-FDG PET/MR imaging is more precise in identifying various aspects of HNC, such as tumor infiltration boundary (T4b status), intracranial invasion, perineural infiltration, prevertebral or retropharyngeal invasion, muscular involvement (such as mandibular/medial pterygoid muscle

invasion), and bone/skull base invasion. This means that contrast-enhanced PET/MR imaging can be used as a dependable technique for determining whether HNC can be locally resected and has similar or better performance than contrast-enhanced 18F-FDG PET/CT (85–89).

The eighth edition of the AJCC Cancer Staging Manual (2018) suggests that 18F-FDG PET/MR imaging has the potential to replace the combination of contrast-enhanced MR imaging and 18F-FDG PET/CT in TNM staging of oral cavity or oropharyngeal cancers. However, hybrid 18F-FDG PET/MR imaging faces a potential challenge in evaluating lung metastases, primarily due to susceptibility and motion artifacts affecting image quality (90, 91).

Hybrid 18F-FDG PET/MR imaging has the potential to enhance the accuracy of gross tumor volume (GTV) demarcation in primary tumors and lymph nodes when devising radiation treatment plans, as it provides greater contrast in soft tissue. However, more extensive research with more patients is required to verify these findings and develop a standardized approach. Multiparametric hybrid 18F-FDG PET/MR imaging has potential applications in assessing therapeutic response and predicting treatment outcomes in HNC patients who have undergone chemotherapy, radiotherapy, or surgery. Several studies have shown that combining PET/MR imaging metabolo-volumetric parameters with tumor cellularity (e.g., MTV/ADC and TLG/ADC) can independently predict treatment failure in surgically resected HNC patients. Furthermore, combining pretreatment SUVmax and ADC can help stratify HNC patients according to their risk level, as high SUVmax and ADC levels are associated with poor clinical outcomes. Although hybrid 18F-FDG PET/MR imaging has numerous potential benefits, its adoption in clinical settings can be challenging due to limited scanner availability, reimbursement concerns, lack of standardized protocols, longer scan times, and a scarcity of radiologists who can interpret PET/MR images. Furthermore, there is inadequate information on the relative effectiveness and cost-effectiveness of 18F-FDG PET/MR imaging compared to 18F-FDG PET/CT or MR imaging alone in patients with HNC. It is uncertain whether regular use of PET/MR imaging can significantly enhance patient outcomes and survival. These concerns require further research (92–94).

SENTINEL LYMPH NODE BIOPSY (SNLB) IN HEAD AND NECK CANCERS

SLNB is a useful surgical technique for managing early-stage head and neck cancers, especially for oral and oropharyngeal squamous cell carcinoma. SLNB procedures can potentially spare a significant proportion (60%–70%) of eligible patients with head and neck cancer from elective lymph node dissection and the associated morbidity if the SLNB results indicate that their lymph nodes are negative for the disease. The techniques utilized for SLNB in head and neck cancers involve the peritumoral and preoperative injection of radiolabeled colloid particles or tilmanocept, and preoperative planar imaging and single photon emission computed tomography-CT (SPECT-CT) are performed after that. Due to the proximity of lymph nodes to tumors in the head and neck, SPECT-CT is often preferred over planar imaging to enable better definition and localization of lymph

nodes relative to anatomical landmarks. SPECT-CT is also beneficial in reducing the obscuring of nodes due to the activity of an injection site close to the tumor. The gamma probe-guided neck dissection is performed during surgery, and it typically involves the use of images and multimodality correlated images that were obtained during preoperative imaging. Sentinel node biopsy has several benefits. It reduces morbidity by limiting lymph node dissection, especially in patients without metastatic spread in their lymph nodes. It can also detect micrometastases and provide more precise staging and prognosis. As more clinical studies and trials are conducted, additional data will emerge to clarify the strengths and limitations of SLNB (95–96).

ARTIFICIAL INTELLIGENCE IN HEAD AND NECK CANCERS

PET imaging-based machine learning models can potentially assist in predicting treatment response, prognosticating outcomes, and forecasting tumor markers in head and neck cancers. Furthermore, these models may aid radiation therapy simulation by segmenting gross tumor and lymph node volumes. However, various obstacles must be resolved before implementing artificial intelligence models in head and neck cancer imaging. The biggest challenge in utilizing AI models for meaningful training, validation, and testing results is the insufficiency of extensive datasets. Most research studies have been conducted on limited datasets, posing a significant obstacle in drawing significant conclusions. The heterogeneity of medical imaging data poses a significant obstacle for AI models. If trained with a specific patient population or imaging environment, these models are prone to overfitting and lack generalizability. Consequently, before implementing AI models, they must be evaluated, tuned, or retrained based on the local setting. Expertise and a significant investment of time are necessary for medical imaging annotations. Moreover, data labeled solely based on the opinion of a single radiologist can be vulnerable to systematic bias (97–100).

CONCLUSION

18F-FDG PET/CT plays a vital role at various time points in the workup and management of head and neck cancers including staging, treatment planning, second primary detection, response evaluation, prognostication, and detection of recurrence. Sound understanding of variants, potential pitfalls, and timing of 18F-FDG PET/CT imaging after therapy is fundamental for accurate interpretation. PET-based response assessment criteria provide a more objective approach for further treatment planning and offer high negative predictive value. PET/MR imaging has unique advantages in HNC due to its high soft tissue contrast and the molecular information which is helpful in head and neck imaging. It is often challenging due to its complex anatomy which may be further complicated after surgery and radiation therapy. Newer molecular imaging agents for hypoxia imaging are promising in HNC as they help in prognostication.

Conflict of Interest: The authors declare that they have no potential conflict of interest with respect to the research, authorship, and/or publication of this chapter.

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