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Review article

Role of Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography in the Evaluation of Head and Neck Carcinoma

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Abstract

Fluorodeoxyglucose (FDG)-positron emission tomography-computed tomography (PET-CT) has been playing a pivotal role in tumor imaging for the past 20 years. Head and neck (HN) cancers are a good example that can illustrate such unique role of FDG imaging contributing to the patient's management. In this review article, we will describe the normal physiological distribution of FDG within HN structures focusing on its limitations and pitfalls. In addition, we will be also describing its role in the initial staging and restaging of the disease, particularly with regard to therapy response assessment. Furthermore, its role in the evaluation of patients with malignant cervical adenopathy from an unknown primary will be described. In 2016, the Royal College of Radiologists in its third edition published evidence-based guidelines for PET-CT use in HN cancer emphasizing its rule in all these clinical scenarios that are being described in this review. Finally, we will be highlighting future directions in the field of molecular imaging of HN tumors with a special emphasis on the new PET tracers.

Keywords: Assessment of response to therapy, fluorodeoxyglucose-positron emission tomography/computed tomography, head and neck cancer, initial staging, restaging

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.[1-5]

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

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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.

Table 1: Distribution of head and neck cancers

Primary tumor	Most common site	Relative occurrence (%)
Lip[a]	Low lip (90%)	15
Oral cavity[a]	Tongue (lateral border)	20
Oropharynx[a]	Tonsillar region	10
Hypopharynx[a]	Pyriform sinus	5
Larynx[a]	True vocal cord	25
Nasopharynx[a]	Roof	3
Nasal cavity and sinuses	Maxillary antrum	4
Salivary gland	Parotid (80%)	15

Adapted from Casciato "Manual of Clinical Oncology." [a]At least 97% are squamous cell carcinomas

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].[3]

The presence of 18F-FDG uptake is highly variable (mild or intense) in the salivary glands, including the parotid, submandibular, and sublingual glands.[3-5] 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.[6] 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.[7]

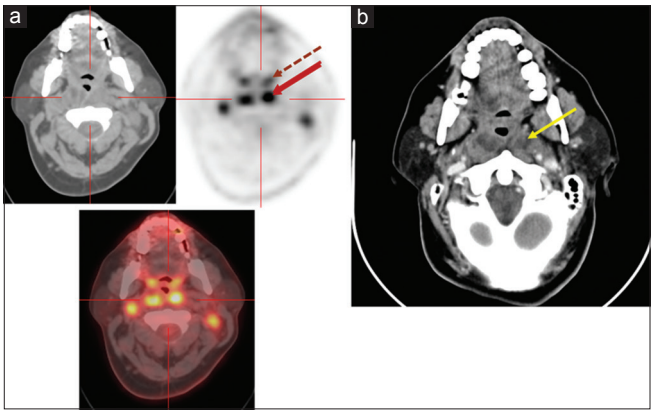

Figure 1: Normal lingual tonsil fluorodeoxyglucose uptake (Panel a/dashed arrow) compared to abnormal retropharyngeal metastatic lymphadenopathy (flat arrow) in a 61-year-old female with a history of nasopharyngeal carcinoma. Note the retropharyngeal nodes in Panel b with central necrosis (yellow arrow)

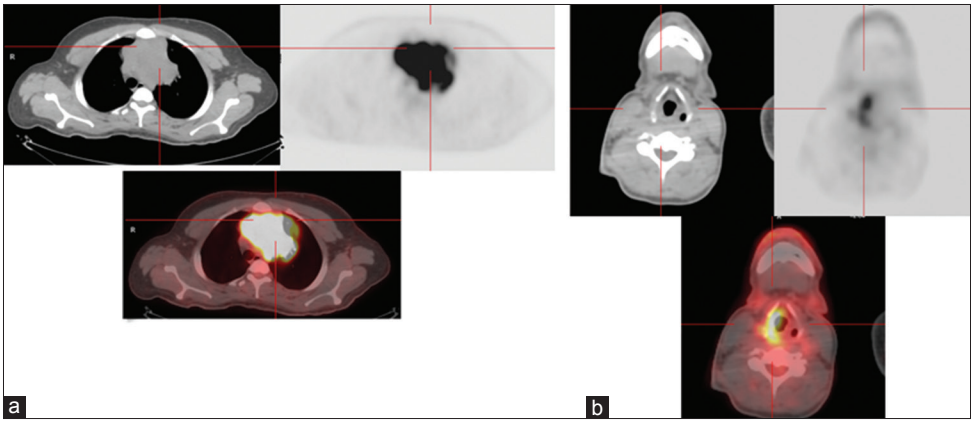

Figure 2: 26 year old male with Hodgkin's lymphoma involving the mediastinum (panel A) affecting mostly the left phrenic nerve with subsequent left vocal cord paralysis. The unilateral right vocal cord uptake is related to the physiological overuse (panel B)

