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FDG-PET and Integrated FDG-PET/CT in Management of Head and Neck Squamous Cell Cancer

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe issues in staging and managing head and neck squamous cell carcinoma.
- Explain the utility of PET and PET/CT in staging primary head and neck malignancy.
- Summarize the difficulty in assessing treatment effect versus recurrent tumor with conventional imaging and the role of PET/CT in this scenario.
- List the advantages of PET/CT versus PET alone in the evaluation of head and neck squamous cell carcinoma.

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Dr. Goldenberg and Dr. Tufano have no significant financial arrangement or affiliation with any manufacturer of any pharmaceutical or medical device and are not affiliated in any manner with any provider of any commercial medical or healthcare professional service.

The incidence of squamous cell carcinoma of the head and neck is greater than 35,000 cases per year.¹ Head and neck cancer accounts for approximately 5% of all malignancies, with squamous cell carcinoma the major histologic subtype. Smoking and other tobacco use, along with alcohol consumption, are well-established risk factors for developing these cancers. Head and neck squamous cell cancer (HNSC) is a heterogeneous disease with distinct patterns of presentation and behavior for each subsite: larynx, oral cavity, oropharynx, hypopharynx, and nose and paranasal sinuses.

More than 50% of these cancers arise in the oropharynx, particularly in the palatine tonsils and the base of the tongue. Approximately 60% of patients with HNSC have locally advanced disease at presentation, and they are usually treated with surgery, radiotherapy, chemoradiotherapy, or a combination of therapies.^{2,3}

Overall, in patients with head and neck cancer, the five-year survival rate is approximately 60% without lymph node metastasis and 30% if metastatic nodes are present. The five-year survival rate for patients with locoregional spread of tumor that is undetected at presentation is 30% for all head and neck cancers. Accurate staging of primary tumors is important during discussions with patients about treatment options and/or long-term prognosis.

The staging systems for head and neck cancer are all clinical and differ from subsite to subsite of the head and neck. They are based on the best possible estimate of the extent of disease before treatment. All head and neck sites, with the exception of the thyroid, use the same classification system for regional lymph nodes (see table).

Assessment of the primary tumor is based on inspection and palpation when possible and by direct endoscopy

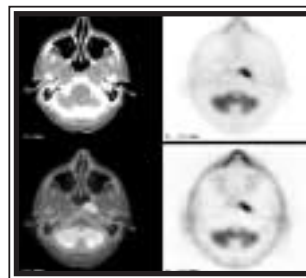


Figure 1. Integrated PET/CT of 60-year-old nonsmoker with a left neck mass of two months' duration. CT scan confirmed left neck adenopathy but revealed no primary tumor. Based on these findings, treatment including surgical excision of neck mass was initially proposed elsewhere. PET/CT reveals primary tumor in nasopharynx, which was treated successfully with radiotherapy alone.

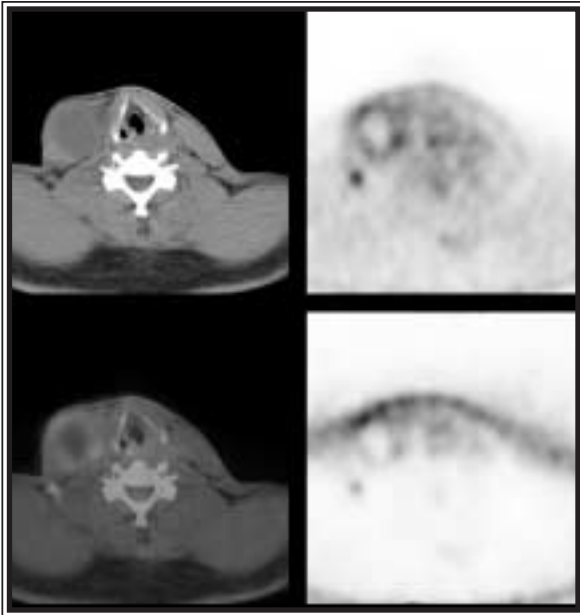


Figure 2. A cystic mass in the neck clinically diagnosed elsewhere as a benign cyst. Integrated PET/CT shows intense FDG uptake in perimeter of mass with a photopenic center. Subsequent surgery confirmed this lesion to be a metastatic lymph node from a very small tonsil cancer.

in less accessible sites such as the larynx. The appropriate nodal drainage areas are examined by careful palpation. Information from diagnostic imaging studies is also used in staging the HNSC patient. MR and CT scans are typically used in the detection and localization of head and neck tumors and the distinction of lymph nodes from surrounding soft tissue and blood vessels.

