Introduction

Head and neck carcinomas are considered one of the most commonly carcinomas worldwide that affect significant numbers of patients every year.

Molecular imaging technique with Whole body 18F-FDG using PET/CT has proved its value in head and neck tumors particularly with regard to initial staging, monitoring of response to therapy, long-term cancer surveillance, and detecting synchronous aero digestive tumors, especially in patients with locally advanced disease. Furthermore, it plays a major role in patients with occult primary head and neck tumors, as it compliments other imaging techniques in this group of patients.[1-3]

Generally, PET/CT imaging with 18F-FDG has a number of advantages compared with the other conventional imaging modalities namely, CT and MRI due to its inherent feature being a whole body technique; it can detect metastases in unexpected locations such as the mediastinum and axilla.

On the other hand, it detects small lesions that are easily missed by conventional imaging, such as small bone...
metastases, which can be missed on chest, abdominal CT and bone scan.[6,7]

In this review article, we will describe in details the role of whole body FDG PET/CT in initial staging and restaging of head and neck malignancies with special focus on its role in therapy response assessment.

Additionally, to accurately interpret 18F-FDG PET/CT findings one must be familiar with the normal physiologic distribution of the tracer, frequently encountered physiologic variants, and benign pathologic causes of 18F-FDG uptake that can be confused with a malignant neoplasm. Therefore, a special section was devoted in the beginning of the review to describe this entity in details and to focus on its limitations and pitfalls.

## Incidence, Histopathologic Classification, and Staging Considerations

Head and neck (HN) cancer usually implies a collection of predominantly squamous cell carcinomas (SCCs) that arise from different HN sites [Table 1].[1]

SCCs account for 90%–95% of oral cavity and laryngeal tumors. Other less frequent tumors would include adenocarcinomas, adenoid cystic carcinomas, and mucoepidermoid carcinomas. In addition, melanoma, lymphoma, and leukemia might involve upper aerodigestive tract.

In the United States, the annual incidence of such variety of cancer diseases is approximately 48,010 per year.[2]

Males are significantly affected more than females, and both incidence and mortality are higher in African-American men.

The criteria for the T classification as established by the American Joint Committee on Cancer for the primary tumor are mainly related to the site, i.e., site specific. Nevertheless, it takes into consideration the size of tumor with increasing the size from T1 to T3.

T4 lesion is further divided into T4a for operable diseases with invasion of the muscle, bone, cartilage, or vessels; while T4b disease is specific for inoperable diseases.

N-staging has a special importance since it has been correlated with the patient’s prognosis.

Distant metastasis (M stage) is also an essential component of the TNM classification; HN most commonly metastasizes to lungs, liver, and bone in the same order of frequency.

## Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography Imaging Technique

Dual-modality imaging has been performed with the hybrid modality positron emission tomography/computed tomography (PET/CT) system for the past 8 years. The system is based on two components: a multislice CT scanner and a full-ring PET tomography.

Our PET/CT system has an axial field of view of 60 cm per bed position and an in-plane spatial resolution of 7 mm. The system acquires the CT first, followed by PET. After examination, CT and PET data sets can be viewed separately or in infused mode on a commercially available computer workstation. All patients were instructed to fast for a minimum of 6 h prior to the examination.

In all patients, 330 MBq of fluorodeoxyglucose (FDG) has been administered 60–90 min prior to the PET/CT examination. Blood sugar should be measured prior to FDG injection and must be within normal range.

Acquisition of whole-body PET/CT with a field of view from the skull to the upper thighs has been acquired. Data are acquired in a caudocranial direction with the patient in the supine position using a standardized breathing protocol; each bed position is 16 cm long and the table moves 15 cm following acquisition of data at each bed position, there is approximately 1 cm overlap between table stations. Image acquisition is performed with 110 mAs, 120 kV, 3.75 mm slice thickness and a 2.4 mm incremental reconstruction. PET data were acquired with the same field of view as CT (base of skull to mid-thigh).

To ensure that high-level 1 nodes are not missed and to avoid artifacts, the standard recommendation is for vertex of skull to thigh imaging with arms down and the patient being silent between injection of FDG and scan.
Acquisition time of PET is adapted in both parts according to the patient’s weight: 4 min per bed position for patients weighing up to 90 kg, 5 min for those weighing over 90 kg.

**Normal Physiological Distribution of Fluorodeoxyglucose, Pitfalls, and Limitations of Fluorodeoxyglucose-Positron Emission Tomography in Evaluating Carcinoma of the Head and Neck**

Brain cortex generally has an intense uptake because glucose is the only source of energy in the brain. 18F-FDG accumulation in the brain is fairly constant and consistent as the brain is known to account for as much as 20% of the total body glucose metabolism in the fasting state.