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. Benzodiazepines 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, supraclavicular 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.[8]

Uptake in the neck adipose tissue is typically bilateral and symmetric, intense, and more often multifocal than linear.[9]

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.[13,14]

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.[15] 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*.[16] 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.[17,18]

The incidence of unsuspected metastatic disease detected by PET/CT in this population is in the range of 7%–15%[19] while the detection of synchronous unsuspected primary tumors was reported in the range of 4%–8% [Figure 4].[16,20-22]

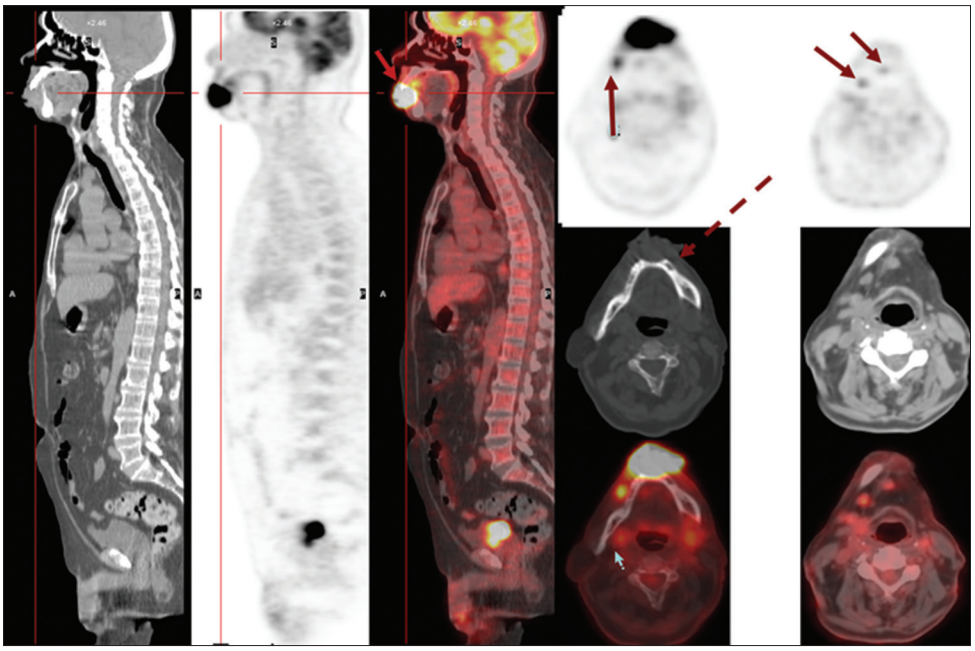

Figure 3: Squamous cell carcinoma of the lower lip with submental and bilateral level II biopsy proved nodal metastases as seen in positron emission tomography/computed tomography images (Flat arrows) in addition to bony mandibular involvement (dashed arrow)

