Positron Emission Tomography in the Evaluation of Synchronous Lung Lesions in Patients With Untreated Head and Neck Cancer

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Background: Positron emission tomography (PET) with the glucose analogue fludeoxyglucose F 18 uses the increased glucose uptake that is observed in neoplastic cells. It can differentiate between benign and malignant pulmonary lesions in patients with lung tumors. Applications of PET in extracranial head and neck neoplasms have included evaluating patients with unknown primary lesions, detecting primary and recurrent head and neck tumors, monitoring response to radiotherapy, and evaluating the N0 neck in oral cavity carcinomas. Its role in determining the presence of synchronous lung lesions has not been defined.

Patients and Methods: A retrospective review of 115 patients who underwent PET between October 1994 and October 1996 was performed to evaluate extracranial head and neck neoplasms. Fifty-nine (51%) previously untreated patients with squamous cell carcinoma of the upper aerodigestive tract were analyzed.

Results: Fifteen patients (25%) had PET scans that were positive for synchronous lung lesions. Five patients had a disease process that did not warrant further investigation; they did not have pathological confirmation of their lung lesions. Of these, 3 died of disease within 2 months of the diagnosis of primary head and neck squamous cell carcinoma, 1 was unavailable for follow-up, and 1 had lung lesions that were considered metastatic and no pathological confirmation of lung lesions was obtained. The remaining 10 patients with positive PET scan findings were investigated further: 8 patients had biopsy-confirmed lung lesions; 5 patients had positive findings on chest x-ray films; 8 had positive findings on computed tomographic scans; and 3 had positive findings on bronchoscopy. The results of 2 PET scans were false-positive. The PET scans were important in altering treatment in 3 patients; of these, 3 had negative findings on chest x-ray films, 2 had positive findings on computed tomographic scans, and 1 had positive findings on bronchoscopy.

Conclusions: The overall sensitivity, positive predictive value, and accuracy of PET were 100%, 80%, and 80%, respectively. The overall accuracy of radiography of the chest, computed tomography of the chest, and bronchoscopy was 70%, 90%, and 50%, respectively. The accuracy of PET over bronchoscopy was statistically significant (P<.05). PET appears to be a promising imaging modality for the detection of synchronous lung lesions in patients with negative findings on chest x-ray films.

PATIENTS AND METHODS

Between October 1994 and October 1996, 115 consecutive patients with a clinical diagnosis of a head and neck malignancy underwent PET scanning at the Veterans Affairs Western New York Health System (VAWNYHCS), Buffalo, NY, as part of an ongoing study to assess the utility of PET with FDG F 18 in the evaluation of head and neck neoplasms. This large study was approved by the institutional review board of VAWNYHCS. Fifty-six patients (49%) with recurrent SCCa or head and neck tumors, such as salivary gland neoplasm, malignant melanoma, thyroid neoplasm, nasopharyngeal carcinoma, metastatic adenocarcinoma, neurogenic neoplasm, and lymphoma, were excluded. Fifty-nine patients (51%) had biopsy-proved, previously untreated primary SCCa of the UADT.

All patients underwent PET scans, which were performed in the following manner: After informed consent was obtained, the patients were positioned in the machine (ECAT 951/31R; Siemens CTI, Knoxville, Tenn). A transmission scan of the body encompassing the head, neck, and thorax was obtained in each patient. Approximately 10 mCi (370 Mbq) of FDG F 18 was intravenously administered to each patient. After a waiting period of approximately 30 minutes for FDG F 18 incorporation into presumed lesions, total body imaging was obtained in the same planes in which transmission data were acquired. Approximately 35 million coincident events were registered, and the images were reconstructed using a Hann filter with a cutoff frequency of 0.3 cycle per pixel. The technical quality of the resulting images was high. Coronal, axial, and sagittal sections were reviewed (Figure 1 and Figure 2). The total average time for the entire PET procedure was approximately 1 hour. No untoward cardiac or respiratory events occurred during PET scanning.

All patients underwent radiography of the chest. Sixteen patients (30%) underwent computed tomography (CT) of the chest. The decision to obtain a CT scan of the chest was at the discretion of the attending otolaryngologist at the VAWNYHCS. All patients underwent a complete head and neck examination in the otolaryngology clinic at the VAWNYHCS. Panendoscopy was performed after the chest radiographic, chest CT, and PET scans were obtained. After disease staging, the patients were presented at a joint head and neck tumor conference. The PET findings were correlated with those of chest radiography, chest CT, bronchoscopy, and lung biopsy or bronchial washings.