Low-to-moderate 18F-FDG uptake occurs in the tonsils and at the base of the tongue because of physiologic activity associated with the lymphatic tissue in Waldeyer’s ring [Figure 1].

A moderate amount of uptake can be seen in the anterior part of the floor of the mouth due to the genioglossus muscle, which prevents the tongue from falling back in supine patients.

If a patient grinds the teeth or chews, the muscles of mastication may appear very prominent. Excessive talking after injection can cause prominent 18F-FDG uptake within the larynx. The laryngeal uptake is normally very subtle, appearing in the form of an inverted V shape. Focal unilateral uptake within the larynx could be due to muscle overuse as in the case of contralateral vocal cord paralysis [Figure 2].

The presence of 18F-FDG uptake is highly variable (mild or intense) in the salivary glands, including the parotid, submandibular, and sublingual glands. Salivary gland uptake may be symmetric or asymmetric.

Asymmetry in the salivary glands could be positional or could be due to surgical or postradiation therapy inflammatory-induced changes. Radiotherapy can decrease the uptake on the irradiated side.

The extraocular muscles, muscles of the oral cavity, and laryngeal muscles accumulate 18F-FDG with varying degrees.

Usually, the thyroid uptake is negligible; ranging from no accumulation to mild uptake. Incidental increased 18F-FDG uptake in the thyroid can be seen in about 2% of scans. Such uptake could be diffuse as in thyroiditis or Graves’ disease. Focal uptake can occur with autonomously functioning thyroid nodules and thyroid malignancies. Patients with focal uptake in the region of the thyroid should be further evaluated because of a higher risk of the finding being associated with malignancy.

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**Figure 1:** Normal lingual tonsil fluorodeoxyglucose uptake (Panel a/dashed arrow) compared to abnormal retropharyngeal metastatic lymphadenopathy (flat arrow) in a 61-year-old female with a history of nasopharyngeal carcinoma. Note the retropharyngeal nodes in Panel b with central necrosis (yellow arrow).

**Figure 2:** 26 year old male with Hodgkin’s lymphoma involving the mediastinum (panel A) affecting mostly the left phrenic nerve with subsequent left vocal cord paralysis. The unilateral right vocal cord uptake is related to the physiological overuse (panel B).
Muscle uptake is typically symmetric, mild-to-moderate linear activity. However, occasionally, the uptake can be focal and unilateral, which could create a diagnostic challenge, especially in HN cancer and lymphoma. Similarly, the use of insulin to adjust the serum glucose level immediately before injection of 18F-FDG can result in 18F-FDG accumulation in skeletal muscle. Benzodiazeptines may be used to decrease paraspinal and posterior cervical muscle uptake in tense patients.

In addition to the muscles, increased 18F-FDG uptake can be seen in the adipose tissue of the neck, supravacuicular regions, around the large vessels in the mediastinum, the axillae, the perinephric regions, and in the intercostal spaces along the thoracic spine in 3.7% of patients undergoing 18F-FDG PET, constituting a potential source of false-positive PET.³⁰

Uptake in the neck adipose tissue is typically bilateral and symmetric, intense, and more often multifocal than linear.¹⁰

One must be familiar with PET/CT limitations; for example, small metastatic nodes, nodes with central necrosis may not always show significant FDG uptake. On the other hand, benign FDG uptake within reactive nodes can cause an interpretation difficulty.

Furthermore, false-positive findings are common, and one must be familiar with the normal physiologic distribution of the tracer, frequently encountered physiologic variants, and benign pathologic causes of 18F-FDG uptake that can be confused with a malignant neoplasm of the HN.

Role of Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography in the Initial Staging, Restaging, and Assessment of Response to Therapy

Initial staging
The Center for Medicare and Medicaid services has approved the utilization of PET/CT for both initial staging and restaging of HN tumors after treatment. Integrated PET/CT now appears to be superior to PET alone, CT, and magnetic resonance imaging (MRI) in identifying the primary tumors. The only limitations arise from tiny in situ tumors that might lead to false-negative results.¹⁰

Metallic beam-hardening artifacts produced by dental amalgam have significantly contributed to lower sensitivity of the enhanced CT in detecting the primary oral cavity and oropharyngeal tumors which are not the case with FDG PET/CT. However, when the question of local invasion and relationship to vascular structures comes into play, enhanced CT and MRI would have better assessment capabilities, but the increasingly use of enhanced PET/CT protocols in such clinical situation appears to have equivalent if not superiority (author’s own experience); literatures are in the stage of development.

