Evaluation of Pulmonary Lesions With FDG-PET*

Comparison of Findings in Patients With and Without a History of Prior Malignancy

Steven B. Knight, MD; Dominique Delbeke, MD, PhD; James R. Stewart, MD, FCCP; and Martin P. Sandler, MD

Study objective: The purpose of this study was to evaluate the accuracy of positron emission tomography (PET) using F-18-fluorodeoxyglucose (FDG) in differentiating benign from malignant pulmonary lesions both in patients with and without a history of prior malignancy.

Design: Forty-eight consecutive patients with pulmonary lesions suspicious for malignancy underwent FDG-PET scanning. Group 1 included 27 patients without and group 2 included 21 patients with a history of malignancy. Pathologic proof of diagnosis was obtained for 32 patients and 16 patients were followed up clinically and radiographically for at least 6 months. The standard uptake ratio (SUR) and the lesion to background (L/B) ratio were determined in 45 patients.

Setting: Vanderbilt University Medical Center.

Results: In group 1, the average SUR and L/B ratio for malignant lesions (n=14) were 8.9±4.9 and 20.6±14.2, respectively. For benign lesions (n=12), the average SUR was 3.3±3.2 and L/B ratio was 5.2±5.5. In group 2, the average SUR and L/B ratio for malignant lesions were not significantly different from group 1. Using either a SUR greater than 2.5 or L/B ratio greater than 5 as an cutoff level to differentiate benign and malignant lesions, the sensitivity and negative predictive value in both groups were 100%. There were five false-positive studies in group 1 and one in group 2, including tuberculosis (n=2), a granulomatous lesion (n=1), an inflammatory lesion (n=1), a schwannoma (n=1), and a fibrous mesothelioma (n=1). The overall accuracy was 88%, 81% in group 1, and 93% in group 2.

Conclusion: FDG-PET can identify malignant pulmonary lesions both in patients without and with a history of prior malignancy with a high sensitivity and negative predictive value for lesions greater than 1 cm (100% in this study). High FDG uptake by some inflammatory processes and benign tumors may cause false-positive results. Semiquantitative evaluation using SUR or L/B ratio provides similar accuracy.

( CHEST 1996; 109:982-88)

| FDG=F-18-fluorodeoxyglucose; L/B=lesion to background; PET=positron emission tomography; ROI=region of interest; SUR=standard uptake ratio |

Key words: emission CT; fluorine; glucose, metabolism; lung, neoplasms

Increasing cost-effectiveness and decreasing the number of invasive procedures are currently two of the major trends in health care. Pursuant to these goals, considerable attention has recently been directed toward the use of metabolic imaging using positron emission tomography (PET) and F-18-fluorodeoxyglucose (FDG) in the evaluation of patients with cancer. Lung cancer, in particular, is of considerable interest, as it remains the leading cause of cancer death in the United States, and it is increasing in incidence worldwide.1,2 It is hoped that metabolic imaging, used in the appropriate setting, will allow significant reduction in the utilization of more costly and invasive surgical methods of diagnosing and staging disease in patients with suspicious pulmonary lesions.

It has been well established that tumor cells demonstrate increased metabolic activity.3 This is due in part to increased number of glucose transporter proteins and increased intracellular enzyme levels of hexokinase and phosphofructokinase, among others, which promote glycolysis.4,7 PET imaging with the glucose analogue FDG can be used to exploit the metabolic differences between benign and malignant cells for imaging purposes.8,9 Although variations in uptake are known to exist among tumor types, elevated uptake of FDG has been demonstrated in all lung cancer cell types10-13 and various malignant primary tumors.

Recent studies have shown that FDG-PET imaging can be used to accurately differentiate benign from

*From the Departments of Radiology and Radiological Sciences (Drs. Knight, Delbeke, and Sandler) and Cardiothoracic Surgery (Dr. Stewart), Vanderbilt University Medical Center, Nashville, Tenn.

