Characterization of pulmonary nodules and mediastinal staging of bronchogenic carcinoma with F-18 fluorodeoxyglucose positron emission tomography

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Abstract

Objective: To evaluate F-18 fluorodeoxyglucose positron emission tomography (PET) in terms of its sensitivity and specificity in diagnosing malignant pulmonary nodules and staging bronchogenic carcinoma. Methods: A retrospective review of any patient that presented to the VA Palo Alto Health Care System with a pulmonary nodule between 9/94 and 3/96 revealed 49 patients (four female, 45 male) age 37-85 (mean 63) with 54 pulmonary nodules who had: chest CT scan; PET scan; and tissue characterization of the nodule. Characterization of each nodule was achieved by histopathologic (N= 44) or cytopathologic (N= 10) analysis. Of the 49 patients, 18 had bronchogenic carcinoma which was adequately staged. Mediastinal PET and CT findings in these 18 patients were compared with the surgical pathology results. N2 disease was defined as mediastinal lymph node involvement by the American Thoracic Society’s classification system. Mediastinal lymph nodes were interpreted as positive by CT if they were larger than 1.0 cm in the short-axis diameter. Results: Sensitivity and specificity for the diagnosis of malignant pulmonary nodules using PET was 93 and 70%, respectively. All nodules (N= 3) that were falsely positive by PET scan were infectious in origin. All nodules (N= 4) that were falsely negative by PET were technically limited studies (outdated scanner, no attenuation correction, hyperglycemia) except for one case of metastatic adenocarcinoma. The sensitivity and specificity of PET in diagnosing N2 disease was 67 and 100%, compared with 56% and 100% for CT scan (not statistically significant). However, one more patient with N2 disease was correctly diagnosed by PET than by CT scan. Conclusion: PET is a valuable tool in the diagnosis and management of pulmonary nodules and may more accurately stage patients with bronchogenic carcinoma than CT scanning alone. © 1997 Elsevier Science B.V.

Keywords: Tomography, emission-computed; Computed tomography, comparative studies; Lung carcinoma, diagnosis; Lung carcinoma, staging; Positron emission tomography

1. Introduction

Management of indeterminate pulmonary nodules and the accurate staging of bronchogenic carcinoma are conundrums which thoracic surgeons have been faced with for years. Until recently, physicians have had to rely on non-invasive anatomic information such as the character of lung nodules by CT (the presence and pattern of calcification, etc.) and the size of mediastinal nodes by CT or more invasive methods such as tissue sampling (mediastinoscopy, CT guided needle, thoracoscopy) to guide clinical decisions in patients with indeterminate lung nodules or bronchogenic carcinoma.

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Positron emission tomography (PET) is a new non-invasive imaging study which provides physiologic as well as anatomic information that may make therapeutic and diagnostic decisions in these patients more accurate and potentially more cost effective. 

PET relies on the principle that neoplastic cells have enhanced glucose metabolism and therefore increased glucose uptake. F-18 Fluorodeoxyglucose (FDG) is a D-glucose analogue labeled with a positron emitting fluorine-18 molecule substituted for a hydroxyl group at the C-2 position. Once FDG has entered the cell, it is phosphorylated and therefore trapped intracellularly. PET quantitates FDG activity in vivo and identifies areas with increased glucose uptake suggestive of malignancy.

In this study we performed a single institution retrospective evaluation of the sensitivity and specificity of PET in differentiating benign and malignant pulmonary nodules as well as staging bronchogenic carcinoma. We also compared CT scan with PET scanning in terms of their ability to diagnose N2 disease.

2. Materials and methods

2.1. Patient selection

Between 9/94 and 3/96, 49 patients (four female and 45 male) age 37–85 (mean 63) with 54 pulmonary nodules were evaluated for the study. All patients had a chest CT scan, PET scan and tissue characterization of the nodule. Pulmonary nodule was defined as any radiopaque density on chest radiograph within the lung fields which could not be explained by a normal anatomic structure. 18 of the 31 patients with bronchogenic carcinoma had complete analysis of their mediastinal nodes (histopathology, PET and CT imaging) and therefore were included in the staging study. Patients, 13, with bronchogenic carcinoma were excluded due to indeterminate mediastinal PET scans (N = 2) or inadequate histopathologic analysis of mediastinal nodes (N = 11).