For statistical analysis, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the PET and CT scans were calculated as follows: sensitivity, number of true-positive results/(number of true-positive results + number of false-negative results); specificity, true-negative results/(true-negative results + false-positive results); positive predictive value, true-positive results/(true-positive results + false-positive results); negative predictive value, true-negative results/(true-negative results + false-negative results); and accuracy (validity), (true-positive results + true-negative results)/total.
The specificity and negative predictive values were 0, because only patients with positive PET scans were selected for inclusion. For chest x-ray films, the sensitivity was 62%, the specificity was 100%, the positive predictive value was 100%, the negative predictive value was 40%, and the accuracy was 70%. For chest CT scans, the sensitivity was 87%, the specificity was 100%, the positive predictive value was 100%, the negative predictive value was 66%, and the accuracy was 90%. For bronchoscopies, the sensitivity was 38%, the specificity was 100%, the positive predictive value was 100%, the negative predictive value was 100%, and the accuracy was 50%. The accuracy of PET over bronchoscopy was statistically significant (P<.05). PET scans demonstrating lung lesions were important in altering treatment in 3 of 10 patients. The results of chest x-ray scans were negative in all 3 patients; those of chest CT scans were positive in 2 of the 3 patients; and those of bronchoscopies were positive in only 1 of the 3 patients.

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The pathogenesis of multiple primary cancers is not well understood, but is thought to be related to the effects of carcinogens on an organ system. In 1953, Slaughter et al\textsuperscript{19} applied the term field cancerization to the oral mucosa. This concept has since been applied to other organ systems, including skin, bladder, colon, breast, and lung.\textsuperscript{5} The phenomenon of neoplastic multicentricity may explain the pathogenesis of multiple UADT tumors that occur in some patients who abuse tobacco and alcohol. These substances may induce multiple areas of premalignant epithelial changes that in turn may give rise to multifocal primary neoplasms. An alternative theory is based on the premise that an initial single transforming event is rare. After this rare initial transformation, the progeny of the single neoplastic cell spread through the mucosa and give rise to a geographically distinct but genetically related tumors.\textsuperscript{16} Recent genetic investigation has found that the local clinical phenomenon of field cancerization seems to involve the expansion and migration of clonally related neoplastic cells.\textsuperscript{17}

PET with FDG F 18 uses abnormal tissue metabolism to detect neoplasms. The radioactive glucose analogue FDG is metabolized in normal tissue and neoplastic tissues in proportion to the rate of tissue glucose metabolism.\textsuperscript{18} It is phosphorylated to FDG-6 phosphate by the intracellular enzyme hexokinase. Deoxyglucose 6 phosphate does not serve as a substrate for further metabolisms, nor does it diffuse back across cell membranes to any significant degree. Deoxyglucose is metabolically trapped in the intracellular space, more so in tumors than in normal tissues,\textsuperscript{19} and can be used to identify tumors based on accelerated glycolytic rates using PET. Because of the higher glycolytic rate of many neoplasms compared with normal tissue, PET-FDG imaging is now being applied to many organ systems for tumor identification.\textsuperscript{19} 19

Rege et al\textsuperscript{14} have shown PET to be a useful diagnostic modality for evaluating patients with unknown primary tumors, monitoring response to therapy, and detecting recurrent tumors of the head and neck. They studied 60 patients with biopsy-proved cancers of the head and neck. Among a group of 4 patients with an unknown primary tumor, PET localized the tumor in 2 patients, whereas magnetic resonance imaging (MRI) was unable to localize the tumor in any patient. Among a group of 30 patients with a known primary tumor, PET detected the tumor in 29 patients, whereas MRI detected the tumor in only 23. Among 10 patients with biopsy-proved recurrent disease and 7 patients with no recurrence, the results of PET were positive in 9 of the 10 patients with recurrence, while those of MRI were positive in 6 of the 10 patients, and the results of PET were negative for recurrent disease in 7 of the 7 biopsy-negative patients, while those of MRI were negative for recurrent disease in 4 of the 7 patients.

Sazon et al\textsuperscript{20} used PET to evaluate 107 patients with abnormal findings on chest x-ray films. All 82 patients with lung cancer had positive results on PET scans. Sazon and colleagues observed false-positive results in 12 of 25 patients with nonmalignant diseases. Sixteen patients with lung cancer and mediastinal metastasis had positive results on PET scans in the mediastinum, and 3 of them had negative results on chest CT scans. Sixteen patients with lung cancer and no mediastinal nodal involvement had negative results on PET scans. Seven of these patients had positive results on CT scans. Sazon and colleagues found an overall sensitivity of 100% and a specificity of 52% in predicting the malignant nature of an abnormality on a chest x-ray film. They also found an accuracy of 100% in predicting mediastinal involvement.

Duhaylongsod et al\textsuperscript{21} studied 100 patients with indeterminate focal pulmonary abnormalities. They found PET to have a sensitivity, a specificity, and an accuracy of 97%, 82%, and 92%, respectively, for detecting lung lesions. Dewan et al\textsuperscript{22} prospectively studied 30 patients who presented with indeterminate solitary pulmonary nodules smaller than 3 cm based on chest x-ray films and chest CT scans. Twenty-seven of 30 pulmonary nodules were correctly characterized on PET scans. The diagnostic sensitivity was 95%, specificity 80%, positive predictive value 90%, and negative predictive value 89%.