There is sufficient evidence indicating an important role for PET/CT in detecting occult primary HN tumors, its sensitivity ranges from 15% to 73% but it is still not sufficiently accurate to replace pan-endoscopy.¹¹,¹² However, one would be cautious in dealing with nodal micrometastases in clinically N0 patients (cN0) since it remains a source of concern for all imaging techniques, including PET/CT that does not have enough sensitivity to replace neck dissection.¹¹,¹²

A prospective report by Schöder et al. of 31 patients with stage N0 disease showed that 18F-FDG PET/CT failed to detect minimally involved (≤3 mm) lymph nodes in three patients and yielded false-positive findings in four patients.¹³ Limited spatial resolution and performance in detecting lesions of <~5 mm leads to false-negative results while the nonspecific localization of FDG within the lymphoid tissues with follicular and parafollicular hyperplasia was the main culprit behind the false-positive findings.

With regard to regional nodal metastases, many studies have shown that PET/CT is superior to CT in the nodal staging of HN cancer [Figure 3].

More recently, Rodrigues et al.¹⁴ reported the sensitivity and specificity of 70% and 82% for WB PET/CT, 91% and 71% for HN PET/CT, and 57% and 88% for contrast-enhanced CT, where CT portion of the HN PET/CT protocol was performed according to an HN soft-tissue protocol, using an intravenous bolus of 100 mL iohexol (Omnipaque™ 300; GE Healthcare) iodinated contrast 1 min before the CT acquisition, PET acquisition time was 150 min in this study.

PET had more impact on management by detecting distant metastases that are related to the whole-body imaging capabilities of PET and its sensitivity to detect lesions that may be overlooked by the conventional imaging modalities, such as subtle bone metastases that may not be detectable on a routine CT or bone scans.¹⁵,¹⁶

The incidence of unsuspected metastatic disease detected by PET/CT in this population is in the range of 7%–15%¹⁷ while the detection of synchronous unsuspected primary tumors was reported in the range of 4%–8% [Figure 4].¹⁸,²⁰,²²
The overall change in the management based on FDG PET findings was observed in up to 31% of the cases, and in a more recent prospective multicenter trial, it has been observed in 13.7% of the cases; the change in management is often due to incidental findings unrelated to the primary HN tumor.

**Detection of unknown primary**

FDG PET/CT plays an important role in the assessment of unknown primary tumors as it can guide clinicians to biopsy the suspicious sites, however, it does not have sufficient sensitivity and positive predictive value (PPV) to eliminate the need for a careful panendoscopy with directed biopsies and tonsillectomy.

In a meta-analysis by Dong et al., the pooled sensitivity of FDG PET/CT across eight studies was 18% and the specificity was 83% in detecting unknown primary tumors of the HN. FDG PET detected 29% of tumors that were not apparent after workup with clinical examination and conventional imaging modalities [Figure 5].
Restaging/disease recurrence detection

Recently, Abgral et al.\textsuperscript{[26]} in a series of 91 patients with HNSCC who have finished their initial therapy reported a sensitivity and specificity of 18F-FDG PET/CT of 100\% (30/30) and 85\% (52/61), respectively. The PPV was 77\% (30/39). The negative predictive value (NPV) was 100\% (52/52). The overall accuracy was 90\% (82/91). Similarly, in a larger series of 108 patients, PET/CT detected local-regional persistent or recurrent HNSCC with a sensitivity of 82\%, a specificity of 92\%, a PPV of 64\%, a NPV of 97\%, and an overall accuracy of 90\%\textsuperscript{[27]}.

A high sensitivity and specificity were also reported by Wong et al.\textsuperscript{[28]} in a series of 143 patients with previously treated HNSCC, the sensitivity and specificity of PET for detecting recurrence overall were 96\% and 72\%, respectively. Similar to other published reports, PET was highly sensitive and specific at regional and distant sites, while at local sites, sensitivity was still high, but specificity was lower because of false-positive findings [Figure 6].

It is worth mentioning that early detection of recurrent HNSCC is critically important for achieving successful surgical salvage; patients with recurrent, early-stage HNSCC who undergo salvage surgery have a 70\% 2-year relapse-free survival (RFS), whereas those with recurrent, advanced stage HNSCC undergoing surgical salvage have just a 22\% 2-year RFS.\textsuperscript{[29]}

Assessment of therapy response

Radiotherapy and surgical intervention are associated with inflammatory-induced process that triggers the migration of lymphoid cells to the site of the inflammation. Conventional modalities such as CT...
and MRI cannot differentiate between viable tumor tissues and postsurgical or radiotherapy-induced inflammatory process. Similarly, FDG nonspecific increased uptake can occur in lymphoid tissue, salivary glands, muscles, and soft tissue, usually as a result of posttreatment inflammation. Therefore, it is wise to wait for 10–12 weeks’ postradiation therapy prior evaluating the response by PET/CT to avoid the confounding inflammatory-induced nonspecific uptake that might lead to false-positive findings.

