

# 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

Patrick K. Ha, MD; Alia Hdeib, BS; David Goldenberg, MD; Heather Jacene, MD; Pavni Patel, MD; Wayne Koch, MD; Joseph Califano, MD; Charles W. Cummings, MD; Paul W. Flint, MD; Richard Wahl, MD; Ralph P. Tufano, MD

**Objective:** To evaluate the role of positron emission tomography and computed tomography (PET-CT) fusion in the management of early-stage and advanced-stage primary head and neck squamous cell cancer.

**Design:** Retrospective analysis, with a blinded evaluation of clinical data and formation of a treatment plan.

**Setting:** Single tertiary academic medical institution.

**Patients:** Thirty-six patients with previously untreated head and neck squamous cell carcinoma who underwent staging CT or magnetic resonance imaging of the neck prior to undergoing PET-CT as part of their initial diagnostic evaluation between July 2000 and January 2005.

**Main Outcome Measures:** Confirmation or alteration of the treatment plan with the addition of the PET-CT information compared with traditional clinical and radiological data alone for early-stage and advanced-

stage disease. When available, histopathological results were correlated with the PET-CT findings.

**Results:** Among the 36 patients, PET-CT provided additional information that confirmed the treatment plan in 25 patients (69%) and altered the treatment plan in 11 patients (31%). Six of 11 patients in the altered-treatment group had their tumors upstaged. Four of 8 patients with early-stage tumors had their treatment plan altered, compared with 7 of 28 patients with advanced-stage disease. Among 18 patients who underwent a surgical intervention for their primary tumor, PET-CT identified the primary tumor in all 18 patients and, based on histopathological findings, correctly staged the regional nodal disease in 9 of 16 patients who had their nodal disease addressed.

**Conclusion:** The use of PET-CT is important in the initial treatment planning of early-stage and advanced-stage head and neck squamous cell carcinoma.

*Arch Otolaryngol Head Neck Surg.* 2006;132:12-16

**H** EAD AND NECK SQUAMOUS cell carcinoma is the sixth most common type of cancer worldwide, with an annual incidence of more than 500 000 cases.<sup>1-3</sup> Head and neck cancer accounted for 6.6% of all new cancer diagnosed between 1985 and 1995, with a stable incidence during the past decade.<sup>1,4</sup> Head and neck squamous cell carcinoma is responsible for approximately 2.1% of all cancer-related deaths in the United States and is associated with significant morbidity and mortality, with a 50% estimated 5-year survival rate that has not changed significantly during the past decades, despite advances in diagnostic and treatment modalities.<sup>1-3</sup>

Although head and neck cancer can be successfully managed with a combination of surgical and chemoradiotherapeu-

tic interventions, the disease has to be well characterized before the most appropriate surgical or medical management can be implemented. Radiographic imaging is an integral part of the initial staging process for head and neck cancer<sup>5</sup> and plays an important role in identifying the local or regional extent of disease, the location of an unknown primary site, and the presence of distant metastases (particularly lung lesions), as well as in directing surgical planning.

Several imaging modalities are recommended as part of the initial evaluation of head and neck tumors, including magnetic resonance imaging and computed tomography (CT). Computed tomography is a well-established diagnostic imaging tool used in the initial staging and surgical planning for head and neck cancer because it provides structural information at a high

#### Author Affiliations:

Departments of Otolaryngology–Head and Neck Surgery (Drs Ha, Goldenberg, Koch, Califano, Cummings, Flint, and Tufano) and Nuclear Medicine (Drs Jacene, Patel, and Wahl), The Johns Hopkins University School of Medicine (Ms Hdeib), Baltimore, Md.

spatial resolution.<sup>6</sup> However, it does not always provide additional needed information, especially in the identification of an unknown primary site.<sup>6,7</sup> Often, contrasts between muscular, connective, and tumor tissue are not easily defined. Tumors of the larynx are particularly difficult to interpret, and there are known intraobserver and interobserver differences in the estimation of gross tumor volumes.<sup>8</sup> Suspicion for nodal disease is often based on size, which does not necessarily reflect the physiological activity within.

