Dynamic Positron Emission Tomography With F-18 Fluorodeoxyglucose Imaging in Differentiation of Benign From Malignant Lung/Mediastinal Lesions*

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**Purpose:** This study was done to evaluate the diagnostic utility of dynamic positron emission tomography (PET) with F-18 fluorodeoxyglucose (FDG) imaging in patients with suspected malignant pulmonary lesions. We wanted to test the hypothesis that the rate of FDG uptake (FDG influx constant values) would differentiate malignant from benign lung or mediastinal lesions.

**Materials and methods:** We performed segmental dynamic PET imaging studies following administration of FDG in 19 patients with indeterminate pulmonary lesions based on chest radiograph and/or CT scans. Patlak analysis was done to compute Ki (FDG influx constant) values and compared with FDG standardized uptake values (SUVs) and histology.

**Results:** FDG Ki values (mean ± SD) were significantly greater (p < 0.01) in all 12 malignant lesions (0.029 ± 0.02) as compared with 7 benign lesions (0.0024 ± 0.0011) with good correlation to the SUV values. Distinct time activity curve patterns were identified in malignant and benign lesions with continued uptake in malignant lesions.

**Conclusion:** Dynamic PET-FDG imaging accurately differentiates malignant from benign pulmonary lesions. In certain cases with equivocal findings on visual analysis and SUV values, dynamic imaging may be further helpful in differentiating benign and malignant lesions.


**Key words:** metabolism; PET; pulmonary

**Abbreviations:** FDG = fluorodeoxyglucose; Ki = Patlak influx constant; PET = positron emission tomography; ROI = region of interest; SUV = standardized uptake value

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Positron emission tomography (PET) using F-18 fluorodeoxyglucose (FDG) has a potential to become a powerful noninvasive diagnostic tool to detect lung cancer. Recent studies have shown sensitivity and specificity of PET-FDG for detecting lung cancer to be in the 90 to 95% and 85 to 95% range, respectively.\(^2\,3\) Differentiation of benign from malignant lesions can be achieved by qualitative analysis of images or by quantitating glucose metabolic rate of tissues.\(^1\,2\) Standardized uptake value (SUV) of FDG accumulation in the cell is commonly used as a quantitative index for differentiating benign from malignant lesions.\(^2\,3\)

It is generally accepted that FDG accumulation in tumors tends to rise in contrast to normal tissue and benign processes where activity decrease with time.\(^2\) Following its IV administration, F-18 FDG is converted to F-18 FDG-6-phosphate by phosphorylation using hexokinase.\(^4\) The rate of uptake of F-18 FDG and accumulation of this tracer in cancer cells is significantly greater and is used clinically to differentiate between malignant lesions and normal tissues or benign process.\(^5\,7\)

In this study, we performed dynamic FDG-PET to determine whether the rate and specific pattern of FDG uptake in otherwise indeterminate lesions could differentiate benign from malignant lesions. These quantitative parameters were compared with visual analysis and SUVs to see if dynamic
imaging would be of additional clinical use or increase the accuracy of FDG-PET. It would be desirable to minimize the false-positive rate and maximize the sensitivity of detecting malignant lesions.

**Materials and Methods**

We studied 19 consecutive patients with an age range of 32 to 78 years referred for F-18 FDG PET studies for suspected malignant lesions in the lungs or in the mediastinum. These successive patients were studied as part of ongoing clinical studies at West Virginia University PET Center. All patients provided an informed consent for the PET studies. All patients fasted for at least 4 h prior to FDG injection. Serum glucose levels ranged from 80 to 160 mg/dL. These patients also had complete workup for suspected lung cancer, including chest radiograph and CT scan of the chest. All of these lesions were considered indeterminate based on CT scan and radiograph findings. The lesion size on CT ranged from 1 to 3.5 cm. All of these lesions were not calcified and considered indeterminate on visual analysis.

Dynamic imaging was acquired on a scanner (GE Advance; General Electric; Milwaukee, WI) equipped with 15 cm field of view and 5 mm full width half maximum transaxial resolution in the center of field of view. The dynamic series was acquired with the field of view centered over the pulmonary lesion of interest. Eighteen dynamic data frames were acquired for 1 h after IV injection of approximately 10 mCi of F-18 FDG. The acquisition sequence was 6 x 20 s, 3 x 1 min, 8 x 5 min, and 1 x 15 min. Patients were asked to lie motionless for the duration of the study. The images were reconstructed using a filter (Hanning) and back projection using a 0.3 cutoff value. The scanner has a 5 mm full width half maximum transaxial resolution in the center of field of view. Static emission scans (5 min each field of view) covering the entire chest in field of view were also acquired at 60 min postinjection. Attenuation correction of the reconstructed images was accomplished by acquiring transmission scan using Ge-68 ring source.

