Solitary Pulmonary Nodules Differentiated by Dynamic F-18 FDG PET in a Region with High Prevalence of Granulomatous Disease

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F-18 fluorodeoxyglucose/Positron emission tomography/Solitary pulmonary nodules/Kinetic analysis.

This study determined whether dynamic F-18 FDG PET imaging could differentiate benign from malignant solitary pulmonary nodules (SPNs). Histopathologically confirmed SPNs (10–35 mm), 24 malignant and 10 benign, from 34 patients were studied through both dynamic and static F-18 FDG PET imaging of all patients. Volumes of interest (VOIs) were placed over the pulmonary nodules using a 50% maximum pixel value threshold. The arterial input function was estimated from a left ventricle-defined VOI. Based on Patlak analysis, we calculated the net FDG phosphorylation rate (Kᵢ) and glucose metabolic rate (MRGlu) of each nodule. The slope values of the time-activity curves (TACs) of the nodules were also determined. Based on the static PET images, maximum and mean standardized uptake values (SUVmax and SUVmean, respectively) were calculated. Benign and malignant SPNs had significantly different values for SUVmax, SUVmean, Kᵢ, MRGlu, and TAC slope, with area under the receiver operating characteristic curves distinguishing benign from malignant nodules. McNemar’s test of marginal homogeneity found all the predictors helpful to detect malignant nodules (all, p > 0.05), and combining Kᵢ and MRGlu, which were generated by dynamic study, yielded a higher specificity of 90%, and a sensitivity of 79%. Among the 10 benign nodules, static SUV imaging correctly classified seven, while dynamic F-18 PET imaging correctly classified nine. Dynamic F-18 FDG PET imaging is valuable in differentiating benign from malignant SPNs, particularly for granulomatous disease.

INTRODUCTION

A solitary pulmonary nodule (SPN) is a single, well-defined pulmonary opacity less than roughly 3 cm in diameter that is completely surrounded by pulmonary parenchyma and is not associated with either atelectasis or adenopathy.1–3 These are found on 0.09% to 0.20% of all chest radiographs.3 Although 30% to 50% of SPNs are malignant and timely diagnosis is critical to the successful treatment of lung cancer,4–5 radiologists have found to use widely divergent strategies to manage SPNs.6 About 80% of the benign lesions are caused by infectious granulomas.7 Differentiating benign and malignant SPNs is particularly important in areas with a high prevalence of granulomatous disease, but it is difficult because their clinical features (symptoms, physical examination, and laboratory results) are nonspecific.7 Though SPNs are assessed by such diagnostic imaging modalities as chest radiography and computed tomography (CT), a large proportion of SPNs are radiographically indeterminate.8

The imaging technique of 2-(F-18)fluoro-2-deoxy-D-glucose positron emission tomography (F-18 FDG PET) has been commonly used to differentiate benign and malignant pulmonary nodules.8–10 This technique estimates cellular glucose metabolism, which is increased in most tumor cells because of increased glucose transporter protein levels and intracellular enzymes such as hexokinase that promote glycolysis.11,12 Most malignant cells have relatively low levels of glucose-6-phosphatase, and so they accumulate F-18 FDG intracellularly. In diagnosing pulmonary nodules or mass lesions, F-18 FDG PET has high sensitivity (96.8%) and good specificity (77.8%).13 However, F-18 FDG is not
a cancer-specific agent, and its use can generate false positive findings that suggest malignancy when actually granulomatous processes, active inflammation, and infections are present.\textsuperscript{14)}

The standardized uptake value (SUV), which is a commonly used semi-quantitative index of tumor glucose metabolism, is helpful in differentiating benign from malignant SPNs,\textsuperscript{9} but these two conditions have a significant overlap in SUVs.\textsuperscript{15)} Dynamic F-18 FDG PET imaging and kinetic modeling have quantitated F-18 FDG kinetic rate constants for capillary transport, the processes of phosphorylation and dephosphorylation, and the metabolic rate of glucose (MRGlu).\textsuperscript{16)} These methods have characterized tumor metabolism, monitored cancer treatment,\textsuperscript{17,18) and proved valuable in differentiating benign from malignant pulmonary lesions.\textsuperscript{19)}

This study aimed to determine the utility of dynamic F-18 FDG PET analyzed by the tissue time-activity curve (TAC), kinetic analysis, and dynamic parameters with static SUV analysis in differentiating malignant SPNs from benign ones.