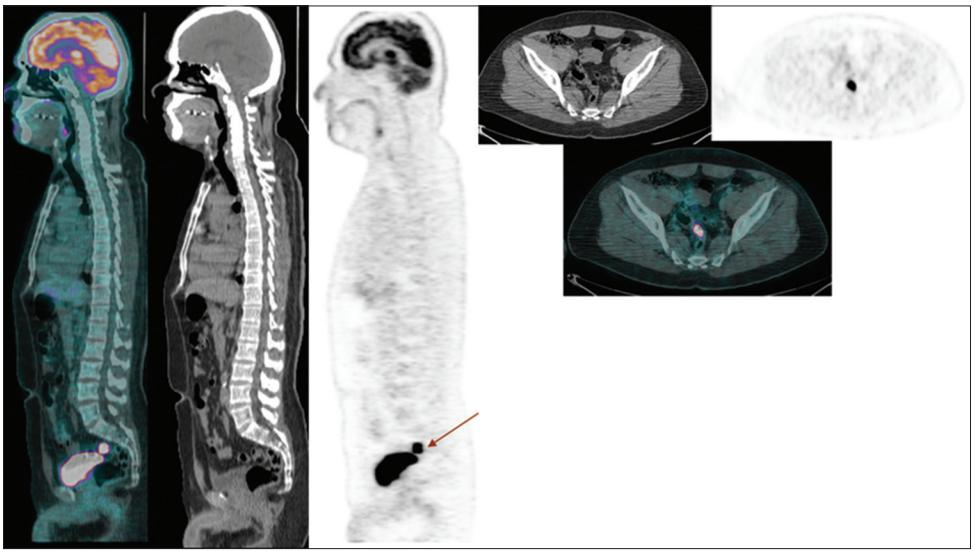

Figure 4: A 42-year-old male with a history of plasmacytoma of the tonsils; his follow-up positron emission tomography/computed tomography revealed focal intense fluorodeoxyglucose uptake within the rectosigmoid region (red arrow); tissue biopsy following colonoscopy was consistent with villous adenoma with high-grade dysplasia

The overall change in the management based on FDG PET findings was observed in up to 31% of the cases,[21,23] and in a more recent prospective multicenter trial, it has been observed in 13.7% of the cases;[24] 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.*,[25] 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*.[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%.[27]

A high sensitivity and specificity were also reported by Wong *et al*.,[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.[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

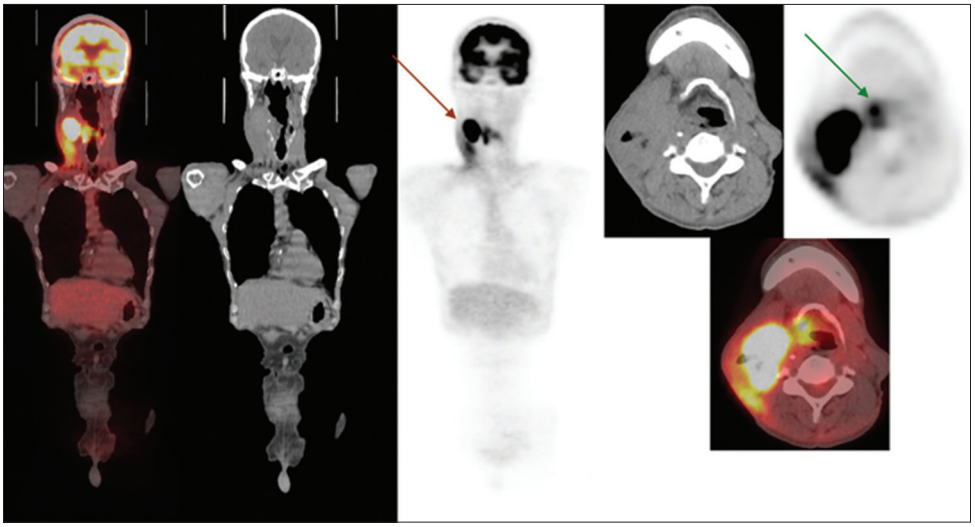

Figure 5: A 67-year-old male who presented with large right neck lymphadenopathy with biopsy-proven adenocarcinoma of unknown primary (red arrow); his subsequent positron emission tomography/computed tomography revealed supraglottic (green arrow) biopsy-proven carcinoma of the presumable primary malignancy

