POSITRON EMISSION TOMOGRAPHY IN THE EVALUATION OF STAGE III AND IV HEAD AND NECK CANCER

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Abstract: *Background.* Detection of metastatic disease in head and neck cancer patients is critical to preoperative planning, because patients with distant metastasis will not benefit from surgical therapy. Conventional radiographic modalities, such as CT and MR, give excellent anatomic detail but poorly identify unenlarged lymph nodes harboring metastatic disease.

Objective. A pilot study was conducted to evaluate the usefulness of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) detection of metastatic disease in patients with advanced-stage head and neck cancer.

Methods. Total body FDG-PET imaging was performed in a prospective manner on 12 consecutive patients with a new diagnosis of stage III or IV mucosal squamous cell carcinoma of the head and neck. Chest CT was also performed on all 12 patients. Patients found to have metastatic disease on either CT or PET imaging underwent procedures to obtain histopathologic confirmation of disease.

Results. Three patients (25%) had FDG-PET scans demonstrating metastatic disease. Two of these patients had no evidence of disease on chest radiograph or chest CT but were noted to have positive FDG-PET imaging within the mediastinal lymphatics. Mediastinoscopy was performed confirming metastatic disease in these patients. The third patient had a peripheral lung lesion detected on chest radiograph, CT, and FDG-PET. This nodule was diagnosed by CT-guided biopsy as squamous cell carcinoma.

Conclusion. FDG-PET scanning detected mediastinal disease in two patients (17%) with advanced-stage head and neck squamous cell carcinoma that was not identified with conventional imaging techniques. PET imaging seems to have significant potential in the detection of occult metastatic disease, particularly in the mediastinal lymphatics. © 2001 John Wiley & Sons, Inc. *Head Neck* **23:** 1056–1060, 2001.

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Accurate evaluation of distant disease in head and neck squamous cell carcinoma patients is critical to determine appropriate therapeutic approach and prognosis. Distant disease in this patient population frequently escapes detection during conventional preoperative evaluation. Because surgical management is reserved for patients with locoregional disease, identification of distant disease is critical and may significantly alter treatment options. At present, routine preoperative assessment of asymptomatic patients is limited to PA and lateral chest radiographs and

liver function tests. Plain chest radiographs detect less than 20% of pulmonary metastasis or second primary tumors compared with chest CT.[1] Chest CT scanning has been found to have a sensitivity of 89% and specificity of 93%[2] in detection of metastatic pulmonary disease.

There is growing evidence that FDG-PET imaging in evaluation of patients with malignancies is superior to CT imaging. FDG-PET is an imaging modality that detects malignancies of small size by measuring the increased metabolic rate of cancer tissue.[3] Because malignant cells have increased glucose use, the radionucleotide-labeled analog of glucose, 2-[18F] flouro-2-deoxy-D-glucose (FDG) can be used to detect tumors by assessment of the increased FDG metabolism of cancer cells compared with normal tissues. In patients with head and neck squamous cell carcinoma, FDG-PET has been demonstrated to be useful in evaluation of patients with recurrent disease in areas with postoperative and radiation changes, as well as in detection of occult cervical lymphatic disease.[4–6]

FDG-PET is considered to be as accurate as CT/MRI for staging patients with occult neck disease and in patients with suspected recurrence.[7,8] Use of FDG-PET for evaluation of the clinically negative neck has demonstrated 100% sensitivity and 90% specificity compared with CT scanning.[2,4] When comparing FDG-PET assessment of cervical metastasis to pathologic, the sensitivity of FDG-PET for cervical N staging varies between 67% and 91%, with a specificity of between 82% and100%. CT imaging cannot accurately detect lymph node metastasis less than 1 cm, whereas lymph node metastasis as small as 0.6 cm can be detected on FDG-PET imaging.[2] Compared with pathologic findings, recurrent disease has been detected at the primary site with an accuracy of 88%.[4] FDG-PET has been found to be especially useful in patients with suspected recurrence who have equivocal MRI studies.[8] Given the success of FDG-PET in detecting occult disease at primary and regional sites, we evaluated the ability of this imaging modality to detect mediastinal and pulmonary metastasis in patients with late stage head and neck cancer.

