

Chapter 2

FDG PET Imaging of Head and Neck Cancers

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Abstract

In initial staging of head and neck cancers, the addition of FDG PET to conventional imaging improves the accuracy for cervical nodal metastases. The sensitivity of FDG PET is, however, limited in nodes <1 cm and in completely necrotic nodes. In the posttherapy setting, PET scans obtained at least 10 weeks after radiotherapy have an excellent predictive value to rule out residual disease. Due to the limited positive predictive value of FDG PET after radiation therapy, a positive PET scan needs to be confirmed before management decisions are made.

Key words: F-18 Fluorodeoxyglucose, Positron emission tomography, Head and neck cancer

1. Introduction

Head and neck cancers are cancers involving all regions of the head and neck, except for the thyroid and central nervous system. Most of these cancers are squamous cell carcinomas. The most common sites are larynx, tongue, floor of the mouth, tonsils, and salivary glands, although these carcinomas can arise in almost any location in the nasopharynx, oropharynx, or hypopharynx. The estimated number of new cases in the USA for 2008 is 47,500, with approximately 11,000 deaths (1). The male:female ratio is about 2:1. Primary risk factors for virtually all head and neck cancers are tobacco and alcohol use. Early-stage head and neck tumors are treated with either surgery or radiotherapy with excellent prognosis. Locally advanced tumors without distant metastasis are typically treated with combination therapies with definitive chemoradiation therapy followed by salvage surgery (if necessary) or surgery and postoperative radiation therapy. Patients with distant metastatic disease have very poor prognosis and are usually referred for palliative chemotherapy or radiation.

2. Diagnosis and Conventional Imaging

A working diagnosis of malignant tumor is usually obtained after history and careful clinical exam. Histologic characterization may be determined with fine needle aspiration (FNA) or biopsy. Flexible endoscopy with multiple biopsies is performed for tumors of the upper aerodigestive tract. Panendoscopy under general anesthesia, which includes laryngoscopy, esophagoscopy, and bronchoscopy, is performed in most patients to visualize and biopsy the primary tumor and to rule out synchronous tumors. CT of the neck with intravenous contrast is often the first-line imaging study to evaluate the extent of primary tumor and for cervical nodal metastasis. MRI may be complementary to CT in staging of primary tumors and is particularly helpful to evaluate for dural involvement of nasopharyngeal and sinonasal tumors. Evaluation for distant disease with chest CT is advised as part of the conventional workup of patients with locally advanced tumors with cervical nodal metastases.

3. FDG PET Imaging Technique of Head and Neck Cancer

FDG PET scans should not be performed if serum glucose level exceeds 200 mg/dl, since high glucose levels compete with FDG resulting in lower tumor uptake of FDG (2). Sedation with benzodiazepines during the uptake phase can be very helpful to reduce normal muscle uptake in the neck. This may be particularly helpful if the scan is not done on a hybrid PET/CT camera, because uptake in normal muscle may be difficult to distinguish from pathologic uptake in cervical lymph nodes. Muscle uptake can be particularly problematic following therapy when unilateral muscle uptake occurs in scalenes, longus colli, pterygoids, or one of the other numerous small muscles in the neck. Another important measure during the uptake phase is to prohibit speech, which results in increased uptake in peri-laryngeal muscles. Intense FDG uptake in brown fat uptake can be problematic, particularly in the supraclavicular fossa (3). This can be minimized by maintaining the uptake room at a relatively high temperature ($\geq 24^{\circ}\text{C}$) (4).

The uptake period should be at least 60 min, and it may be advantageous to delay even longer to 90 or 120 min, since tumor to background ratio steadily increases with time (5). The resolution of the PET images can be improved by using a smaller pixel size than is routinely used for body imaging. The default voxel size for most PET-CT systems is approximately 4 mm. This means that the spatial resolution is about 10 mm. If the voxel size is reduced to 2 mm, a resolution of 5–6 mm can be obtained.

Interpretation of the PET images of head and neck is challenging and requires more experience than in most other areas of the body because many normal anatomic structures in the neck show elevated uptake of FDG compared to nearby soft tissue. These tissues include the salivary glands, lingual, palatine, and pharyngeal tonsils, base of the tongue, floor of the mouth and the laryngeal, pterygoid and strap muscles of the neck. Many of these are demonstrated in an atlas of head and neck PET imaging published in the *Seminars of Nuclear Medicine* (6).