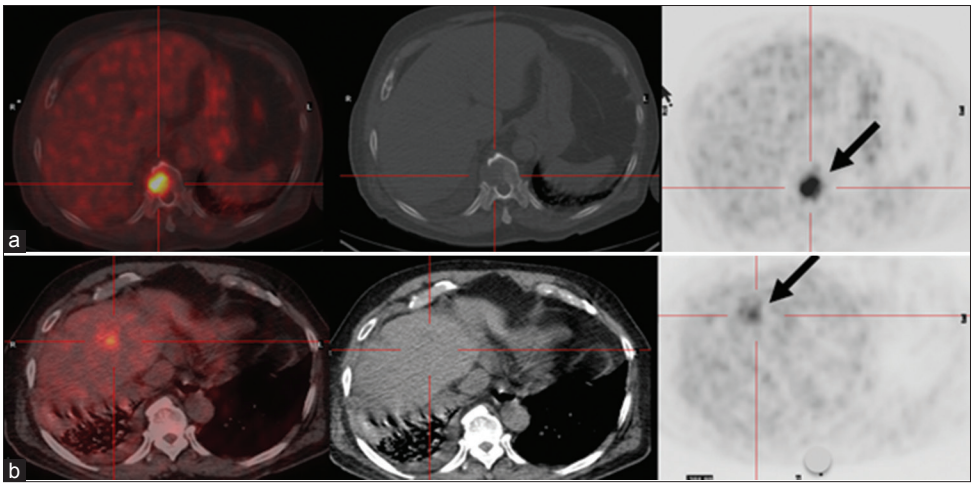

Figure 6: 81 year old male with a history of laryngeal carcinoma, his PET CT revealed bone and liver metastases (black arrows in a and b)

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[4] 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*.[30] 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*.[31] 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*.[32] 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.[33] 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.[34-36]

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

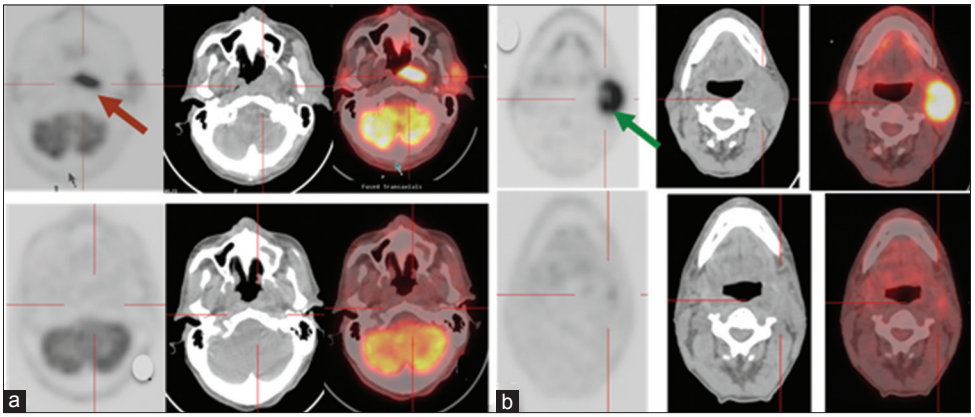

Figure 7: 63 year old male with a history of SCC of the nasopharynx (red arrow) with necrotic nodal metastases (green arrow) before (Panel A) and post chemoradiotherapy (Panel B)

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.

References

1. Casciato DA. Manual of Clinical Oncology. 7th ed. Philadelphia, USA: Lippincott Williams and Wilkins; 2012.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.
3. Abouzied MM, Crawford ES, Nabi HA. 18F-FDG imaging: Pitfalls and artifacts. J Nucl Med Technol 2005;33:145-55.
4. Goerres GW, Von Schulthess GK, Hany TF. Positron emission tomography and PET CT of the head and neck: FDG uptake in normal anatomy, in benign lesions, and in changes resulting from treatment. AJR Am J Roentgenol 2002;179:1337-43.
5. Kamel EM, Goerres GW, Burger C, von Schulthess GK, Steinert HC. Recurrent laryngeal nerve palsy in patients with lung cancer: Detection with PET-CT image fusion – Report of six cases. Radiology 2002;224:153-6.
6. Kang KW, Kim SK, Kang HS, Lee ES, Sim JS, Lee IG, *et al.* Prevalence and risk of cancer of focal thyroid incidentaloma identified by 18F-fluorodeoxyglucose positron emission tomography for metastasis evaluation and cancer screening in healthy subjects. J Clin Endocrinol Metab 2003;88:4100-4.
7. Van den Bruel A, Maes A, De Potter T, Mortelmans L, Drijkoningen M, Van Damme B, *et al.* Clinical relevance of thyroid fluorodeoxyglucose-whole body positron emission tomography incidentaloma. J Clin Endocrinol Metab 2002;87:1517-20.
8. Cohade C, Mourtzikos KA, Wahl RL. "USA-Fat": Prevalence is related to ambient outdoor temperature-evaluation with 18F-FDG PET/CT. J Nucl Med 2003;44:1267-70.
9. Cohade C, Osman M, Pannu HK, Wahl RL. Uptake in supraclavicular area fat ("USA-Fat"): Description on 18F-FDG PET/CT. J Nucl Med 2003;44:170-6.
10. Veit-Haibach P, Luczak C, Wanke I, Fischer M, Egelhof T, Beyer T, *et al.* TNM staging with FDG-PET/CT in patients with primary head and neck cancer. Eur J Nucl Med Mol Imaging 2007;34:1953-62.
11. AAssar OS, Fischbein NJ, Caputo GR, Kaplan MJ, Price DC, Singer MI, *et al.* Metastatic head and neck cancer: Role and usefulness of FDG PET in locating occult primary tumors. Radiology 1999;210:177-81.
12. Nabili V, Zaia B, Blackwell KE, Head CS, Grabski K, Sercarz JA. Positron emission tomography: Poor sensitivity for occult tonsillar cancer. Am J Otolaryngol 2007;28:153-7.
13. Kyzas PA, Evangelou E, Denaxa-Kyza D, Ioannidis JP. 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: A meta-analysis. J Natl Cancer Inst 2008;100:712-20.
14. Nahmias C, Carlson ER, Duncan LD, Blodgett TM, Kennedy J, Long MJ, *et al.* Positron emission tomography/computerized tomography (PET/CT) scanning for preoperative staging of patients with oral/head and neck cancer. J Oral Maxillofac Surg 2007;65:2524-35.
15. Schöder H, Carlson DL, Kraus DH, Stambuk HE, Gönen M, Erdi YE, *et al.* 18F-FDG PET/CT for detecting nodal metastases in patients with oral cancer staged N0 by clinical examination and CT/MRI. J Nucl Med 2006;47:755-62.
16. Rodrigues RS, Bozza FA, Christian PE, Hoffman JM,