**PET Data Analysis**

**Time Activity Curves and Patlak Analysis:** Input function curve was derived by drawing a region of interest (ROI) in the left ventricle on the images, including the left ventricle in the field of view. Correction for partial volume effect was not made. Although this could result in overestimation of the Patlak influx constant (Ki) value, the general shape of the input function and the relative value of indexes would not be affected. The time activity curve of FDG uptake in the lesions was calculated by using ROIs placed within the lesion. ROIs were drawn in the slice with maximum tumor diameter. The ROI was drawn within the hottest part of the lesion showing increased FDG uptake. In other lesions with no detectable FDG uptake, the ROI was drawn as close as possible to the abnormality on chest radiograph or CT. Transmission scans were also utilized to accurately position the ROI over the area of interest. ROIs were also placed in the normal mediastinal tissues to compute the time activity curve in the mediastinal structures. Patlak analysis was then performed to compute FDG uptake influx constant (Ki) values.

Final diagnosis was obtained in all patients based on histological examination of either biopsy or surgical specimens. SUVs in the tumor or mediastinum were calculated based on the activity concentration present at the end of scan and corrected for the patient's body weight and dose injected as follows:

\[
SUV = \frac{\text{tissue activity (measured counts/pixel/s) \times calibration factor}}{\text{Injected F-18-FDG dose in mCi/body weight (kg)}}
\]

PET scan interpretation was based on visual qualitative analysis of images by two different viewers and lesions were classified as malignant or benign based on visual assessment of degree of the FDG uptake. Histologic diagnosis was not available at time of interpretation. Ratio of FDG activity in the lesion and the mediastinum assessed visually was used as criteria for differentiation between benign and malignant lesions. Malignant lesions should have lesion/mediastinal ratio of >1 while benign lesions should have ratio of <1.2,3

**Results**

The histologic specimens were obtained by needle biopsy (n = 10), thoracotomy (n = 8), or bronchoscopy (n = 1). Lesions ranged in size from 1 to 3.5 cm.

**Histology**

Histologic diagnosis was recorded to confirm malignant vs benign nature of the lesion. Final disease diagnosis confirmed 12 malignant and 7 benign lesions (lesions size, 1 to 3.5 cm). The specific tissue histology in malignant lesions included squamous cell (n = 6), adenocarcinoma (n = 3), and non-small cell carcinoma (n = 3). The benign histologic subtypes were granuloma (n = 3), nonspecific inflammation (n = 2), or reactive inflammation (n = 2). Benign lesions were confirmed to show no change in size up to 1 year follow-up. Multiple mediastinal lymph node lesions were present in seven patients; the lesions were classified as malignant (n = 5) or benign (n = 2). Both benign mediastinal lesions were seen in patients with benign solitary pulmonary nodule pathology findings. SUV values also differentiated between benign and malignant mediastinal lesions.

**PET Findings**

All malignant lesions (n = 12) were found to show the characteristic glucose hypermetabolism on visual

| Table 1—Summary of Various Cell Types, SUV Values, and Ki Values of Benign Lung Lesions |
|---|---|---|---|
| No. | SUV | Ki | Mediastinal SUVs |
| 1 | 0.4 | 0.001 | 1.08 |
| 2 | 0.81 | 0.004 | |
| 3 | 1.5 | 0.003 | |
| 4 | 1.75 | 0.003 | 2.0 |
| 5 | 1.6 | 0.004 | |
| 6 | 0.9 | 0.003 | |
| 7 | 2.0 | 0.002 | |
Table 2—Summary of Cell Types, SUV Values, and Patlak Analysis Results in Malignant Lung Lesions