4. Staging of Head and Neck Cancers

Head and neck cancers are staged according to the TNM classification (7). Although the description of T-stage varies with the site of the primary tumor, generally tumors <2 cm are staged as T1, 2–4 cm as T2, >4 cm as T3, and tumors invading into adjacent neck structures are staged as T4. Cervical nodes are staged as N1 for a single ipsilateral node <3 cm, N2 indicates single or multiple nodes between 3 and 6 cm, and N3 refers to node(s) >6 cm in greatest dimension. Metastatic disease, which is most commonly seen in the lungs, bone, and liver, results in an M1 designation.

Involvement of neck nodes is an important prognostic factor and therapeutic determinant for all head and neck cancers. Thus, it is important to have a solid understanding of the nodal anatomy and the standard system for describing the location of nodes to be able to effectively communicate with the referring surgeons (8). Level IA nodes are submental nodes close to midline and Level IB are more lateral and anterior to the posterior edge of the submandibular glands. These nodes receive drainage from the anterior oral cavity. Level II nodes are between the base of the skull and the inferior margin of the hyoid bone. They are further classified into IIA and IIB nodes. Level IIA nodes are anterior to the posterior aspect of the internal jugular vein and IIB nodes are posterior to the vein. Level III nodes are between the inferior border of the hyoid and inferior border of the cricoid cartilage. Level II and Level III nodal metastases are seen with tumors of the oral cavity, pharynx, and larynx. Level IV nodes are inferior to the cricoid and extend to the level of the clavicle. Metastatic disease in level IV nodes is usually associated with tumors of the hypopharynx, larynx, cervical esophagus, or thyroid. Level V nodes are in the posterior triangle and are between the posterior border of the sternocleidomastoid muscle and the trapezius muscle. Level V nodes are classified as VA if they are between the skull base and the inferior border of the cricoid cartilage and VB if they are between the cricoid and clavicle. Level V nodes are at highest

risk for metastases from nasopharynx, oropharynx, and posterior scalp. Level VI nodes are the anterior compartment nodes, medial to the common carotid artery and extend from the hyoid to the manubrium. Metastatic disease at level VI is commonly associated with thyroid cancer, larynx, hypopharynx, and cervical esophagus.

Diagnostic criteria for cervical nodal metastases with CT or MRI are based primarily on nodal size. The nodes are considered to be metastatic if >15 mm for jugulodigastric nodes and >10 mm for other neck nodes. In addition, round shape with central necrosis, presence of more than three nodes or presence of extracapsular invasion also indicates metastatic disease. However, $>40\%$ of metastatic nodes are <10 mm in size (5) and many larger nodes simply represent reactive inflammatory lymph nodes. FDG uptake in a lymph node is significantly more accurate in predicting nodal metastases. PET-CT scan of a patient with cervical nodal metastases from a tonsillar cancer is shown in Fig. 1. In comparative studies, sensitivity and specificity of PET in detection of nodal metastases was found between 70–100% and 82–94%, respectively, compared to 58–85% and 58–96% for CT/MRI (9–12). FDG PET may be falsely negative in small nodes <1 cm in diameter or in completely necrotic nodes. False-positive FDG uptake in cervical nodes can be due to inflammation. Because of significant overlap between inflammatory and metastatic nodes, quantitation of uptake using standardized uptake values (SUV) does not appear to significantly improve the interpretation accuracy of FDG PET in cervical lymph nodes.