Manuscript received July 6, 1995; revision accepted November 15.

Reprint requests: Tom Elers, Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Room D-1011 MCN, 21st Ave South and Garland Ave, Nashville, TN 37232-2675
malignant focal pulmonary abnormalities, including solitary pulmonary nodules and focal pulmonary masses.14-17 FDG-PET has also demonstrated considerable promise in detection of both intrathoracic and extrathoracic metastases in patients with pulmonary masses using whole-body scanning techniques.18 Recent data also suggest that FDG-PET is significantly more accurate than CT for noninvasively staging mediastinal disease.19,20

The purpose of this study was to evaluate the accuracy of FDG-PET in differentiating benign from malignant pulmonary lesions both in patients with and without a history of prior malignancy using either the standard uptake ratio (SUR) or the lesion to background (L/B) ratio for the semiquantitative analysis.

MATERIALS AND METHODS

Patient Population

This study included 48 consecutive patients who underwent an FDG-PET scan for clinical evaluation of a pulmonary lesion. There were 36 men and 12 women ranging from 33 to 88 years of age. Thirty patients had a pathologic diagnosis of the suspicious lesion within 6 weeks of the PET scan. Tissue was obtained by thoracotomy (n=22), endobronchial biopsy (n=4), pleural biopsy (n=1), mediastinoscopy (n=1), and fine-needle aspiration (n=2); 2 patients had evidence of malignancy by pleural cytologic study, and the presence or absence of malignancy was established with clinical and radiologic (chest radiograph and/or chest CT) follow-up ranging from 6 to 19 months in 16 patients. A lesion was considered malignant if it had increased in size on radiographic studies and this was demonstrated in eight patients with follow-up CT scan performed between 6 to 12 months after their initial evaluation. A lesion was considered benign if, without treatment, the size had not changed on CT and the patient had not developed clinical signs and symptoms suggesting a malignancy. At the time of the review, radiographic and clinical follow-up were available for the eight patients with a presumably benign lesion from 6 to 16 months after the initial follow-up.

PET Imaging

PET was performed with a tomograph (Siemens ECAT 933/08/16) that has eight rings of detectors to collect 15 transaxial images of 8 mm in thickness. The axial field of view is 12.5 cm, the intrinsic resolution at the center of the field of view is 4.8 mm, and the reconstructed resolution is 6.5 x 6.5 x 8 mm (full width half maximum). The sensitivity as measured by scanning a 20-cm-diameter cylindrical uniform phantom is 13,000 cps/mCi/mL in the direct planes. The scanner software estimates and corrects for random events using the standard window technique. The PET scanner is calibrated weekly with a phantom containing a known activity of germanium-68 and the calibration factor is determined as follows: nanocuries per milliliter in the phantom divided by counts/pixel/seconds.

Patients were fasted for at least 4 h prior to the PET scan. The patients were scanned in three sequential bed positions to include the entire chest. A transmission scan was performed for 10 min per bed position to correct for photon attenuation using a germanium-68 ring source. After the IV administration of 570 MBq (10 mCi) of FDG, emission images were acquired for 15 min per bed position. The uptake period between FDG injection and the beginning of the emission scan was 62±23 min. Accurate positioning of the patient between transmission and emission scan was performed using laser marks.

Image Analysis

The official chest radiograph and CT interpretation, rendered at the time of the examination and without knowledge of the PET scan findings, is provided. All PET images were interpreted independently by two experienced observers using correlation with a chest CT and/or a chest radiograph. For two patients, only a chest radiograph was available. The readers of the PET scan were blinded to the chest radiograph and CT interpretation, although the radiographic studies were available to provide the location of the lesion.

The images were analyzed semiquantitatively using the L/B ratio and the SUR in 45 patients. In three patients, semiquantitative evaluation was not performed because of motion artifacts (n=1) and partial volume effect (n=2, lesions <1 cm). For analysis of the PET images, the region of interest (ROI) for the lesion was placed at the site of maximal uptake activity and adjusted to the size of the lesion, ranging from 0.62 to 2 cm². The ROI for the background was placed in a homologous region of the lung contralateral to the lesion. The SUR was calculated as follows: SUR=ROI activity (μCi/mL)/injected dose (mCi)/weight (kg).