Structural tomographic imaging such as CT or MRI can precisely delineate gross disease. Neither technique, however, can adequately rule out persistent or recurrent cancer.⁴ Early detection of a recurrence of head and neck cancer following definitive treatment may lead to less radical salvage surgery and a better outcome for the patient.

Accurate initial evaluation of the primary tumor and nodal status is paramount. Until recently, this evaluation relied solely on a combination of clinical evaluation coupled with anatomic imaging studies such as CT or MRI. PET technology is now being used as an adjunct to clinical and anatomic

radiographic methods. Its role in staging and surveillance in HNSC continues to be elucidated.

FUNCTIONAL IMAGING MECHANISM

Functional PET imaging using fluorine-18 fluorodeoxyglucose permits the differentiation of viable malignant tissue from normal tissue and from nonviable remnants by direct visualization of metabolic activity in vivo.

PET is a functional imaging tool that is increasingly being used in the staging, therapeutic monitoring, and restaging of many malignancies. FDG, an analog of glucose, has high uptake in a wide

range of tumors relative to surrounding normal tissues.^{5,6} Glucose metabolism in growing squamous cell carcinomas is enhanced and accounts for the increased uptake on FDG-PET studies. The glucose analog 2-deoxy-D-glucose is transported into the cell and metabolized in the glycolytic cycle. After phosphorylation with hexokinase to DG-6-phosphate, the compound remains in the malignant cells, where it can be used for imaging.

Neoplastic cells, because of their proliferation, incorporate more fluorine-labeled deoxyglucose, needed for nucleic acid synthesis. Upregulation of protein and glucose transporters and other enzymatic systems may manifest as increased tracer uptake.

CLINICAL UTILITY OF PET

The use of FDG-PET has direct clinical benefits in several areas:

- *Primary tumors.* The treatment of primary squamous cell carcinoma of the head and neck is dependent on staging of the tumor. Detection of extension into adjacent tissues and structures is

important, and this is done by physical examination as well as conventional anatomic imaging with CT and MRI, which are highly sensitive for primary disease (67% to 88%) but lack specificity (50% to 75%). FDG-PET has an equivalent sensitivity (71% to 95%) but is more specific (67% to 100%).⁷

- *Regional lymph node status.* Lymph node involvement dramatically reduces survival, and treatment must change in these cases. Clinical palpation is inaccurate, with false-negative rates of 5% to 44% and false-positive rates of 13% to 25%.⁸ With conventional imaging, the sensitivity for detection of lymph node involvement ranges from 36% to 95%, and the specificity from 58% to 97%.⁹ The diagnosis of involved nodes on CT or MRI is often based on size, generally using a high end of normal (1 to 1.5 cm) to differentiate benign from malignant disease. This approach is problematic, as multiple or large lymph nodes may simply be reactive to the underlying process (i.e., inflammatory), and small nodes may contain cancer cells. It has been shown that more than 40% of metastases are actually found in lymph nodes smaller than 1 cm. These are often missed with conventional imaging.

Because PET is a metabolic tool, it can define disease in small nodes and exclude it in large ones. Many studies have confirmed this ability. Overall, the data show that FDG-PET is both more sensitive (70% to 100%) and more specific (84% to 100%) than conventional imaging for detecting nodal metastasis.

- *Unknown primary.* The diagnosis of an occult primary tumor is made only if no primary tumor is detected after careful search and the primary tumor fails to appear during therapy. Although only 2% of cancers in the head and neck region present as a malignant lymph node with no known site of disease, these cases present an important issue in head and neck cancer and are a therapeutic challenge. Three-year disease-free sur-

vival rates following surgery and/or radiation therapy for unknown squamous cell carcinoma primaries range from 40% to 50% in N1 patients to 38% for N2 and 26% for N3 disease. Patients who later develop detectable primary lesions have poor survival rates compared with those patients whose primaries remain occult.