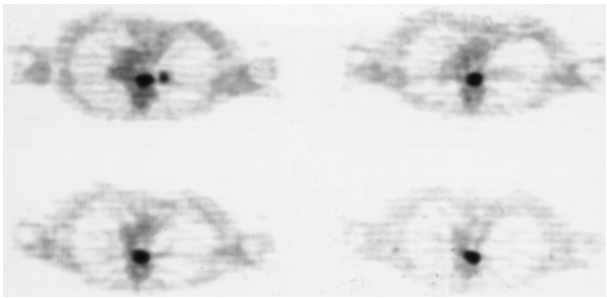

FIGURE 1. Panels from FDG-PET scan of patient, showing multiple foci of increased uptake in the mediastinum. The patient's CT scan of the chest was entirely normal.

METHODS

Patients. Twelve consecutive patients who were seen between January 1999 and July 1999 with a new diagnosis of stage III or IV mucosal squamous cell carcinoma of the upper aerodigestive tract were prospectively enrolled in the study. Patients were considered for the study after direct laryngoscopy and pathologic confirmation of disease. Plain chest radiographs, chest CT, and PET imaging were systematically performed in a manner that allowed for blinded interpretation by the radiologists. All patients with positive imaging (FDG-PET and/or CT imaging) were biopsied to obtain histopathologic confirmation of disease, establishing the presence or absence of disease in the chest rather than the number of nodes. CT criteria of lymph node metastases included central lucency (necrosis), indistinct nodal margins, or a size greater that 1.0 cm.

Imaging. PET was performed on a scanner (Picker PQ600, 1998) after patients underwent at least 4 hours of fasting. Transmission scanning for attenuation correction was performed before emission scanning with a germanium 68-ring source. Whole-body scanning was performed approximately 30 minutes after intravenous administration of 370 MBq (10 mCi) of FDG. Images were reconstructed with a Hann filter, resulting in approximately 12-mm full width at half maximum in-plane resolution. No quantitative analysis was performed, but the tomographic images were assessed qualitatively. Any hypermetabolic focus compared with the activity of normal muscular or lymphoid tissue and salivary glands was considered abnormal. Images were then evaluated by a radiologist without knowledge of chest CT findings.

RESULTS

Three patients (25%) of the 12 patients enrolled in the study had FDG-PET scans that identified

Table 1. Summary of patients enrolled.

Pt.	Age	Gender	Rec.	Primary tumor	Stage	CF	CCT	PET
1	61	M	N	Unknown	TxN3	–	–	+
2	57	M	Y	Supraglottic larynx	T3N0	–	–	–
3	61	M	N	Pyriform sinus	T4N0	–	–	–
4	66	M	Y	Supraglottic larynx	T3N0	+	+	+
5	61	M	Y	Base of tongue	T2N2	–	–	–
6	63	M	Y	Soft palate	T3N0	–	–	–
7	76	M	Y	Pharyngeal wall	T2N1	–	–	–
8	53	M	N	Supraglottic larynx	T3N0	–	–	–
9	56	M	Y	Base of tongue	T4N0	–	–	–
10	78	M	N	Supraglottic larynx	T3N0	–	–	+
11	60	M	N	Pyriform sinus	T4N0	–	–	–
12	62	M	N	Pyriform sinus	T4N1	–	–	–

Abbreviations: CCT, chest CT; CF, plain chest film; N, no; PET, positron emission tomography; Pt, patient number; Rec, recurrence; Y, yes; –, pulmonary metasis not visualized; +, pulmonary metasis visualized.