Statistical Analysis

Data were expressed as mean±SD. The SUR and L/B ratio were compared for the two groups of patients, respectively, using the two-sample Student’s t test. A p value <0.05 was considered statistically significant.

To assess the reproducibility of the analysis, ROIs have been drawn and SUR measured by two independent observers. The two sets of data were compared by the Student’s t test for paired data and showed no significant difference (p=0.4).

RESULTS

Patients were divided in two groups based on whether they had a history of prior malignancy. There were 27 patients with new pulmonary lesions and no history of malignancy (group 1) and 21 patients with a history of prior malignancy (group 2). The prior malignancies in patients from group 2 were the following: Hodgkin’s disease (n=1), melanoma (n=4), carcinoma of the colon (n=9), breast (n=2), cervix (n=2), lung (n=2), and kidney (n=1). All patients had surgical treatment of their primary malignancy and presented for evaluation of recurrent or metastatic disease.

Most patients presented with an indeterminate lung nodule (27/48 patients) or with a large abnormality on chest radiograph and CT of unclear etiology (6/48 patients). In six patients from group 1, malignancy was suspected on CT. These six lesions had FDG uptake with SUR greater than 2.5 and L/B ratio greater than 5. Malignancy was confirmed in four patients after histologic examination and in one patient after 19 months follow-up with massive dissemination of the disease. In one of these six patients, however, pathologic examination proved that the lesion was a benign schwannoma. In eight patients from group 2, lung nodules were interpreted as being metastases on radiographic studies because of evidence of metastatic disease elsewhere at the time of evaluation. These eight lesions had increased FDG uptake with an SUR greater than 2.5 and L/B ratio greater than 5. In one
of these patients, however, a wedge resection of the lesion proved it to be benign. In another patient with a history of colectomy for colon carcinoma, previous resection of a lung metastasis, and rising carcinoembryonic antigen level, the CT was interpreted as post-surgical changes and a follow-up CT showed multiple new lesions and that the original lesion had increased in size. The PET scan showed increased FDG uptake in the lesion.

A pathologic diagnosis was not obtained in eight patients with malignant lung lesions and eight patients with benign lung nodules. These patients had true-positive and true-negative PET scans, respectively. Among the eight patients with malignant lung lesions, one patient from group 1 had a 4-cm hilar mass that was interpreted as being malignant on CT but the patient refused surgery. Seven patients from group 2 had unresectable disease. Follow-up radiographic studies showed progression of the disease in all these patients.

For the eight patients with a benign nodule (five in group 1 and three in group 2), a follow-up CT scan showed no significant change in the size of the nodule and the patients did not develop clinical signs and symptoms suggesting a malignancy.

Table 1 shows means and SDs for SUR and L/B ratio in both groups of patients. There was no significant difference between the mean SUR and L/B ratio, respectively, from malignant lesions in patients without (group 1) and with (group 2) a history of prior malignancy (p>0.05). Both the SUR and L/B ratio were significantly higher in malignant lesions compared with benign lesions in both groups of patients using the SUR or the L/B ratio (p<0.001). Figure 1 shows the distribution of the SUR (Fig 1, top) and L/B ratio (Fig 1, bottom) in malignant and benign lesions from both groups of patients with the cutoff level chosen to differentiate malignant from benign lesions. A typical true-positive lesion is shown in Figure 2.