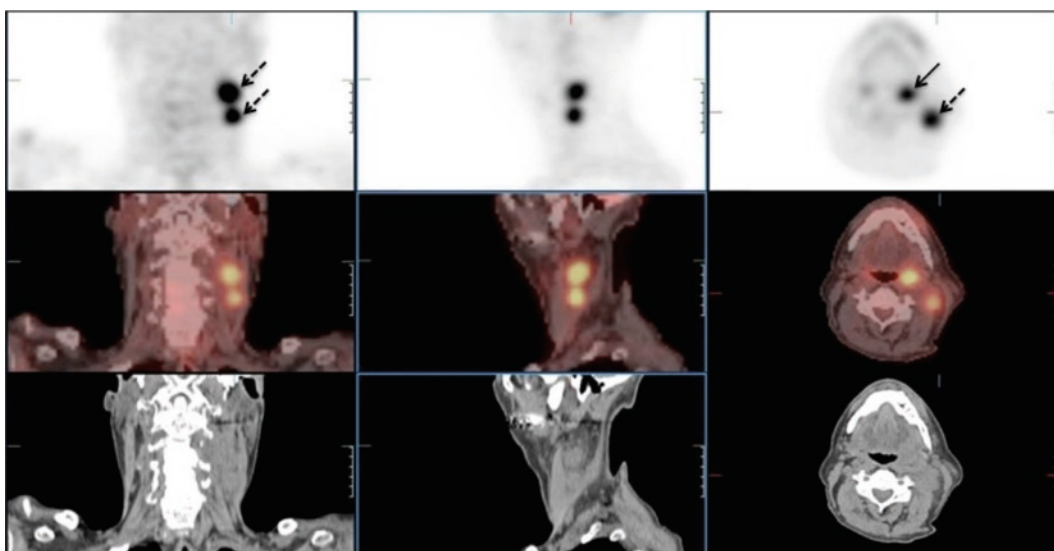


Fig. 1. Left tonsillar carcinoma (*arrow*) with two left level IIB metastatic neck nodes (*dashed arrows*).

The clinically negative neck (N0 neck) is particularly challenging. Only 25–30% of patients with N0 neck are found to have metastatic neck nodes at surgery. This means that the majority of patients with N0 neck undergoing a potentially morbid neck dissection are unlikely to benefit from this procedure. In three studies totaling 48 patients, where a sentinel node biopsy with immunohistochemistry was used as the gold standard, the detection rate of PET for nodal involvement in clinically N0 patients was limited between 0 and 30% (13–15). Integrated PET-CT may improve the accuracy in clinically N0 neck, with a reported sensitivity and specificity of 67 and 85%; however, this is still not sufficient to replace surgical staging in these patients (16). Sentinel node biopsy with immunohistochemistry appears significantly more accurate in patients with clinical N0 neck.

A major advantage of FDG PET over conventional imaging in pretherapy staging of head and neck cancer is its ability to detect synchronous and/or metastatic disease in the chest and abdomen (17). A PET scan in the initial staging is most helpful with in patients with advanced local disease (Stage III or IV). Several studies suggest that PET finds unexpected distant metastasis in approximately 10% of patients with locally advanced head and neck cancer (18–21).

5. Carcinoma of Unknown Primary

Squamous cervical nodal metastases from an unknown primary tumor constitute approximately 2% of newly diagnosed head and neck cancers. The most common sites of the primary tumor are tonsil and base of tongue (22). These patients are routinely treated with wide-field radiation therapy, which includes the entire pharynx, larynx, and bilateral neck. The wide-field irradiation definitely reduces the risk of tumor recurrence; however, it causes significant morbidity particularly in terms of xerostomia (23). Correct localization of the primary tumor substantially reduces the complications associated with radiotherapy by decreasing the size of the radiation portal and may also improve survival (22). The initial conventional workup of patients with a squamous cell nodal metastasis with unknown primary includes CT of the neck followed by endoscopy and directed biopsies. Even after such an extensive workup the detection rate of the primary tumor is <50%.

The current FDG PET literature on carcinoma of unknown primary includes a number of small single-center studies with variable diagnostic workup before the PET scan. In a meta-analysis which included 16 studies with PET in 302 patients, the average detection rate of the primary tumor with FDG PET was 24.5% with additional regional metastases found in 15.9% and distant

metastases in 11.2 % of patients (24). The detection rate of the primary tumor with PET is not different in studies where FDG PET is only performed after a negative endoscopy and conventional imaging (25–30). It seems therefore reasonable to obtain an FDG PET as the initial imaging study in patients with carcinoma of unknown primary. If the FDG PET scan is negative, a primary tumor is found subsequently only in 12% of patients (24).

6. Detection of Residual and Recurrent Disease After Treatment

Early detection of recurrent head and neck cancer is important because the disease-free survival after salvage surgery is highly dependent on the stage of the recurrent tumor. The 2-year disease-free survival is 67–73% for stage I or II recurrent tumor compared to 22–33% for stage III and IV disease (31). Diagnosis of recurrence is difficult with CT or MRI because of the loss of symmetry and inflammation associated with healing from surgery and with radiotherapy. Routine biopsy of treated areas is also not recommended because of increased risk of bleeding and infection in irradiated tissue and potential false-negative biopsies due to sampling errors. FDG PET is more sensitive and specific than CT or MRI in detection of residual or recurrent disease (32).