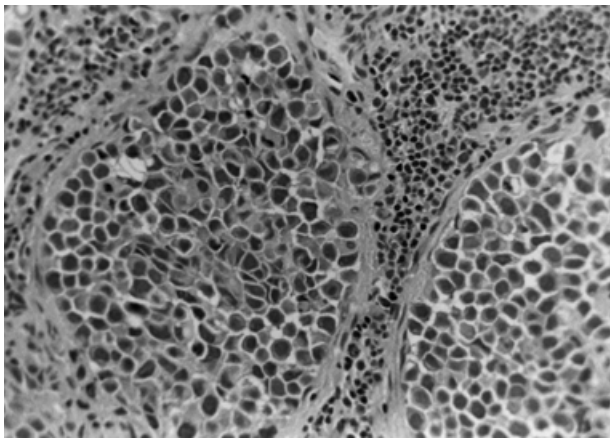

FIGURE 2. Histologic slide from mediastinal lymph node biopsy obtained from patient 1 (H & E stain, original magnification ×250) showing foci of squamous cell carcinoma within a background of lymph node tissue.

malignant disease within the thoracic cavity (Table 1). However, two of these patients (17%) had mediastinal lymphatic involvement detected by FDG-PET imaging that was not seen on chest CT or plain chest films (Fig. 1). Histopathologic confirmation of squamous cell carcinoma was obtained by mediastinoscopy in these two patients (Fig. 2). The third patient had a peripheral lung nodule detected on FDG-PET, CT, and preoperative plain chest films. The pulmonary nodule was diagnosed as squamous cell carcinoma by CT-guided biopsy. The primary disease was detected by FDG-PET imaging in all patients. All nine subjects who had negative imaging for distant disease went on to curative treatment and have not shown evidence of metastatic disease over the 24- to 28-month follow-up period. Although false negatives are possible, no study patient had metastatic disease develop during the minimum follow-up period of 24 months.

DISCUSSION

Anatomic imaging modalities have significantly advanced the ability to detect the presence of metastatic disease within the head and neck and within the thoracic cage. Currently, CT imaging is the criterion standard for radiographic evaluation of locoregional disease in head and neck cancer. CT is especially useful in mapping the extent of involvement in the primary tumor and in regional metastases.

The generally accepted size limit for detecting pathologic nodes using CT imaging is greater than 1.0 cm. This limits the usefulness of CT imaging, because more than 40% of all lymph node metastases are localized in nodes smaller than 1.0 cm.[9,10] Although MRI has gained importance in treatment planning,[11] the specificity of MRI in nodal detection has not been proven to be superior to CT.[6] Because FDG-PET imaging has been shown to detect disease in pathologic nodes as small as 0.6 cm,[6] its use in identification of nodal disease in head and neck cancer is growing. In addition, the use of whole-body FDG-PET imaging allows evaluation of the entire body for metastatic disease compared with CT, which is limited to the site chosen for imaging.

Despite the limited number of patients studied, the results of this pilot study suggest the potential for FDG-PET imaging to increase detection of pulmonary and mediastinal metastatic disease. As previous authors have concluded,[3,4] it is in the diagnosis of occult disease that

FDG-PET may significantly have an impact on patient care. Most importantly, accurate and timely diagnosis of pulmonary metastasis can eliminate the morbidity and mortality associated with extensive head and neck procedures, eliminate false hopes of surgical cure, and result in timely and appropriate treatment of metastases or synchronous primary tumors. Critics of the routine use of the FDG-PET imaging of the thorax cite the low yield of true positive studies and a high incidence of false positivity. In the largest head and neck cancer study to date, Keyes et al,[12] reported a 16% incidence of FDG uptake in the chest of 56 patients with a variety of tumor types. Most squamous cell carcinomas were stages I and II (68%), thus early tumors. In their analysis, only two patients were confirmed as truly positive for metastases (4%).[12] On the basis of these results, they concluded that "there is no compelling reason to include the entire chest region in the PET scan volume during the evaluation of head and neck cancers." A major difference between this study and ours is that the former did not perform biopsies and pathologic analysis of all hypermetabolic foci—only follow-up imaging was used to classify the remaining lesions as false positives. Also, our study was selectively applied only to stage III and IV squamous cell carcinomas, which may account for the higher incidence of metastases. Finally, a recent meta-analysis of 1474 pulmonary lesions revealed that FDG-PET had a sensitivity and specificity of 96.8% and 77.8%, respectively, in detecting malignancy.[13] In our study we had a 100% specificity and sensitivity. The reason for our variation from the reported data is likely because of the number of patients in the study and the level of experience of the interpreting radiologists. The latter point was also alluded to in the Keyes et al[12] study, in which it was stated that with increasing experience there was lower incidence of false positives.