**MATERIALS AND METHODS**

**Patients**

Our study was approved by the Institution Review Board of our hospital, and written informed consent was obtained from all participants. Our study included 50 patients without a known history of malignancy who were referred to our PET/CT center for SPN evaluation between January 2009 and June 2010. Patients with lesions greater than 10 mm in diameter (n = 44) on chest CT scans were selected, which minimized the partial volume effect (PVE) on F-18 FDG PET imaging. All patients underwent dynamic and static F-18 FDG PET/CT imaging and diagnostic chest CT scans to determine the malignant potential of their lung lesions. The interval between PET/CT and diagnostic chest CT examinations was less than one month. Only those 34 patients with available pathologic diagnoses were enrolled for analysis. Their pulmonary nodule diagnoses were confirmed either by biopsy (n = 10) or surgical resection (n = 24).

**PET/CT image acquisition**

All patients fasted for at least six hours before PET/CT examinations. Before injections, serum glucose levels were tested via finger stick sampling and determined to be <150 mg/dL. The F-18 FDG PET images were obtained using a Discovery ST PET/CT scanner (General Electric, Milwaukee, WI, USA) equipped with high-resolution bismuth germanate detectors and a 16-slice CT scanner. The scanner can simultaneously acquire 47 transverse planes that are 3.74 mm thick and encompass a 50 cm axial field of view.

The patients lay supine on the imaging bed of the PET/CT camera, with both arms extended out of the field of view. First, a low-dose unenhanced CT scan of the region of interest (ROI) was performed to correct PET attenuation by a standard protocol using 120 kV, 70 mAs, a tube-rotation time of 1.0 second per rotation, and a pitch of 1.4. We intravenously administered 5.2 MBq/kg (0.14 mCi/kg) of F-18 FDG, and then dynamic images were immediately acquired for 50 minutes in 2D mode in 51 frames: 18 frames of 10 seconds, 14 of 30 seconds, 10 of 60 seconds, 5 of 120 seconds, and 4 of 300 seconds. The cross-sectional sinogram data were corrected for dead time, decay, random coincidences, and attenuation. The PET images were then reconstructed using ordered-subsets expectation maximization iterative algorithms with 30 subsets, two iterations, and 128 × 128 pixels. We obtained an in-plane resolution of 6.2 mm and an axial resolution of 4.8 mm.

After the dynamic studies, the patients were asked to void before the static PET/CT scans that occurred 60 minutes after the F-18 FDG was injected. Attenuation was again corrected by the protocol described above. Static PET scans were acquired at 30–40 min (5 minutes per bed) in 2D mode, from the thighs to the head, and the reconstruction parameters were the same as those of dynamic studies.

**Data analysis**

Dynamic F-18 FDG PET/CT imaging

**Image-derived input function**

We defined the input function needed to estimate the kinetic parameter by placing circular 1.0 cm diameter ROIs over the blood-pool area of the left ventricle. These were used in as many planes as possible on the early time frames that best showed activity after the bolus. We checked for myocardial uptake contamination by copying the ROIs to the last time frame, and we minimized PVE by placing the ROIs at least two pixels away from the myocardial wall. A volume of interest (VOI) formed by these ROIs was copied to each time frame, and used to create a TAC.