<table>
<thead>
<tr>
<th>No.</th>
<th>Cell Type*</th>
<th>SUV</th>
<th>Ki</th>
<th>Mediastinal SUVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adeno</td>
<td>3.7</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Sq cell</td>
<td>2.18</td>
<td>0.021</td>
<td>4.55</td>
</tr>
<tr>
<td>3</td>
<td>Sq cell</td>
<td>9.58</td>
<td>0.023</td>
<td></td>
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<tr>
<td>4</td>
<td>Non-small cell</td>
<td>11.67</td>
<td>0.023</td>
<td>4.94</td>
</tr>
<tr>
<td>5</td>
<td>Sq cell</td>
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<td>0.013</td>
<td>5.20</td>
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<tr>
<td>6</td>
<td>Adeno</td>
<td>2.39</td>
<td>0.01</td>
<td></td>
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<tr>
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<td>Sq cell</td>
<td>10.12</td>
<td>0.023</td>
<td>5.4</td>
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<tr>
<td>8</td>
<td>Sq cell</td>
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<td>11.34</td>
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<tr>
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<td>Sq cell</td>
<td>8.4</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Non-small cell</td>
<td>5.4</td>
<td>0.011</td>
<td></td>
</tr>
</tbody>
</table>

*Adeno = adenocarcinoma; Sq = squamous.

analysis while benign lesions did not show any significant FDG uptake. Two readers interpreted the scans independently without knowledge of histologic findings. There was complete agreement between two different viewers regarding the malignant or benign nature of these lesions based on visual analysis of FDG uptake. In patients with SUV from 1.5 to 3 range lesion/mediastinal ratio was helpful in visual interpretation as mediastinal uptake is usually 2 to 2.5. SUV values were further used for differentiation in borderline cases.

Mean value ± SD of SUVs in malignant lesions was 7.12 ± 3.34, which was significantly higher (p < 0.01) than benign lesions (1.32 ± 0.61). Mean ± SD of SUVs in normal mediastinal ROIs was 2.04 ± 0.49. Using the t test, SUVs in malignant lesions were statistically higher than SUVs of benign lesions. The range of SUVs was 0.4 to 2.0 in benign (Table 1) and 2.18 to 11.12 in malignant lesions (Table 2). Time activity curves of malignant lesions showed a characteristic pattern of gradually increasing FDG uptake up to 60 min and beyond. No definite plateau effect was seen until 50 to 60 min. This pattern was designated as “type A” curve pattern. A typical example of curve A is shown in Figure 1. However, benign lesions demonstrated an initial rise with rapid downslope without plateau effect shown in Figure 2 (“type C” curve pattern). Ten of 12 malignant lesions showed curve “A” type patterns. Two of 12 malignant lesions showed progressively increasing uptake but with plateau seen at 50 to 60 min. This type of pattern was considered to represent a malignant process but “type B” curve. This pattern differed from a type “A” curve by early demonstration of peak by 50 to 60 mins.

Graphic derived Ki (K Patlak) values for FDG influx were computed for all studies using Patlak analysis. K Patlak value for benign lesions ranged from 0.001 to 0.004 (Table 1). The mean ± SD of Ki in benign lesions was 0.0024 ± 0.0011. Ki values for ROIs drawn in normal mediastinum ranged

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21845/ on 04/26/2017)
Figure 2. Time activity curve of FDG uptake in a benign lung lesion showing rapid uptake followed by rapid and then gradual washout component. The washout pattern in benign lesion (curve “C” pattern) is similar to the pattern of curve derived from ROI drawn in left ventricle.

Figure 3. K Patlak (K) values of FDG uptake in benign (n = 7) as compared with malignant (n = 12) lesions.
from 0.0010 to 0.0041 with mean ± SD of 0.0015 ± 0.0014. K Patlak values for malignant lesions ranged from 0.01 to 0.082 (Table 2). Mean ± SD of Ki in malignant lesions was 0.029 ± 0.02 (Fig 3). Using Student’s t test, there was statistically significant difference (p < 0.01) between Ki values for benign and malignant lesions.

In 12 malignant lesions, varying SUV values were seen in different histologic tissue types. There was no relationship between different histologic types and SUV values. Similarly, varying Ki values were noted in different histologic tissue types. No relationship between Ki values and histologic diagnosis was again seen.

Two lesions demonstrating reactive inflammation on histology had K Patlak values of 0.004 and 0.001. Time activity curve in these two lesions displayed configuration corresponding to “type C” curve pattern.

There was good correlation between SUV values and K Patlak indexes (Figs 3 and 4). All lesions showing SUV values >2 were found to depict time activity curve of “type A.” Three lesions showed SUV values of FDG uptake to be in 2 to 3 range, which might be considered indeterminate since this represents uptake intermediate between benign and malignant values.

Two lesions with SUVs of 2.18 and 2.39 showed malignant histology and had curve “type A” pattern. In these two lesions with borderline high SUVs, Ki values were of additional clinical benefit in confirming malignancy. In a third lesion with SUV of 2.0, Ki value was 0.002 and the curve showed pattern of benign lesion. This was confirmed as benign on histologic study.