There is no question that in patients with advanced head and neck tumors, the emotional and physical impact associated with resection and reconstruction are considerable. Equally considerable are the health care dollars spent on these procedures. Previous studies have demonstrated the potential cost-effectiveness of preoperative FDG-PET imaging in avoiding surgery in patients with metastatic disease or unresectable tumors.[14] In agreement with these findings, our study demonstrates that savings from contraindicated surgical procedures would exceed the cost of FDG-PET imaging. The cost-effectiveness of FDG-PET imaging was analyzed by using Health Care Financing Administration (HCFA) reimbursement rates for FDG-PET imaging.[15] Currently, insurance payer reimbursement for FDG-PET imaging of the thorax varies regionally in the United States, and this has been a major obstacle to its routine use in head and neck cancer staging. Demonstration that overall health care costs would decrease as a result of FDG-PET use may be an impetus to approve physician requests for its use. Analysis of HCFA reimbursement rates for FDG-PET imaging and surgical management of disease was conducted to determine cost-effectiveness of the population in this study (Table 2). In the study population (n = 12), two patients avoided surgery as a result of metastatic disease detected on FDG-PET. The cost for 12 FDG-PET scans, as well as three diagnostic procedures, was subtracted from the cost of the two major head and neck procedures that were avoided by detection of metastatic disease. Total saving to third-party payers would have been $17,484 across our study population. In fact, FDG-PET imaging would remain cost-effective if metastatic disease were identified in one of every nine patients. Similar analyses need to be conducted on a much larger scale to determine whether diagnostic strategies that include FDG-PET represent a good value for the health care dollar. An interesting point to note is that the patients with confirmed metastases had either advanced laryngeal primary lesions or extensive neck disease (Table 1). A larger analysis focusing on these particular parameters may be very revealing on the basis of our data.

Ultimately, we believe identification of pulmonary metastases or nodal disease in the chest will likely prove more clinically useful than FDG-

Table 2. Cost analysis. Average reimbursement by third-party payers for major head and neck ablation and reconstruction.

Professional	$4,900
Hospital	$16,248
Total	$21,148
Whole body PET	$1,912
Mediastinoscopy	$654
CT-guided needle biopsy	$560
Savings to insurance payers in study population: $17,484*	

**Calculation: [(total procedural reimbursement) × (patients detected with metastatic disease using FDG-PET data)] – [(reimbursement for whole body PET) × (no. patients in the study)] – [cost of diagnostic procedures].*

PET imaging of the clinically negative neck for several reasons. First, evaluation of the thoracic region is technically easier than evaluation of the cervical lymphatics, because it is farther from the strong signal produced by the primary tumor. Second, cervical false-positive lesions occur frequently because of asymmetric cervical muscular uptake resulting from contraction of the neck muscles. The lack of muscles within the lung parenchyma and upper mediastinum makes interpretation of chest FDG-PET less likely to give false positives. And finally, detection of pulmonary disease is more likely to have an impact on clinical management than identification of occult disease within the neck.

In conclusion, the results of this study suggest that FDG-PET imaging is superior to CT imaging of the chest in detection of occult metastatic disease in head and neck squamous cell cancer, particularly for pathologic involvement of mediastinal lymphatics. Further studies with more patients are warranted to assess the cost-effectiveness and the sensitivity and specificity of preoperative FDG-PET imaging in patients with advanced-stage head and neck cancer.

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