**TACs of pulmonary nodules**

We analyzed F-18 FDG uptake in the pulmonary nodules by defining the VOIs with the last frames of the dynamic acquisition (45–50 min). We placed the VOIs semi-automatically with a threshold of 50% of the maximum pixel value within the nodule, and then the VOIs were copied to the dynamic imaging sequence to obtain TACs. For standardization, the curves were normalized for blood pool by dividing the tissue TAC by the blood pool TAC.\textsuperscript{20)} We used linear regression to calculate the slope of the late-phase normalized TAC where the curve became stable (TAC slope).\textsuperscript{20)}

**Graphic patlak analysis**

We estimated the net FDG phosphorylation rate, \( K_s \) (ml blood/min/cm\(^3\) tissue), of pulmonary nodules by graphic Patlak analysis.\textsuperscript{21)} We calculated the MRGlu of the pulmonary nodule as: \( \text{MRGlu} = K_s \times \text{plasma glucose/LC} \) (µmol/
min/100 g), where LC is a lumped constant indicating the ratio of F-18 FDG uptake to glucose uptake, which accounts for the difference between the uptake of normal glucose and that of F-18 FDG. We set the lumped constant to 1 and assumed it was constant over time, since no studies on the actual value of the LC in tumors outside of the central nervous system have been reported. The dynamic PET data was evaluated with PMod software (PMod Technologies, Adliswil, Switzerland).

Static F-18 FDG PET/CT imaging

All the F-18 FDG PET/CT studies were interpreted by the consensus of two nuclear medicine physicians unaware of the histological results. The VOIs were placed semi-automatically over the nodules, using a threshold of 50% of the maximum pixel value within the lesion. The maximum SUV (SUV\text{max}) and mean SUV (SUV\text{mean}) values were calculated as: SUV\text{max} = maximum tissue concentration [MBq/g] / (injected dose [MBq]/body weight [g]) and SUV\text{mean} = mean tissue concentration [MBq/g] / (injected dose [MBq]/body weight [g]).

Statistical analysis

Quantitative parameters were presented by median and interquartile range. The Wilcoxon rank sums test compared malignant to benign groups and compared the diagnostic performance of conventional SUV and dynamic methods. Parameters distinguished benign from malignant nodules and determined a cut-off point with receiver-operating-characteristic (ROC) curves. We also calculated areas under the ROC curve (AUC), sensitivities, specificities, and McNemar’s test. Data were analyzed with SPSS 15.0 (SPSS, Inc., Chicago, IL, USA). A P value < 0.05 was considered statistically significant.

RESULTS

We analyzed 34 patients (19 men, 15 women) of 60 ± 11 years (mean ± standard deviation; range = 38–79 years) with SPNs. The nodules were 23.9 ± 8.0 mm (range, 10 to 35 mm). The patients with the 24 malignant nodules were 60 ± 10 years old, and the patients with the 10 benign nodules were 58 ± 9 years old (Table 1). Biopsy results diagnosed 9 of the 24 malignant nodules and 1 of the 10 benign nodules, and surgical specimens diagnosed the remaining nodules.

The median size of the nodules was 26 mm, ranging from 10 mm to 35 mm, with the interquartile range from 16 mm to 30.2 mm. The values of SUV\text{max}, SUV\text{mean}, K_i, MRGlu, and TAC slope were all significantly higher in malignant nodes than in benign nodes (Table 2). The K_i value clearly separates the granuloma nodules from the malignant nodules, and also the non-granuloma and malignant nodules (Fig. 1). The distributions of SUV\text{max}, SUV\text{mean}, and MRGlu did not significantly differ between the granuloma and malignant nodules.

The lung nodules had two categories of normalized TAC patterns (Fig. 2): type I had a continuously rising slope without a plateau, and type II had an initial peak followed by a flat curve. Malignant nodules and granulomas tended to have the type I pattern, with it being observed for 22 (92%) of the malignant SPNs. Of the 10 benign SPNs analyzed, five of the six granulomas had a type I pattern. The non-granuloma benign nodules all had the type II pattern, and so did 2 (8%) of the malignant SPNs. When we used available pathological data to further analyze 14 SPNs that were type I and malignant, we observed 13 with moderate or poor differentiation, and one was a well-differentiated adenocarcinoma.