Positron emission tomography (PET) using the radiolabeled glucose analogue fluorodeoxyglucose F 18 is used in the initial evaluation and in the detection of recurrence of various types of cancer, including colon, lung, and head and neck cancer.<sup>9</sup> Positron emission tomography allows for the visualization of metabolically active tissues and is useful in the detection of head and neck tumor lymph node involvement.<sup>10</sup> It is used for initial staging, for defining regional or distant nodal disease, for localizing unknown primary tumors, and for identifying recurrent disease.<sup>6,10,11</sup> However, the lack of precise anatomical resolution that is necessary for surgical and radiotherapeutic planning limits its usefulness as a single diagnostic modality.<sup>6,10</sup> A newer imaging modality, PET and CT fusion (PET-CT), allows for simultaneous image acquisition and coregistration of metabolic and anatomical data, expanding the benefits of PET or CT alone.<sup>6,10</sup>

Although the use of PET-CT in the evaluation of head and neck cancer is promising, its role in treatment planning has not been completely elucidated. The objective of this study is to determine the role of PET-CT in the initial evaluation and the subsequent management (whether surgical or medical) of patients with suspected head and neck squamous cell cancer at a tertiary head and neck cancer center. We assessed whether the addition of PET-CT data, compared with CT or MRI alone, contributed to the treatment planning process. Herein, we report the results of the analysis of 36 patients who underwent PET-CT as part of the initial evaluation for head and neck cancer.

## METHODS

### PATIENTS

We reviewed the medical records of all patients between July 2000 and January 2005 who were initially seen for evaluation of suspected head and neck squamous cell cancer. Thirty-six patients had no previous treatment for their lesions and underwent CT or magnetic resonance imaging before undergoing PET-CT as part of their staging workup. Patients with non-squamous cell malignancies were excluded from the study, as were patients with previous surgical or chemotherapeutic treatment for the suspected lesions. The initial clinical evaluation consisted of a standard head and neck clinical examination and contrast-enhanced CT or magnetic resonance imaging. Eighteen of 36 patients eventually received surgical treatment for their disease, and their pathology specimens were analyzed by routine histopathological examination.

### IMAGE ACQUISITION AND ANALYSIS

Imaging was performed on a Discovery LS PET-CT scanner (GE Medical Systems, Milwaukee, Wis), which produces 2 synchro-

**Table 1. Patient Demographics Based on Whether the PET-CT Findings Confirmed or Altered the Treatment Plan**

Demographic	Confirmed Treatment (n = 25)	Altered Treatment (n = 11)
Gender		
Male	19	9
Female	6	2
Age, mean (range), y	58.3 (17-81)	59.2 (40-80)
Primary tumor site		
Paranasal sinus	0	1
Nasopharynx	4	0
Oral cavity	1	3
Oropharynx	10	3
Larynx or hypopharynx	6	3
Unknown	4	1

Abbreviation: PET-CT, positron emission tomography and computed tomography.

nous images, one relying on CT and the other on PET using the radiolabeled glucose analogue <sup>18</sup>F. A comprehensive description of the functional and technical logistics of the PET-CT scanner has been previously published by Beyer et al.<sup>12</sup> Briefly, the CT portion of the examination, which produces images with detailed anatomical resolution, was performed without the use of intravenous contrast agents. The PET portion requires the administration of the radiolabeled glucose analogue <sup>18</sup>F before image acquisition. This technology relies on the avid uptake of glucose by highly metabolically active tissues, such as tumors and on the subsequent positron emission from the metabolized radiolabeled glucose. Positrons collide with electrons and emit gamma rays that are converted into a computer image. This PET image is fused with the CT image by a computer algorithm to provide a detailed PET-CT image. The images obtained from the PET-CT scanner were reviewed by board-certified nuclear medicine physicians (H.J., P.P., and R.W.) with extensive clinical experience in PET-CT image interpretation.

## STUDY DESIGN

Clinical information, including initial symptoms, physical examination findings, and results of conventional diagnostic testing, was analyzed in a blinded fashion by one of us (R.P.T.). Treatment plans were then generated using only this information. The PET-CT results were then revealed, and new PET-CT-informed clinical assessments and treatment plans were generated. For each patient, the PET-CT results were categorized as providing additional information that altered the treatment plan or that confirmed the treatment plan. In patients who underwent surgery, the PET-CT results were correlated with histopathological findings.

## RESULTS

Thirty-six patients met the inclusion criteria and had their cases reviewed. Using PET-CT, the treatment plan was confirmed in 25 (69%) of 36 patients. In 11 (31%) of 36 patients, PET-CT provided additional information that altered the treatment plan. **Table 1** gives the demographic data for these 2 groups. Only 1 of 5 unknown primary tumor sites was identified on PET-CT that led to an alteration of the treatment plan.