Butterfield RI, Christensen CR, *et al.* Comparison of whole-body PET/CT, dedicated high-resolution head and neck PET/CT, and contrast-enhanced CT in preoperative staging of clinically M0 squamous cell carcinoma of the head and neck. J Nucl Med 2009;50:1205-13.

17. Fleming AJ Jr., Smith SP Jr., Paul CM, Hall NC, Daly BT, Agrawal A, *et al.* Impact of [18F]-2-fluorodeoxyglucose-positron emission tomography/computed tomography on previously untreated head and neck cancer patients. Laryngoscope 2007;117:1173-9.
18. Scott AM, Gunawardana DH, Bartholomeusz D, Ramshaw JE, Lin P. PET changes management and improves prognostic stratification in patients with head and neck cancer: Results of a multicenter prospective study. J Nucl Med 2008;49:1593-600.
19. Branstetter BF 4th, Blodgett TM, Zimmer LA, Snyderman CH, Johnson JT, Raman S, *et al.* Head and neck malignancy: Is PET/CT more accurate than PET or CT alone? Radiology 2005;235:580-6.
20. Ishimori T, Patel PV, Wahl RL. Detection of unexpected additional primary malignancies with PET/CT. J Nucl Med 2005;46:752-7.
21. Zanation AM, Sutton DK, Couch ME, Weissler MC, Shockley WW, Shores CG. Use, accuracy, and implications for patient management of [18F]-2-fluorodeoxyglucose-positron emission/computerized tomography for head and neck tumors. Laryngoscope 2005;115:1186-90.
22. Porceddu SV, Jarmolowski E, Hicks RJ, Ware R, Weih L, Rischin D, *et al.* Utility of positron emission tomography for the detection of disease in residual neck nodes after (chemo) radiotherapy in head and neck cancer. Head Neck 2005;27:175-81.
23. Ha PK, Hdeib A, Goldenberg D, Jacene H, Patel P, Koch W, *et al.* The role of positron emission tomography and computed tomography fusion in the management of early-stage and advanced-stage primary head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck Surg 2006;132:12-6.
24. Lonneux M, Hamoir M, Reychler H, Maingon P, Duvillard C, Calais G, *et al.* Positron emission tomography with [18F] fluorodeoxyglucose improves staging and patient management in patients with head and neck squamous cell carcinoma: A multicenter prospective study. J Clin Oncol 2010;28:1190-5.
25. Dong MJ, Zhao K, Lin XT, Zhao J, Ruan LX, Liu ZF. Role of fluorodeoxyglucose-PET versus fluorodeoxyglucose-PET/computed tomography in detection of unknown primary tumor: A meta-analysis of the literature. Nucl Med Commun 2008;29:791-802.
26. Abgral R, Querellou S, Potard G, Le Roux PY, Le Duc-Pennec A, Marianovski R, *et al.* Does 18F-FDG PET/CT improve the detection of posttreatment recurrence of head and neck squamous cell carcinoma in patients negative for disease on clinical follow-up? J Nucl Med 2009;50:24-9.
27. Ryan WR, Fee WE Jr., Le QT, Pinto HA. Positron-emission tomography for surveillance of head and neck cancer. Laryngoscope 2005;115:645-50.