The role of PET in the follow-up of head and neck cancer was reviewed in a meta-analysis by Isles et al. (33). The mean pooled sensitivity and specificity of FDG PET for recurrent disease at primary site following radiotherapy or chemoradiation therapy was 94 and 82%, respectively. For diagnosis of recurrent disease in neck nodes, the mean sensitivity was 74% and mean specificity was 84%, with a positive predictive value of 49% and a negative predictive value of 96% (33). A true positive FDG PET-CT for recurrent tumor is demonstrated in Fig. 2. The largest single-center study regarding PET for recurrent disease included 188 patients, who were imaged for suspected recurrence within 12 months of completion of definitive treatment with surgery and radiation therapy or combined chemoradiation therapy (34). The sensitivity and specificity for FDG PET in the assessment of the treatment response in the neck was 86 and 97%, respectively. Patients with positive post-RT PET findings had significantly worse 3-year overall survival and disease-free survival (34).

Many patients with locally advanced head and neck cancer, particularly originating from larynx and hypopharynx, are treated with initial radiation and chemotherapy, which results in functional preservation. These patients may subsequently undergo salvage surgery if residual disease is present and PET-CT seems to be the most accurate way to make that determination. Greven et al. reported a sensitivity and specificity of 100 and 90% in

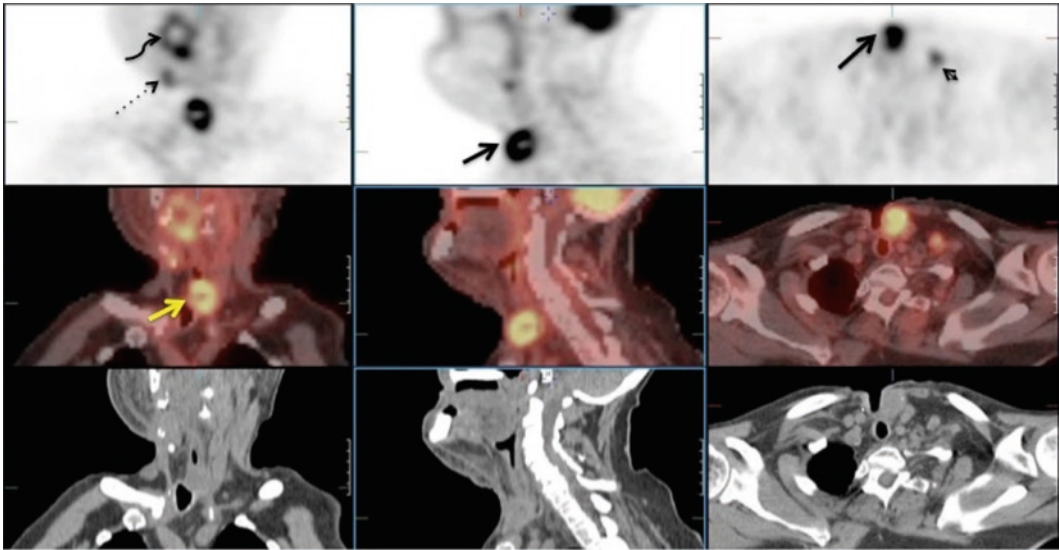


Fig. 2. Supraglottic malignancy treated with surgery, chemotherapy, and radiation, which was completed 3 months prior to the FDG PET-CT scan. PET-CT shows a large necrotic tumor in the right base of the tongue (*curved arrow*), as well as recurrent tumor adjacent to the tracheostomy (*solid arrow*) and a metastatic right level III neck node (*dashed arrow*). The uptake in the lower left neck is in the left anterior scalene muscle and is benign (*arrowhead*).