Goerres et al. reported a high sensitivity and specificity for residual disease of 90.9% and 93%, respectively. They studied 26 patients with advanced HN cancer who have received concomitant chemoradiotherapy. PET findings were compared with the histopathology of PET-positive cases and clinical follow-up for 6 months in PET-negative patients.

In a larger group of patients, Ong et al. studied 65 patients by FDG PET/CT (84 hemi necks) 8 weeks’ postconcurrent chemoradiotherapy. The standard of reference consisted of histopathology of neck dissection specimens or clinical and imaging follow-up. Their reported sensitivity and specificity were 71% and 89%, respectively, while the PPV and NPV were 38% and 97%, respectively. Interestingly, the false-positive nodal uptake was related to either inflammation or granulomatous diseases, which are known causes of increased 18F-FDG uptake in lymph nodes.

Similarly, Yao et al. in 53 patients (70 hemi necks) who were imaged with PET or PET/CT 15 weeks’ posttherapy and using neck dissection or clinical follow-up as the standard of reference reported their reported sensitivity, specificity, PPV, and NPV as 100%, 94%, 43%, and 100%, respectively.

One can conclude from the published data that a negative PET/CT 2–3 months after radiotherapy is good enough in excluding any residual disease; while a positive PET/CT would necessitate further clinical evaluation and sometimes imaging-guided biopsy to exclude the presence of residual disease [Figure 7].

Future Directions

New tracers to image-specific molecular target

Two PET radiotracers might have potential in HN applications in the future; the first of which is thymidine analog 3'-deoxy-3'-18F-fluorothymidine (18F-FLT). It is mainly used for the visualization of proliferating tumor cells. Once crossed the cell membrane by a special transporter (membranous human nucleoside transporter 1), 18F-FLT will go through phosphorylation process by the cytosolic thymidine kinase 1 (TK-1) enzyme and will be intracellularly trapped. Since TK activity is a reflection of cellular proliferation, FLT uptake should correlate with tumor proliferation rate.

FLT uptake has been shown in different tumor types of HN cancer, specifically the larynx and oral cavity malignancy and nonsmall cell lung cancer.

The utilization of FLT postchemoradiotherapy to measure the actual remaining proliferating volume of the tumor is an advantage over FDG that might give false-positive reading in these circumstances due to the inflammatory-induced process by the therapy. Furthermore, the changes in the 18F-FLT PET signal during therapy in patients with HN carcinomas of the HN treated with radiotherapy alone or with concomitant chemotherapy might serve as a marker for the residual proliferative portion of the tumor that might help in tailoring delivered treatment.

The second potentially promising PET tracer is PET hypoxia imaging tracer, for example, 18F-fluoromisonidazole. It
is a nitroimidazole PET tracer that is reduced and bound to cell constituents under hypoxic conditions.[37]

Hypoxic regions within the tumor mass are usually radioresistant; therefore, noninvasive imaging using PET can provide a spatial map of the intratumoral distribution of hypoxia before and during treatment. Such information can be used to optimize radiotherapy planning.[37-39]

**Delineation of radiotherapy target volume**

There is growing interest in utilizing FDG PET for growth target volume (GTV) delineation during radiotherapy planning. 18F-FDG PET has the potential to identify tumor areas or lymph nodes missed by CT or MRI and identify parts of the GTV potentially requiring an additional radiation dose.[38]

Daisne et al.[40] in a well-designed study have investigated the role of co-registered CT, MRI, and 18F-FDG PET in GTV delineation of patients undergoing laryngectomy. Compared with the reference surgical specimen, 18F-FDG PET came closest to depicting the true tumor volume. All modalities overestimated the extent of the tumor, 18F-FDG PET by an average of 29%, CT by 65%, and MRI by 89%. However, no modality managed to depict superficial tumor extension.

Nevertheless, the use of FDG PET in this regard is still under development to overcome the known limited spatial and temporal resolution and to standardize a reproducible method for signal segmentation/target tumor volume delineation.

Furthermore, integrated PET/MRI imaging has the potential of improving radiotherapy planning / GTV delineation particularly with regard to oropharyngeal and oral cavity tumors.[41]

**Conclusion**

FDG PET/CT has proved its usefulness in the management of HN malignancy, particularly with regard to the initial assessment of regional nodal metastases (N status), detection of distant metastases (M status), identification of an unknown primary, and detection of synchronous primary tumor.

In addition, it plays also an important role in monitoring the response to therapy and long-term surveillance.

The introduction of new PET tracers to image specific molecular and biological markers such as tissue hypoxia and tumor proliferative index will impact on the success of individualized radiation and chemotherapy.

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**Conflicts of interest**

There are no conflicts of interest.

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