28. Wong RJ, Lin DT, Schöder H, Patel SG, Gonen M, Wolden S, *et al.* Diagnostic and prognostic value of [(18)F] fluorodeoxyglucose positron emission tomography for recurrent head and neck squamous cell carcinoma. J Clin Oncol 2002;20:4199-208.
29. Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: When do the ends justify the means? Laryngoscope 2000;110:1-18.
30. Goerres GW, Schmid DT, Bandhauer F, Huguenin PU, von Schulthess GK, Schmid S, *et al.* Positron emission tomography in the early follow-up of advanced head and neck cancer. Arch Otolaryngol Head Neck Surg 2004;130:105-9.
31. Ong SC, Schöder H, Lee NY, Patel SG, Carlson D, Fury M, *et al.* Clinical utility of 18F-FDG PET/CT in assessing the neck after concurrent chemoradiotherapy for locoregional advanced head and neck cancer. J Nucl Med 2008;49:532-40.
32. Yao M, Smith RB, Graham MM, Hoffman HT, Tan H, Funk GF, *et al.* The role of FDG PET in management of neck metastasis from head-and-neck cancer after definitive radiation treatment. Int J Radiat Oncol Biol Phys 2005;63:991-9.
33. Shields AF, Grierson JR, Dohmen BM, Machulla HJ, Stayanoff JC, Lawhorn-Crews JM, *et al.* Imaging proliferation *in vivo* with [F-18] FLT and positron emission tomography. Nat Med 1998;4:1334-6.
34. Menda Y, Boles Ponto LL, Dornfeld KJ, Tewson TJ, Watkins GL, Schultz MK, *et al.* Kinetic analysis of 3'-deoxy-3'-(18) F-fluorothymidine ((18)F-FLT) in head and neck cancer patients before and early after initiation of chemoradiation therapy. J Nucl Med 2009;50:1028-35.
35. Troost EG, Bussink J, Slootweg PJ, Peeters WJ, Merkx MA, van der Kogel AJ, *et al.* Histopathologic validation of 3'-deoxy-3'-18F-fluorothymidine PET in squamous cell carcinoma of the oral cavity. J Nucl Med 2010;51:713-9.
36. Yap CS, Czernin J, Fishbein MC, Cameron RB, Schiepers C, Phelps ME, *et al.* Evaluation of thoracic tumors with 18F-fluorothymidine and 18F-fluorodeoxyglucose-positron emission tomography. Chest 2006;129:393-401.
37. Lehtiö K, Eskola O, Viljanen T, Oikonen V, Grönroos T, Sillanmäki L, *et al.* Imaging perfusion and hypoxia with PET to predict radiotherapy response in head-and-neck cancer. Int J Radiat Oncol Biol Phys 2004;59:971-82.
38. Rajendran JG, Hendrickson KR, Spence AM, Muzi M, Krohn KA, Mankoff DA. Hypoxia imaging-directed radiation treatment planning. Eur J Nucl Med Mol Imaging 2006;33 Suppl 1:44-53.
39. Thorwarth D, Eschmann SM, Paulsen F, Alber M. Hypoxia dose painting by numbers: A planning study. Int J Radiat Oncol Biol Phys 2007;68:291-300.
40. Daisne JF, Duprez T, Weynand B, Lonneux M, Hamoir M, Reychler H, *et al.* Tumor volume in pharyngolaryngeal squamous cell carcinoma: Comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. Radiology 2004;233:93-100.
41. Troost EG, Schinagl DA, Bussink J, Boerman OC, van der Kogel AJ, Oyen WJ, *et al.* Innovations in radiotherapy planning of head and neck cancers: Role of PET. J Nucl Med 2010;51:66-76.