Our data are consistent with these studies. The overall sensitivity of PET in detecting lung lesions in our study was 100%, the positive predictive value was 80%, and the accuracy (validity) was 80%. There was selection bias inherent in our study in that only patients with positive results on PET scans were included, which precluded us from detecting any false negative results.

Previous studies\textsuperscript{13} have reported the overall incidence of synchronous lesions in the entire UADT to be between 2% and 16%. Our study examined the incidence of synchronous lung lesions in patients with primary SCCa of the UADT. The incidence of synchronous, pathologically proved lung lesions detected by PET in our study was 15% (8 of 54 patients). These figures are higher than those of other investigators who reported on the incidence of second lung lesions. Leipzig et al\textsuperscript{13} found a 3.3% incidence of a second primary lung lesion; Maisal and Vermeersch,\textsuperscript{3} a 3.8% incidence; McGuirt,\textsuperscript{23} a 3.7% incidence; and Atabek et al,\textsuperscript{11} a 5.4% incidence. The reason the incidence of synchronous lung lesions in patients with head and neck cancer in our study differs from that in other studies is unclear. This discrepancy may be because our institution is a tertiary Veterans Affairs referral center and patients are often referred late in their disease process.

Oncological management was changed based on the PET findings in 3 of 10 patients. Patient 3 had positive results on PET scan and negative results on CT scan of the chest. The findings of radiography of the chest were also negative. He underwent treatment for his head and neck primary tumor and a second PET scan 6 months later. The results of the latter were again positive, and a second CT scan of the chest was performed. A lesion was now apparent on the CT scan. This correlated with the findings on the PET scan. Patient 3 underwent resection of an early-stage pulmonary tumor. Patient 4 had negative findings on chest x-ray films and underwent CT of his chest on the basis of the PET scan findings. A lesion that correlated with the PET scan was found on the CT scan of the chest, and the patient underwent treatment of that lesion, followed by treatment of the primary tumor in his head and neck. Patient 9 was found to have multiple metastatic nodules throughout the lungs and liver on his PET scan. The surgical treatment of the primary tumor in his head and neck was canceled, and
he underwent palliative chemotherapy for metastatic lung disease and a synchronous primary tumor. There were 2 PET scans (patients 2 and 6) with positive results in our study. The PET scan of patient 2 revealed a lesion in his right lung. After treatment of the tumor in his head and neck, he underwent a CT scan of his chest, the results of which were negative. A follow-up CT scan of his chest did not reveal any lesion. Patient 2 is alive without evidence of disease after 18 months of follow-up. The PET scan of patient 6 showed a left upper lobe lesion. The results of a follow-up scan of the chest were negative. The patient was followed up clinically and has had no evidence of disease after 10 months of follow-up. The treatment of patients with false-positive results on lung PET scans is problematic. Follow-up evaluation detected a primary tumor in the lung in 1 of our 3 patients with false-positive results, while the other 2 patients remained free of disease. It is possible that their follow-up was not long enough. Currently, patients with positive results on PET scans and negative results on CT scans of the chest are followed up with serial CT scans: the first is performed at 3 months; the rest are performed at 6-month intervals. A larger number of patients will be required before we can evaluate or comment on the utility of serial follow-up CT scans.

In 1979, Weaver et al. recognized that early diagnosis of lung cancer is difficult, with fewer than 30% of proved lung cancers identified on bronchoscopy. Some authors have shown that the presence of synchronous primary tumors or metastasis in the lung decreases patient survival. Others have shown that with the proper patient selection, pulmonary resection of lung metastasis is a potentially curable measure. PET appears to show promise in identifying synchronous lung lesions, which may have an impact on the choice of treatment in this patient population.

Our study demonstrated that of the 8 patients with carcinoma of the lung that correlated with the findings of pathologic examination of tissue, 4 had normal findings on chest x-ray films. Three of these 4 patients had CT scans of the chest that confirmed the PET scan findings. One patient’s lesion did not show up until a CT scan was obtained 6 months later. At our institution, we routinely order CT scans of the chest in cases involving advanced-stage neck disease. Three of the 4 patients who had positive findings on PET scan and normal findings on chest x-ray films had N0 neck disease. Consequently, a CT scan of the chest would not have been part of the routine in these patients. The fourth patient had N1 neck disease, and in that type of case it is arguable whether a CT scan of the chest should be part of the routine. We are currently evaluating the role of routine CT scanning of the chest in patients with head and neck cancer.

CONCLUSIONS

PET is a dynamic imaging modality that is increasingly being applied to the investigation of extracranial head and neck neoplasms. We investigated the ability of PET to determine the presence or absence of synchronous lung lesions in patients with UADT SCCa.

Fifteen patients had PET scans that were positive for primary UADT and synchronous lung lesions. In 5 of these patients, the PET findings added little to their overall prognosis or treatment course. Of the remaining 10 patients, 3 had their treatment changed because of the findings on the PET scans. PET appears to be a promising imaging modality for the investigation and detection of second primary lesions in the lung.

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REFERENCES