Granuloma had significantly lower TAC slope and K_i val-

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<th>Table 1. Pathology of SPN diagnosis</th>
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<td>SPN diagnosis</td>
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<td>---------------------</td>
</tr>
<tr>
<td>Malignant</td>
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<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
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<td>Bronchioloalveolar carcinoma</td>
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<tr>
<td>Total</td>
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<tr>
<td>Benign</td>
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<td>Granulomatous inflammation</td>
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<td>Chronic inflammation</td>
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<td>Chondroma</td>
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<td>Total</td>
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*Includes 2 mycobacterial and 1 cryptococcal infections

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<th>Table 2. The gender, nodule size, SUV, and quantitative parameters by dynamic F-18 FDG PET imaging of the malignant and benign nodules</th>
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<td>Male (%)</td>
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<tr>
<td>13 (54.17)</td>
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<tr>
<td>Size (mm)</td>
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<tr>
<td>SUV\text{max}</td>
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<tr>
<td>SUV\text{mean}</td>
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<tr>
<td>K_i (ml/min/cm^3)</td>
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<tr>
<td>MRGlu (μmol/min/100 g)</td>
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<td>TAC slope (1/min)</td>
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Abbreviations: SUV\text{max}, maximum standardized uptake value; SUV\text{mean}, mean standardized uptake value; K_i, net FDG phosphorylation rate; MRGlu, glucose metabolic rate; and TAC slope, slope of late phase of normalized time-activity curve.

*Values are presented as median (95% confidence interval) unless otherwise indicated.

*P < 0.05 considered statistically significant.
ues than malignant nodules (Fig. 1C and E), though their SUV\textsubscript{max}, SUV\textsubscript{mean}, and MRGlu values were not significantly different (Fig. 1A, B, D). However, based on an ROC analysis (Fig. 3), the AUCs of SUV\textsubscript{max} of 0.86 (95% confidence interval = 0.69–0.95), SUV\textsubscript{mean} of 0.85 (0.69–0.95), K\textsubscript{i} of 0.89 (0.75–0.98), MRGlu of 0.84 (0.68–0.94), and TAC slope of 0.87 (0.71–0.96) distinguished benign from malignant nodules (Table 3). The K\textsubscript{i} value had greatest AUC, although the difference did not reach statistical significance as compared with SUV\textsubscript{max} or SUV\textsubscript{mean} (P = 0.17 and 0.15, respectively). The cut-off values were generated by ROC analysis to determine the optimal tradeoff between sensitivity and specificity. McNemar’s test of marginal homogeneity found all the predictors helpful to detect malignant nodules.
Combining $K_i$ and MRGlu reached a higher specificity of 90%, but the sensitivity was lower at 79%. The SUV method correctly classified seven of the 10 benign nodules, while the dynamic F-18 FDG PET imaging correctly classified nine of the 10 benign nodules, which increased the specificity from 70% to 90%.

**DISCUSSION**

Our data revealed that utility of dynamic F-18 FDG PET imaging with kinetic modeling to characterize SPNs and to distinguish between granuloma and malignant nodules. Granulomatous disease is well-known to give false positive results with FDG PET imaging by conventional SUV analysis. In our study, granuloma had significantly lower TAC slope and $K_i$ values than malignant nodules (Fig. 1), though their SUV values were not significantly different from malignant nodules. Our study finds that the dynamic method has the potential to differentiate granulomatous disease from malignancy among SPNs.

Our study found that the $K_i$ and MRGlu values in malignant SPNs were significantly higher than those of benign SPNs. Since $K_i$ is the net metabolic clearance rate of F-18 FDG, it has been used to evaluate pulmonary lesions since it may represent the metabolic activity of tumor tissue. Malignant pulmonary lesions had significantly higher $K_i$ values than benign lesions in a one hour dynamic FDG PET study, and, with a cut-off of 0.025/min, 85% sensitivity and 85% specificity were found in diagnosing malignant pulmonary lesions. These values are in good agreement with the 83% sensitivity we found for $K_i$ with the cut-off value of 0.014/min.