2.2. PET imaging

PET imaging was performed on a CTI Exact 921 scanner (CTI, Knoxville, TN). Patients were injected with 10–15 mCi of F-18 deoxyglucose after a fasting period of at least 4 h. Transmission scans were started 40 min post-injection for 1–2 million true coincidence counts per transaxial plane. Emission scans were started 60 min post-injection for 1 million true coincidence counts per transaxial plane. Images were reconstructed using multiple fields of view and a Hahn filter with a 0.5 cycle/pixel cut off and standard vendor-supplied software. All scans done before April 1, 1995 (N = 9) were performed on a single ring scanner with a transaxial resolution of 11 mm full width at half maximum (FWHM) and a field of view (FOV) of 7 cm. All scans done after April 1, 1995 (N = 40) were done on a three ring scanner which has a transaxial resolution of 6 mm FWHM and a FOV of 16 cm.
Fig. 1. CT scan of a 72 year old man with microscopic N2 disease found after right lower lobectomy. This axial image demonstrates a lobulated right lower lobe mass.

2.3. CT imaging

CT imaging was performed prior to PET scanning in all cases. The images were obtained on a GE high speed advantage helical scanner (GE Medical Systems, Milwaukee, WI). Contiguous images, 1 cm, were obtained after bolus intravenous injection of 150–200 ml of diatrizoate meglumine (Hypaque 60%, Sterling, New York, NY) at 2 ml/s by power injector and standard scanning indices were used.

2.4. PET interpretation

All PET scans were interpreted by one investigator (G.M.S.) and were classified as either positive or negative, based on the subjective evaluation of FDG uptake. Images were viewed in the axial, coronal and sagittal planes. Chest radiographs and CT findings were available at the time of initial PET interpretation. At the conclusion of the study the mediastinal images were reread by two investigators (P.S. and G.M.S.) without knowledge of patient identity or clinical data (including CT findings, pathology results, or the initial PET reading) and classified as either positive, negative or indeterminate. Blind rereading of the mediastinal images did not differ from the initial PET readings. Indeterminate mediastinal PET scans were those scans (N = 2) which showed diffuse low glucose uptake within the mediastinum. Indeterminate scans were read as such because they did not exhibit focal high intensity uptake (suggestive of mediastinal nodal involvement: PET positive) or zero uptake (suggestive of no mediastinal nodal involvement: PET negative). All positive mediastinal PET scans were assigned to a specific nodal station as defined by the American Thoracic Society’s classification system.

2.5. CT interpretation

All chest CT scans were interpreted by one investigator (P.S.). Mediastinal lymph nodes that measured greater than 1 cm in the short axis were considered positive. All positive nodes were assigned to specific nodal stations as defined by the American Thoracic Society’s classification system.

2.6. Pathologic diagnosis of pulmonary and mediastinal lesions

All pulmonary nodules were analyzed by histopathology (N = 44) or cytopathology (N = 10). Histologic specimens were obtained by surgical resection (N = 40: lobectomy, pneumonectomy, or wedge resection) or by autopsy (N = 2). Cytopathology specimens were obtained by fine needle aspiration (N = 8), bronchial brushings (N = 3), or bronchial washings (N = 1). All malignant cases that were diagnosed using cytopathologic methods represented advanced disease (Stage IIB or IV) and did not warrant resection with subsequent histopathologic analysis. For the 18 patients included in the staging study, mediastinal nodes were analyzed histologically after resection (N = 14), necropsy (N = 1), or mediastinoscopy (N = 3).
2.7. Statistical analysis

Sensitivity and specificity in the diagnosis of neoplastic lung disease were calculated for PET scanning. In addition, sensitivity and specificity of PET and CT scanning were calculated and compared using the McNamara test with regard to mediastinal staging in bronchogenic carcinoma.

PET mediastinal staging results are shown in Table 4. There were six true positive, nine true negative, and three false negative scans. There were no false positive scans. The sensitivity and specificity of PET in diagnosing N2 disease was 67% and 100%, respectively. Using the McNamara test, there was no statistically significant difference between PET and CT in diagnosing N2 disease. However, one more patient with N2 disease was correctly diagnosed by PET than by CT scan.