The threshold SUR of 2.5 using FDG-PET has been reported previously in the literature to provide optimal sensitivity and specificity in patients with a solitary lung nodule to differentiate benign from malignant nodules and was therefore chosen in this study. An L/B ratio of 5 identified the same lesions as a threshold SUR of 2.5 as being benign or malignant. In the group of patients without a history of prior malignancy (group 1), there were five false-positives using either the SUR with a cutoff level of 2.5 or the L/B ratio with a cutoff level of 5 to differentiate malignant from benign lesion. Two false-positive lesions were due to tuberculosis: a left upper lobe collapse/ left lower lobe consolidation.
Figure 2. True-positive (large cell carcinoma). Top: CT scan showing a 3-cm right upper lobe lesion. Bottom: FDG-PET scan showing increased uptake in the lesion (SUR, 9.3; L/B ratio, 9.0).

Figure 3. False-positive (schwannoma). Top: CT scan showing a 3-cm paraspinal mass in the right upper lobe (arrow) and several small mediastinal lymph nodes. Bottom: FDG-PET scan showing a large focal area of increased uptake (SUR, 6.7) corresponding to the paraspinal mass (arrow) and smaller foci of increased uptake in the mediastinum (SUR, 6.7; L/B ratio, 9.0).

For both group of patients, the sensitivity and negative predictive value were 100%. The accuracy was 81% for group 1 and 95% for group 2 (Table 2).

**Discussion**

PET provides a unique opportunity to study physiologic processes. Previous studies have demonstrated the usefulness of FDG-PET in the evaluation of pulmonary lesions. In this study, we compared the accuracy of FDG-PET to differentiate malignant from benign lesions in patients without and with a history of prior malignancy using two different parameters for semiquantitative measurements.

The two groups of patients were compared first using the SUR that requires attenuation correction of the images to measure the absolute uptake in the lesion. This also implies perfect registration of the transmission and emission images, which is not infrequently a problem when studying patients with large body habitus, patients who are unable to maintain their arms out of the field of view, and patients who are unable to lie...
Figure 4. False-positive (fibrous mesothelioma). Top: CT scan showing a large loculated mixed-density collection tracking in the major fissure. Bottom: FDG-PET scan: corresponding axial plane showing diffusely increased uptake in the entire posterior right lung field with a focus of greatest activity (SUR, 4.6) in the posterolateral right lower lobe (arrow) (SUR, 4.6; L/B ratio, 5.1).

still for a prolonged period of time. Therefore, the data were also compared using either the SUR or the L/B ratio. As found by Lowe et al., the analysis gave equivalent diagnostic information using either the SUR or L/B ratio.

In this study, there was no correction made for partial volume averaging. The influence of partial volume averaging has been well described in the literature. To assess the activity in an anatomic structure by PET imaging, the sampled volume should exceed the physical dimension of the resolution element by a factor of 2. If the sampled volume is smaller, the activity will be underestimated. Partial volume effect can play an important role in underestimating activity in lesions measuring less than 1 cm or in necrotic lesions with a thin viable rim, classifying these lesions benign instead of malignant. Therefore, in this study, semiquantitative evaluation was not performed on the two lesions less than 1 cm.

FDG uptake in bronchial carcinomas has been demonstrated to be influenced significantly by plasma glucose levels. Recent data have also shown that SUR overestimates FDG uptake in large patients and that correcting the FDG uptake for body surface area was preferable to body weight. In this study, the patients were fasted for at least 4 h before FDG injection. However, FDG uptake was not corrected for plasma glucose levels and the SUR was calculated using the body weight and not the body surface area.

As the patients were referred for a PET scan on clinical grounds and the findings on the PET scan may have influenced the treatment of some patients, this study is limited by a bias in the selection of the patients. For example, patients with a small indeterminate lung nodule and a normal PET scan are unlikely to be referred for a biopsy and the effect is to decrease the false-negative rate and therefore increase the sensitivity of the test. In this study, however, there were as many patients with an abnormal PET scan who were not referred for surgery because of unresectable disease, and this could decrease the false-positive rate and the specificity.