The high sensitivity of PET makes it very valuable for specifically investigating these patients. Several studies have shown that PET identifies the site of the tumor in about 40% to 60% of cases (Figures 1 and 2).^{10,11}

• **Second primary tumor and synchronous distant metastases.** Unfortunately, despite progress in radiation therapy, chemotherapy, and surgical reconstruction, the overall survival rate for squamous cell carcinoma of the head and neck has not improved appreciably in the last two decades.¹² One factor that may significantly affect survival for patients with HNSC is the development of a second primary cancer within the head and neck. The risk of developing a second primary tumor translates to a lifetime incidence of 30% or more of patients who survive their initial HNSC.¹³ As many as 10% of patients with a primary HNSC may have a second synchronous tumor in the head and neck at the time of diagnosis. These tumors, as well as distant metastases, have important implications for management.¹⁴

One advantage of FDG-PET imaging over other imaging modalities is its ability to scan the entire body for disease activity, which may not be feasible or practical with other techniques. Using FDG-PET as a whole-body imaging modality allows detection of ongoing second primary tumors and metastases to other organs. Stokkel et al reported that FDG-PET detected a second primary tumor in 12 of 68 patients with primary head and neck cancers. Among these 12 patients, only five had tumors that were also detected by clinical or radiological exami-

nations.⁷ Goerres et al noted that in five of 34 patients with squamous cell cancer of the oral cavity, additional findings revealed by the whole-body PET resulted in a change of treatment plan.¹⁵

• **Treatment assessment and recurrence.** The assessment of patients after treatment of cancer of the head and neck is more difficult than assessment before treatment. Treatment itself—surgery, radiotherapy, or chemotherapy—leads to distortion of the anatomy, which can interfere with the clinical and radiological assessment of the region.

Differentiation between recurrence and post-treatment changes and scarring often requires surgical biopsy. Biopsy of the treated region is invasive, however, and can lead to wound complications. Metabolic imaging with FDG-PET is highly accurate in differentiating between post-treatment changes and recurrent cancer.

Collins et al demonstrated that if the results from both fine-needle biopsy and FDG-PET were combined, a sensitivity of 94% for detecting recurrent head and neck cancer can be achieved.¹⁶ Others, however, reported a sensitivity of

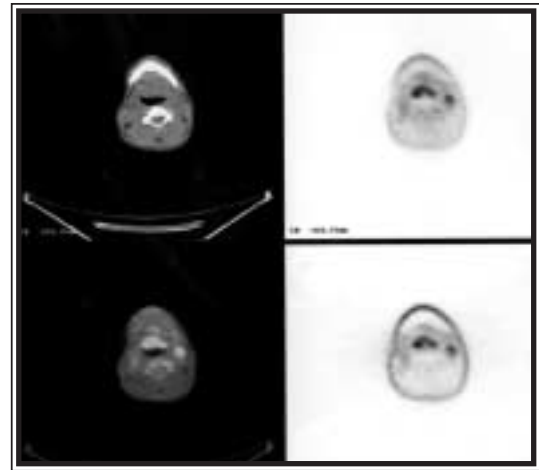


Figure 3. CT scan alone is unrevealing, while PET scan shows intense uptake but is unable to localize tumor adequately. Integrated PET/CT shows intense FDG uptake in the vallecula, indicating a supraglottic cancer.

over 90% with FDG-PET alone in the evaluation of recurrent head and neck cancers.¹⁷

INTEGRATED PET/CT

Although it is highly sensitive, PET suffers from imprecise anatomic localization of radiotracer uptake. FDG is also taken up by muscles and inflammatory processes as well as certain metabolically active organs such as the tonsils and salivary glands. Thus PET may provide imprecise information on the exact location of focal abnormalities. In the head and neck region, this range of error may mean the

REGIONAL LYMPH NODE STAGING IN HNSC

NX	Regional lymph nodes cannot be assessed, information not known
N0	No regional lymph node metastasis
N1	The cancer has spread to one lymph node (on same side of head or neck as primary tumor), which is smaller than 3 cm (about 1-1/4 inch)
N2	<ul style="list-style-type: none"> •a: The cancer has spread to one lymph node, larger than 3cm but smaller than 6cm (about 2-1/2 inches), on same side as primary tumor •b: The cancer has spread to multiple lymph nodes, none larger than 6 cm, on same side as primary tumor •c: The cancer has spread to one or more lymph nodes, none larger than 6 cm, on both sides of the neck or on side opposite primary tumor
N3	The cancer has spread to a lymph node larger than 6cm

difference between discovering a tumor of the base of tongue versus an adjacent tonsillar mass or a supraglottic versus a glottic lesion in the larynx (Figure 3).

These distinctions have important implications for therapy. The limitations of separate CT and PET imaging may be compensated for when the two modalities are used in a complementary way. High-resolution anatomic information produced by CT adds significant data to tissue characterization delivered by PET. Computerized coregistration of CT and PET can negate the shortcomings of PET and "marry" functional and anatomic imaging in a clinical scenario in which both are critically important.