Each patient's American Joint Committee on Cancer stage was recorded, first using only the physical exami-

**Table 2. TNM Stages Before and After PET-CT in the Confirmed-Treatment and Altered-Treatment Groups**

TNM Stage	Confirmed Treatment (n = 25)	Altered Treatment (n = 11)
Before PET-CT		
I	2	2
II	2	2
III	4	2
IV	17	5
After PET-CT		
I	1	0
II	2	0
III	5	4
IV	17	7

Abbreviation: PET-CT, positron emission tomography and computed tomography.

nation and conventional imaging results and then adding the PET-CT information. **Table 2** gives the stages before and after PET-CT, separated into stages that confirmed the treatment plan and stages that altered the treatment plan. Eight patients had early-stage disease (stage I or II), and 4 of them had treatment plan alterations based on the PET-CT results. Twenty-eight patients were initially staged with advanced-stage disease (stage III or IV), and 7 of them had treatment plan alterations based on the results of PET-CT.

A detailed list of the patients for whom the treatment plan was altered as a result of the PET-CT findings is given in **Table 3**, along with their TNM stage before and after PET-CT. Six of 11 patients had their disease upstaged. Five of the 11 had neck disease that was detected by PET-CT alone, while 3 of the 11 had suspicious lesions in their lungs identified.

Eighteen (50%) of 36 patients underwent a surgical intervention for their primary tumor, and PET-CT identified all 18 of the primary tumor sites. Sixteen patients had their nodal disease addressed, and PET-CT correctly identified the nodal stage in 9 of them, based on histopathological findings. Two patients had lung lesions that were suspicious for malignancy on PET-CT that subsequently were found to be reactive or inflammatory, while PET-CT correctly identified a lung metastasis in 1 patient. One patient had a reactive neck node on final histopathological examination that was considered malignant on PET-CT, and 1 patient had lymph nodes positive for squamous cell carcinoma contralateral to the primary tumor that were not identified by PET-CT. The latter patient underwent surgical salvage 6 months after completion of combined chemotherapy and radiotherapy management. Based on final histopathological findings, 3 patients were incorrectly staged on PET-CT because of underestimated numbers of lymph nodes, generally as a result of a cluster of nodes being read as a single node.

#### COMMENT

Head and neck squamous cell carcinoma is a disease associated with significant morbidity and mortality. These

tumors can be successfully treated with surgical intervention and chemoradiotherapeutic regimens, although the stage of the cancer has to be accurately characterized in advance so that an appropriate therapeutic plan can be tailored to the patient. Diagnostic imaging plays an important role in the initial staging process for head and neck squamous cell cancer by helping to identify the extent of locoregional invasion and whether it has metastasized to distant sites. Traditional diagnostic imaging studies such as CT, magnetic resonance imaging, and ultrasonography have well-documented strengths and limitations. None of these techniques has emerged as the test of choice for every patient.

Positron emission tomography for head and neck cancer has gained popularity recently, and PET has been compared with traditional imaging modalities for different uses, including identifying primary lesions, other unknown primary lesions, nodal disease, and distant metastases.<sup>7</sup> Overall, the sensitivity and specificity of PET compare favorably with those of other techniques, and most studies<sup>8,13-17</sup> found PET to be superior. However, some critics of PET cite a lack of anatomical correlation as a major flaw in its use in treatment planning.<sup>18</sup>

As a diagnostic tool, PET-CT provides information about the metabolic activity of the suspected cancer and its exact anatomical location.<sup>6,19</sup> Investigators have capitalized on this delineation of physiological and anatomical detail by planning localized radiotherapy for oropharyngeal and nasopharyngeal carcinomas in which more normal tissue is spared from the harmful effects of radiotherapy.<sup>20</sup> However, PET-CT is costly compared with conventional imaging techniques, and the question of which patients benefit from an initial PET-CT workup is still being answered. In a recent study,<sup>21</sup> investigators examined 36 untreated patients with head and neck squamous cell carcinoma by PET-CT to determine their tumor stages and any potential alterations of chemoradiotherapeutic protocols based on the results. Ultimately, 9 patients had treatment plan alterations as a result of their PET-CT findings.