These data support the findings of previous studies suggesting that FDG-PET imaging is very sensitive for detection of malignancy in patients with discrete pulmonary lesions such as a solitary pulmonary nodule or focal pulmonary masses. In this study, a similar sensitivity of 100% was found in both groups of patients with and without a prior history of malignancy. It is important to note that using a cutoff level of 2.5 for the SUR and 5 for L/B ratio, there were no false-negatives in this group of patients with lesions greater than 1 cm (n=45). Therefore, in the evaluation of pulmonary lesions greater than 1 cm, FDG-PET has the potential to be able to exclude the presence of a malignancy with great certainty and to obviate the need of more expensive and invasive procedures in these patients. Although this study is limited by the small number of patients with benign disease, it is in agreement with similar observations reported by other investigators.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=27)</th>
<th>Group 2 (n=21)</th>
<th>All Patients (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence, %</td>
<td>55</td>
<td>77</td>
<td>65</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>100 (15/15)</td>
<td>100 (17/17)</td>
<td>100 (32/32)</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>58 (7/12)</td>
<td>75 (3/4)</td>
<td>62.5 (10/16)</td>
</tr>
<tr>
<td>Positive PV,* %</td>
<td>75 (15/20)</td>
<td>94 (17/18)</td>
<td>84 (32/38)</td>
</tr>
<tr>
<td>Negative PV,* %</td>
<td>100 (7/7)</td>
<td>100 (3/3)</td>
<td>100 (10/10)</td>
</tr>
<tr>
<td>Accuracy, %</td>
<td>81 (22/27)</td>
<td>95 (20/21)</td>
<td>88 (42/48)</td>
</tr>
</tbody>
</table>

*PV=predictive value.
A recent analysis of potential cost benefits projected that appropriate utilization of FDG-PET in the evaluation of solitary pulmonary nodules alone would result in annual cost savings of $165 million by decreasing the need for thoracotomies and transthoracic needle aspirations. A significant reduction in patient morbidity and mortality was also projected.28

Limitations of PET as a Diagnostic Tool

There is overlap between FDG uptake of malignant lesions and some infectious processes mainly due to the presence of macrophages. Although it is well known that macrophages have high FDG uptake, they may not constitute the only mechanism for FDG uptake at inflammatory sites.29 Active granulomatous processes such as tuberculosis and histoplasmosis have been reported to accumulate FDG and cause false-positive scans in the evaluation of malignancy with PET.15,16 Two of the six false-positive FDG-PET scans presented with large, poorly marginated chest radiograph abnormalities, one of which proved to be tuberculosis. These findings suggest caution should be taken when interpreting FDG-PET images in patients with non-focal abnormalities on chest radiographs. In this study, there was also increased FDG uptake in a schwannoma (Fig 3) and a fibrous mesothelioma (Fig 4). Both of these lesions were categorized as false-positive because neither demonstrated definite malignant characteristics on biopsy specimens (although the fibrous mesothelioma demonstrated focally increased cellularity), and there was no evidence of recurrence within the 12 months of follow-up.

Conclusion

FDG-PET is an accurate imaging modality to differentiate malignant from benign pulmonary lesions both in patients with and without a history of prior malignancy. The interpretation was equivalent using either the SUV or the L/B ratio, and the overall accuracy was 88%. Owing to its high sensitivity and negative predictive value for pulmonary lesions greater than 1 cm, FDG-PET can exclude the presence of a malignant lesion with great certainty, preventing further evaluation of some patients with expensive and invasive procedures.

Acknowledgments: The authors thank Nancy Buchheimer for excellent technical assistance and John Bobbitt for preparation of the figures.

References

3 Warburg O. Versuche und uberlebendem carcinomgewebe (methoden). Biochem Z 1923; 142:317-33
4 Flier JS, Mueckler MM, Usher P, et al. Elevated levels of glucose transport and transporter messenger RNA are induced by rats or src oncopenes. Science 1987; 235:1492-95
24 Kessler RM, Ellis JR, Eden M. Analysis of emission tomographic
scan data: limitation imposed by resolution and background. J Comput Assist Tomogr 1984; 8:514-22