Originally, this result was achieved with image fusion techniques involving studies performed at different times with different machines in different settings. Alignment schemes when such scans are taken at different times have not been com-

pletely successful, however, especially when dealing with structures not fixed in a bony vault. Today, integration of separate PET and CT image sets into a single study can be achieved with software fusion, and several commercial packages have been developed for this purpose.

Integrated PET/CT provides physicians with additional information on staging of cancers, restaging of cancers, patient prognosis, and effectiveness of cancer therapies. Advantages include superior lesion localization from near-perfect anatomic/functional registration with fewer motion artifacts, better distinction between physiologic uptake and pathological uptake, consolidation of patient's imaging studies, and shorter scan time (average 30 minutes to complete versus 60 minutes with standard PET) by using CT for attenuation correction. The last aids in patient comfort and minimizes claustrophobia problems.

CONCLUSION

The diagnosis and follow-up of squamous cell carcinoma of the head and neck is traditionally based on clinical evaluation and anatomic imaging studies such as contrast-enhanced CT or MRI. Though enormously helpful in locating suspicious areas, these modalities cannot always differentiate persistent or recurrent tumor from inflammation or post-treatment changes.

FDG-PET has been shown to be useful in the detection and staging of primary and recurrent squamous cell carcinoma of the head and neck. PET has also demonstrated its utility in the diagnosis of the unknown primary and in surveillance following medical and surgical treatment of head and neck cancer.

The advent of combined PET/CT scanners has augmented the potential for valuable information to be provided by the imaging community to the clinicians who treat head and neck cancers.

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REFERENCES

- Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. *NEJM* 2001;345(26):1890-1900.
- Forastiere AA, Urba SG. Experimental therapeutic approaches for recurrent head and neck cancer. *Cancer Treat Res* 1995;4:263-281.
- Forastiere AA. Overview of platinum chemotherapy in head and neck cancer. *Semin Oncol* 1994; 21:20-27.
- Stern WB, Silver CE, Zeifer BA, et al. Computed tomography of the clinically negative neck. *Head Neck* 1990; 12:109-113.
- Di Chiro G, Brooks RA. PET quantitation: blessing and curse. *J Nucl Med* 1988;29:1603-1604.
- Di Chiro G, Fulham MJ. Virchow's shackles: can PET-FDG challenge tumor histology? *AJNR* 1993; 14:524527.
- Stokkel MP, ten Brock FW, van Rijk PP. The role of FDG PET in the clinical management of head and neck cancer. *Oral Oncol* 1998; 34:466-471.
- Ali S, Tiwari R, Snow G. False positive and false negative neck nodes. *Head Neck* 1985;8:78-82.
- Braams JW, Pruijm J, Freiling NJ, et al. Detection of lymph node metastases of squamous cell cancer of the head and neck with FDG-PET and MRI. *J Nucl Med* 1995;36:211-216.
- Jungehulsing M, Scheidhauer K, Damm M, et al. 2-[F]-fluoro-2-deoxy-d-glucose positron emission tomography is a sensitive tool for the detection of occult primary cancer (carcinoma of unknown primary syndrome) with head and neck lymph node manifestation. *Otolaryngol Head Neck Surg* 2000; 123:294-301.
- Kole AC, Nieweg OE, Pruijm J, et al. Detection of unknown occult primary tumors using positron emission tomography. *Cancer* 1998;82:160-166.
- Vokes EE, Weichselbaum RR, Lippman SM, et al. Head and neck cancer. *NEJM* 1993;328:184-194.
- Bhattacharyya N, Nayak VK. Survival outcomes for second primary head and neck cancer: a matched analysis. *Otolaryngol Head Neck Surg* 2005;132(1):63-68.
- Wax MK, Myers LL, Gabalski EC, et al. Positron emission tomography in the evaluation of synchronous lung lesions in patients with untreated head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2002; 128:703-707.
- Goerres GW, Schmid DT, Gratz KW, et al. Impact of whole body positron emission tomography on initial staging and therapy in patients with squamous cell carcinoma of the oral cavity. *Oral Oncol* 2003;39:547-551.
- Collins BT, Gardner LJ, Verma AK, et al. Correlation of fine needle aspiration biopsy and fluoride-18 fluorodeoxyglucose positron emission tomography in the assessment of locally recurrent and metastatic head and neck neoplasia. *Acta Cytol* 1998;42:1325-1329.
- Zhuang H, Kumar R, Mandel S, Alavi A. Investigation of thyroid, head, and neck cancers with PET. *Radiol Clin North Am* 2004; 42(6):1101-1111, viii.



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