Our study sought to determine which patient population would benefit most from an initial workup with PET-CT and, most important, how the information provided would affect the therapeutic options. Overall, there was an alteration of the treatment plan in 11 (31%) of 36 patients, most often as a result of upstaging the tumor. This is a significant proportion of patients affected by the results of a single imaging modality. Many of the treatment plan alterations included the addition of chemotherapy or radiotherapy so that a multimodality approach was favored. Suspicious lung nodules requiring further workup accounted for alteration of the treatment plan in 3 patients. These patients were in the advanced-stage group, and although 2 of them had false-positive test results, PET-CT seems to be an acceptable screening tool for distant metastases. Missed distant metastases in this patient population may result in inappropriately aggressive treatment. The detection of additional pathologic neck lymphadenopathy contributed to treatment plan alterations in 7 patients, and identification of an unknown primary tumor led to an alteration of the treatment plan in 1 patient. In 4 of 8 patients with early-stage lesions and in 7 of 28 patients with advanced-

**Table 3. Characteristics of the Altered-Treatment Group**

Patient No.	Primary Tumor Site	TNM Stage		Treatment Plan Alteration
		Before PET-CT	After PET-CT	
1	Unknown primary	Tx N2b M0	T2 N2b M0	Identification of primary site in oropharynx; focused therapy
2	Supraglottis	T1 N0 M0	T3 N0 M0	Upstage; tumor found in preepiglottic space, favor surgical option or chemotherapy
3	Oropharynx and supraglottis	T2 N0 M0/T1 N0 M0	T2 N1 M0/T1	Upstage; identified neck metastasis, options: chemoradiotherapy, surgery and radiotherapy
4	Oropharynx	T1 N0 M0	T1 N1 M0	Upstage; identified neck metastasis, options: chemoradiotherapy, surgery and radiotherapy
5	Oral cavity	T4 N2b M0	T4 N2c M0	Must address the contralateral neck
6	Supraglottis	T2 N0 M0	T2 N1 M0	Upstage; identified neck metastasis, combined chemoradiotherapy now an option
7	Oral cavity	T4 N0 M0	T4 N2b M0	Identified neck metastasis; must address
8	Oral cavity	T3 N1 M0	T4 N2b M0	Upstage; identified multiple neck metastases, consider more extensive resection of primary carcinoma and management of the neck
9	Oropharynx	T4 N2b M0	T4 N2b M1	Identified lung nodule; must further characterize
10	Maxillary sinus	T4 N0 M0	T4 N1 M1	Identified neck metastasis and lung nodule; treatment of neck differs, must characterize lung nodule
11	Supraglottis	T3 N1 M0	T3 N2b M1	Upstage; identified multiple neck metastases and lung nodule; requires evaluation of lung and possibly more extensive treatment of neck

Abbreviation: PET-CT, positron emission tomography and computed tomography.

stage lesions, the initial stage was altered because of the PET-CT findings, indicating that patients of all stages could benefit from the additional information that PET-CT provides. Patients with early-stage disease were most often upstaged secondary to the detection of suspicious nodal metastasis. Patients with advanced-stage disease may benefit from the detection of distant metastases and of contralateral neck involvement.

Of the 36 patients in this study, 18 underwent surgical resection of the primary tumor. All 18 primary sites were correctly identified by PET-CT. However, nodal staging was not as accurate, with 9 (56%) of 16 patients appropriately staged. Many of the patients in this study received radiotherapy with or without chemotherapy, precluding further histopathological correlation. An accurate statistical validation of PET-CT findings cannot be performed until greater numbers of patients can be studied. Although PET-CT is adept at delineating the extent of the primary tumor, it has some limitations in defining the number of suspicious nodes, particularly when there is a large cluster of lymph nodes with tumor involvement. However, this limitation may be compensated for by the ability of PET-CT to delineate where nodal disease is located in the neck and whether there is unilateral or bilateral nodal disease.

### CONCLUSIONS

Although it is a relatively new diagnostic imaging modality, PET-CT plays a significant role in the initial staging and in the therapeutic management planning for untreated head and neck squamous cell cancer. The results of our study show that PET-CT is useful in the staging and treatment planning of patients with early-stage and advanced-stage disease. Patients with early-stage dis-

ease can benefit from the detection of occult regional metastases, and those with advanced-stage disease can benefit from the detection of distant metastases and from a more precise definition of the extent of regional spread. This preliminary study supports the use of PET-CT in the initial evaluation of all patients with untreated head and neck squamous cell cancer, although further investigation is warranted.

**Submitted for Publication:** May 2, 2005; accepted August 21, 2005.

**Correspondence:** Ralph P. Tufano, MD, Department of Otolaryngology–Head and Neck Surgery, The Johns Hopkins University School of Medicine, 601 N Caroline St, Sixth Floor, Baltimore, MD 21287-0910 (rtufano@jhmi.edu).

**Author Contributions:** Drs Ha and Tufano had full access to all the data in the study and take responsibility for the integrity of the data and for the accuracy of the data analysis.