**DISCUSSION**

The high metabolism and increased rate of glucose consumption of cancer is associated with increased level of glycolytic enzymes and overexpression of glucose transporters as compared with the surrounding normal tissues. It is well accepted that increased rates of transport and phosphorylation of the glucose analog and decreased rate of dephosphorylation of the phosphorylated sugars are important factors in the cellular mechanisms for tumor hypermetabolism. Significant correlation has been de-
scribed between FDG uptake and number of viable cancer cells in \textit{in vitro} and \textit{in vivo} tumor studies.\textsuperscript{11,12} PET-FDG scanning is now being advocated for clinical use in differentiation of benign and malignant pulmonary lesions.

Quantitative analysis (absolute glucose metabolic rate) as well as semiquantitative analysis (SUV determination) analyzed by computer SUV values has been reliable in detecting hypermetabolism due to malignant lesions. The sensitivity and specificity of the SUV method for differentiating between benign and malignant lesions has been found to be similar to the visual analysis and ranges between 90\% and 95\%. In most of the clinical PET sites, visual analysis is still the preferred method of interpretation with SUVs mainly used as an additional help. The clinical value of segmental dynamic imaging in separation of benign and malignant pulmonary lesions, however, has not been addressed.

Segmental dynamic scanning allows one to assess the temporal kinetics or rate of FDG uptake in the cells. The continually increasing FDG uptake in malignant cells, as demonstrated by “type A” curve patterns in our study, is probably secondary to elevated glucose transporter levels and elevated enzymes in tumor cells.\textsuperscript{13} Our study also suggests continuation of this progressive FDG tumor uptake beyond 60 min in most patients (Fig 5). A similar finding of continuous rise in the FDG uptake in malignant tissues has been reported on dynamic studies in ovarian cancers by Hubner et al.\textsuperscript{14} The lack of slowdown or even washout as observed in normal tissues may be due to low phosphatase content in malignant cells. Our study clearly documents the high specificity (no false positives) of observing this curve pattern in lung cancer. Occasionally, in patients with equivocal SUV values (between 2 and 3), dynamic data may be of use in confirming malignancy. In our study, two patients with malignant lesions had borderline high SUVs but unequivical high Ki values.

Previously, some investigators have speculated whether inflammatory cells, namely neutrophils or macrophages, could also depict the continued accumulation of FDG uptake.\textsuperscript{15} In our series, initial increase with gradual washout pattern was typically seen in benign lesions harboring inflammatory processes. It is possible that inflammatory lesions in three patients in our series lacked the critical number of inflammatory white cells to show significant FDG uptake. However, false-positive FDG uptake is observed only in small percentage of patients with inflammatory lesions in our experience as well as based on the experience of other investigators.\textsuperscript{9,16,17} Thus, SUV values and dynamic imaging patterns could independently differentiate benign inflammatory from malignant process.

Several investigators in the past have failed to find correlation between different histologic tissue types of malignant tumors and amount of FDG uptake or
SUV values. Specifically, no correlation has been reported between lung cancer histologic types and SUV values of FDG uptake. Our initial results also confirm lack of relationship between histologic subtypes and FDG quantitative uptake values. Thus, no relationship has been found between FDG influx constant (Ki) values and different cell types of lung cancer.

Our study confirms the different time activity patterns of FDG uptake in malignant vs benign lesions. However, these preliminary data fail to demonstrate that Ki values are superior to SUV values. SUV values have already been found to be a useful parameter for differentiation between malignant and benign lesions. For routine clinical use, SUV values have been shown to be simple and reliable in differentiation of benign and malignant lesions. With no added benefit, the prolonged patient scan time required for dynamic studies (1 hour during postinjection) may not be justifiable. With widespread clinical use of PET-FDG in lung nodules and lung cancer, any further improvement in accuracy would be an asset. The few patients with borderline SUVs ranging from 2 to 3 might benefit from dynamic data in establishing the diagnosis with greater confidence. It would be possible to perform a repeat PET study with dynamic protocol in the small percentage of patients with equivocal SUVs between 2 and 3 (15% of patients in our study). However, the benefit in this relatively small percentage of patients with equivocal SUVs has to be confirmed and measured. Further studies in larger number of patients may be needed to evaluate the exact incremental value of Ki analysis in the diagnosis of lung lesions.

References


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