28 patients with head and neck cancer who were imaged 4 months after completion of radiotherapy (35). Yao et al. found a similar high negative predictive value in 53 patients who were imaged with FDG PET at 3 months posttreatment (100%); however, the specificity was lower at 43% (36). A negative FDG PET study after chemoradiation has a very high negative predictive value even when there is residual nodal enlargement on follow-up CT. Comparing PET studies obtained at a median of 3 months after treatment with histology from salvage surgery in 39 patients with residual nodal enlargement after chemoradiation, Porceddu et al. have reported a negative predictive value of 97% for PET and a positive predictive value of 71% (37). Although there is general agreement that a 3-month postradiation PET scan has an acceptable accuracy, earlier PET imaging may be desirable, as many surgeons prefer to perform the salvage surgery within 6–8 weeks after radiation, before postradiation fibrotic changes develop in the neck (38). At least two studies have shown that 1-month posttherapy PET has an unacceptably low sensitivity. Greven et al. have reported that the sensitivity of 1-month PET for detection of residual disease was only 59% compared to 100% for 4-month posttherapy PET (35). In another study, Rogers et al. have reported a sensitivity of 45% for a 1-month posttherapy FDG PET in comparison to the 6–8 week posttreatment surgical histopathology (39). Data for accuracy of FDG PET scans obtained between 1 and 3 months after therapy is limited; however,

in a recent meta-analysis the sensitivity of PET was significantly lower if performed earlier than 10 weeks after completion of radiation therapy (33). In summary, a PET scan performed 10–12 weeks months after radiation or chemoradiation therapy has a high negative predictive value so that patients with negative studies can be safely followed up without intervention. A positive PET finding needs to be confirmed before management decisions are made as postradiation changes lower the specificity of FDG PET.

False-positive FDG uptake in the posttherapy setting is seen secondary to reactive inflammatory changes from treatment, infection, or osteoradionecrosis. There is a significant overlap in SUV between recurrent tumors and posttherapy changes and no SUV cutoff has been found to outperform visual analysis by an experienced reader. If the initial biopsy after a positive PET scan fails to demonstrate tumor, a follow-up PET scan is suggested in 2–3 months (40, 41). Tumor is very unlikely if the uptake on the follow-up PET scan is decreased (consistent with healing), whereas repeat biopsy is usually necessary if the SUV is unchanged or has increased in the interval.

7. Radiotherapy Planning with PET-CT

FDG PET-CT is beginning to be used frequently as an adjunct to radiotherapy treatment planning. One of the most obvious uses is to include all sites that are identified as FDG avid tumor in the radiation field since tumors with high FDG uptake have a high recurrence rate and poor prognosis (42). The FDG PET data needs to be imported into the treatment planning computer and co-registered with the treatment planning CT scan to be able to incorporate it into the radiation treatment planning. For precise co-registration, the same immobilization head mask should be used for the treatment planning CT and the PET or PET/CT scan. In a pilot study by Ciernik et al., the co-registration of PET/CT with the planning CT images was highly successful with average deviations of 1.2 ± 0.8 mm in the x -axis, 1.5 ± 1.2 mm in the y -axis, and 2.1 ± 1.1 mm in the z -axis (43). Paulino et al. were able to consistently obtain a co-registration error of <5 mm (44). Incorporation of FDG PET into radiotherapy planning may significantly alter the target gross tumor volume (GTV). The GTV may be increased because a metabolically active tumor can be detected in normal sized nodes. The PET-based GTV may be smaller than CT-based GTV in some patients because the tumor may not be metabolically active in its entirety or because of benign enlarged nodes that are not hypermetabolic.

Paulino et al. compared the CT-based and PET-CT-based GTV in 40 patients who underwent intensity-modulated radiation

therapy (IMRT) for squamous cell carcinoma of the head and neck (44). They found that the PET-based GTV was significantly smaller compared to CT-based GTV and furthermore metabolically active tumor would have been underdosed in approximately 25% of patients if only CT-based GTV was used for IMRT. Heron et al. found that the nodal target volume was approximately 43% higher with PET-based GTV compared with CT-based GTV as PET identified additional hypermetabolic nodal metastases that were too small to detect using CT (45). In addition to treatment volume, FDG PET can also change the intent from curative to palliative therapy by identification of distant metastases (46). Although the use of PET is gaining more acceptance in the radiation oncology community, issues remain that need to be addressed before PET/CT is used as a routine tool for radiotherapy planning in head and neck cancer (47). Contouring the tumor volume with PET is not standardized; the target volume on PET will be significantly overestimated with an increased window level and can be underestimated by lowering the PET window. 50% of the tumor/image maximum intensity has been used by some groups (48), while others have used intensity of liver uptake (45) or standardized uptake value (SUV) of 2.5 for their threshold standard (49). So far, there have been no studies showing that the changes in treatment volume actually improve outcome.

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