**Financial Disclosure:** None.

### REFERENCES

- McMahon S, Chen AY. Head and neck cancer. *Cancer Metastasis Rev.* 2003;22:21-24.
- Mao L, Hong WK, Papadimitrakopoulou VA. Focus on head and neck cancer. *Cancer Cell.* 2004;5:311-316.
- Hunter KD, Parkinson EK, Harrison PR. Profiling early head and neck cancer. *Nat Rev Cancer.* 2005;5:127-135.
- Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. *N Engl J Med.* 2001;345:1890-1900.
- Kutler DI, Wong RJ, Kraus DH. Functional imaging in head and neck cancer. *Curr Oncol Rep.* 2005;7:137-144.
- Schoder H, Yeung HW, Gonen M, Kraus D, Larson SM. Head and neck cancer: clinical usefulness and accuracy of PET/CT image fusion. *Radiology.* 2004;231:65-72.

7. Schoder H, Yeung HW. Positron emission imaging of head and neck cancer, including thyroid carcinoma. *Semin Nucl Med.* 2004;34:180-197.
8. Kubota K, Yokoyama J, Yamaguchi K, et al. FDG-PET delayed imaging for the detection of head and neck cancer recurrence after radio-chemotherapy: comparison with MRI/CT. *Eur J Nucl Med Mol Imaging.* 2004;31:590-595.
9. Stokkel MP, ten Broek FW, van Rijk PP. The role of FDG PET in the clinical management of head and neck cancer. *Oral Oncol.* 1998;34:466-471.
10. Goerres GW, von Schulthess GK, Steinert HC. Why most PET of lung and head-and-neck cancer will be PET/CT. *J Nucl Med.* 2004;45(suppl 1):66S-71S.
11. Daisne JF, Sibomana M, Bol A, Cosnard G, Lonneux M, Gregoire V. Evaluation of a multimodality image (CT, MRI and PET) coregistration procedure on phantom and head and neck cancer patients: accuracy, reproducibility and consistency. *Radiother Oncol.* 2003;69:237-245.
12. Beyer T, Townsend DW, Brun T, et al. A combined PET/CT scanner for clinical oncology. *J Nucl Med.* 2000;41:1369-1379.
13. Adams S, Baum RP, Stuckensen T, Bitter K, Hor G. Prospective comparison of 18F-FDG PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. *Eur J Nucl Med.* 1998;25:1255-1260.
14. Di Martino E, Nowak B, Hassan HA, et al. Diagnosis and staging of head and neck cancer: a comparison of modern imaging modalities (positron emission tomography, computed tomography, color-coded duplex sonography) with panendoscopic and histopathologic findings. *Arch Otolaryngol Head Neck Surg.* 2000; 126:1457-1461.
15. Jones J, Farag I, Hain SF, McGurk M. Positron emission tomography (PET) in the management of oro-pharyngeal cancer. *Eur J Surg Oncol.* 2005;31:170-176.
16. Muylle K, Castaigne C, Flamen P, et al. 18F-fluoro-2-deoxy-D-glucose positron emission tomographic imaging: recent developments in head and neck cancer the evolving role of surgery in the management of head and neck tumors. *Curr Opin Oncol.* 2005;17:249-253.
17. Hannah A, Scott AM, Tochon-Danguy H, et al. Evaluation of 18 F-fluorodeoxyglucose positron emission tomography and computed tomography with histopathologic correlation in the initial staging of head and neck cancer. *Ann Surg.* 2002;236:208-217.
18. McGuirt WF, Greven K, Williams D III, et al. PET scanning in head and neck oncology: a review. *Head Neck.* 1998;20:208-215.
19. Hany TF, Steinert HC, Goerres GW, Buck A, von Schulthess GK. PET diagnostic accuracy: improvement with in-line PET-CT system: initial results. *Radiology.* 2002; 225:575-581.
20. Nishioka T, Shiga T, Shirato H, et al. Image fusion between 18FDG-PET and MRI/CT for radiotherapy planning of oropharyngeal and nasopharyngeal carcinomas. *Int J Radiat Oncol Biol Phys.* 2002;53:1051-1057.
21. Koshy M, Paulino AC, Howell R, Schuster D, Halkar R, Davis LW. F-18 FDG PET-CT fusion in radiotherapy treatment planning for head and neck cancer. *Head Neck.* 2005;27:494-502.

### Correction

**Error in Title.** In the Original Article by Yueh et al titled "Development and Validation of the Effectiveness of the Auditory Rehabilitation Scale," published in the October issue of the ARCHIVES (2005;131:851-856), an error occurred in the title. The correct title is "Development and Validation of the Effectiveness of Auditory Rehabilitation Scale." This correction was made previously to online versions of this article.