3. Results

The histologic results of the 54 pulmonary nodules are shown in Table 1. There were 33 cases of lung cancer, ten cases of metastatic lung disease, and 11 cases of benign disease. PET scan results are shown in Table 2. There were 40 true positive, seven true negative, four false negative, and three false positive scans when compared with the actual histopathologic results. The sensitivity and specificity of PET in diagnosing malignant lung nodules was 93% and 70%, respectively. All false positive nodules were granulomas. Three of the four false negative nodules were evaluated with poor quality PET scans (hyperglycemia at the time of the scan, no attenuation correction or performed on an outdated [single ring] scanner).

Results of mediastinal staging with CT are shown in Table 3. There were five true positive, nine true negative, and four false negative scans. There were no false positive scans. The sensitivity and specificity of CT in diagnosing N2 disease was 56% and 100% respectively.

4. Discussion

For years, physicians have relied on noninvasive imaging studies such as the chest radiograph and CT scan to make clinical decisions in patients with pulmonary nodules and in patients with bronchogenic carcinoma. Unfortunately, the chest radiograph and CT scan have poor sensitivities and lack sufficient specificity for critical clinical decision making. [3,8,11] Due to these inadequacies, physicians have had to resort to more invasive methods such as thoracoscopy, bronchoscopy, mediastinoscopy, CT guided needle biopsy, and even open thoracotomy.

The goal of any diagnostic test should be to yield as much accurate information as possible at the lowest possible cost to the patient, in both a physiologic as well as a fiscal sense. The gold standard in the diagnosis and management of lung malignancies is histopathology. However, the procedures used to obtain tissue are expensive (hospital costs, physician fees, etc.) and can
be quite morbid. PET is a new noninvasive imaging modality that relies on metabolic rather than anatomic properties of neoplastic tissue to reach a diagnosis of malignancy.

Our study accurately differentiates benign from malignant pulmonary lesions and is in agreement with several other investigators. [1,2,5] The three false positive examinations in our study were in patients with granulomas, which is also consistent with other reports. [1,2,5] The metabolically active inflammatory tissue within infectious lesions has been postulated to have a high glucose metabolism similar to neoplastic cells. [1,2,5] Quantitative analysis of the images may allow the differentiation between metabolically active benign lesions and malignant ones, and therefore reduce the false-positive rate. Three of the four false negative results in the diagnosis of pulmonary nodules were due to technically limited studies and can be explained on that basis. We have no explanation for the technically adequate false negative study in a patient with metastatic renal cell carcinoma.

In our study there was no significant difference between CT and PET in staging the mediastinum which differs from other investigators who have shown PET to be superior to CT in diagnosing N2 disease in bronchogenic carcinoma. [4,6,7,9,10] However, our study did accurately diagnose one more patient with N2 disease by PET than by CT (Figs. 1–3). The small number of patients in our study as well as selection and verification bias may explain why this trend did not achieve statistical significance.

In evaluating new diagnostic modalities, it is most desirable to use the gold standard (histology) as the only reference point for measuring performance. This can result in significant verification bias in a study like this, since many patients with mediastinal disease and most patients with distant metastasis are excluded from subsequent surgery and therefore definitive pathologic evaluation. As a result, patients with negative PET findings are over-represented in the study. Such selection bias increases the proportion of negative results, both true and false, thereby reducing the measured sensitivity and increasing the measured specificity of the diagnostic modality being studied. This explains why the sensitivity for both CT and PET in mediastinal staging was low and the specificity was so high in our study when compared with other investigators. [4,6,7,9,10] We could have reduced this bias by including patients with advanced stage disease and accepting less than histological means of measuring performance such as follow-up PET or CT.

Selection bias may also have had an impact on the evaluation of PET in the diagnosis of pulmonary nodules as a few patients with negative PET scans were not referred to surgeons for definitive diagnostic procedures and thus not included in the study.

On the basis of our findings and those of other investigators, we believe that PET is a reliable and powerful diagnostic modality that can be used for the diagnosis and management of patients with pulmonary nodules and in the staging of patients with bronchogenic carcinoma. Further studies are needed to address whether PET should be used as an adjunctive study or as the only study prior to making clinical decision such as whether to operate on a patient with lung cancer or to remove an undiagnosed pulmonary nodule. In addition, cost effectiveness studies should be undertaken prior to advocating the routine use of PET in the management of lung cancer.

Fig. 3. Coronal whole body PET image of the same patient showing FDG uptake in the right lower lobe and the mediastinum.

References