The TAC patterns of malignant nodules (●), granulomas (○), and non-granuloma benign nodules (▼) of the lung are compared, with each TAC representing the mean of all patient studies for the specific categories. Malignant nodules and granulomas tended to show a type I TAC pattern. In contrast, the non-granuloma benign nodules all showed a type II TAC pattern.

The ROCs of SUV$_{\text{max}}$ (○), SUV$_{\text{mean}}$ (◇), $K_i$ (●), MRGlu (□), and TAC slope (△) are compared from the 34 SPNs. The AUCs along with 95% confidence intervals (CIs) distinguishing benign from malignant nodules for SUV$_{\text{max}}$, SUV$_{\text{mean}}$, $K_i$, MRGlu, and TAC slope. The $K_i$ value had greatest AUC, although the difference did not reach statistical significance as compared with SUV$_{\text{max}}$ or SUV$_{\text{mean}}$ ($P = 0.17$ and 0.15, respectively).

Table 3. SPNs characterized by conventional SUV analysis and dynamic F-18 FDG PET imaging

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<tr>
<th></th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC</th>
<th>McNemar’s P</th>
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<tbody>
<tr>
<td>SUV$_{\text{max}}$</td>
<td>5.05</td>
<td>0.83</td>
<td>0.7</td>
<td>0.856</td>
<td>0.7055</td>
</tr>
<tr>
<td>SUV$_{\text{mean}}$</td>
<td>3.35</td>
<td>0.88</td>
<td>0.7</td>
<td>0.850</td>
<td>1.0000</td>
</tr>
<tr>
<td>$K_i$</td>
<td>0.014</td>
<td>0.83</td>
<td>0.8</td>
<td>0.888</td>
<td>0.2568</td>
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<tr>
<td>MRGlu</td>
<td>7.90</td>
<td>0.83</td>
<td>0.8</td>
<td>0.842</td>
<td>0.4142</td>
</tr>
<tr>
<td>TAC slope</td>
<td>0.021</td>
<td>0.79</td>
<td>0.8</td>
<td>0.869</td>
<td>0.2568</td>
</tr>
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</table>

Our data revealed that utility of dynamic F-18 FDG PET imaging with kinetic modeling to characterize SPNs and to distinguish between granuloma and malignant nodules. Granulomatous disease is well-known to give false positive results with FDG PET imaging by conventional SUV analysis. In our study, granuloma had significantly lower TAC slope and $K_i$ values than malignant nodules (Fig. 1), though their SUV values were not significantly different from malignant nodules. Our study finds that the dynamic method has the potential to differentiate granulomatous disease from malignancy among SPNs.

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The TAC pattern from dynamic F-18 FDG PET imaging is valuable in differentiating benign from malignant lesions. High-grade sarcomas reached a peak activity concentration approximately four hours after injection, while benign lesions took 30 minutes. Pancreatic cancer has been shown to have a TAC late phase with a rising slope, while non-malignant pancreatitis has a descending slope. Malignant pulmonary lesions have been shown to have continually increasing F-18 FDG uptake, while benign lesions showed an initial rise followed by a rapid down slope in the TAC pattern from a one hour dynamic PET study. We found that malignant SPNs had a continuously rising slope, and non-granuloma benign SPNs had a flat slope in during the late phase of the TAC.

Although the TAC patterns of malignant SPNs and granulomas were similar in our study, the $K_i$ and TAC slope had significant differences between the two conditions. In agreement with our study, the uptake of F-18 FDG in granulomas was found to significantly increase with time, and granulomas had a mean F-18 FDG uptake at each time point that was comparable to that of malignant tumors in a dynamic PET study of rats. On the contrary, benign pulmonary

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**Fig. 2.** The TAC patterns of malignant nodules (●), granulomas (○), and non-granuloma benign nodules (▼) of the lung are compared, with each TAC representing the mean of all patient studies for the specific categories. Malignant nodules and granulomas tended to show a type I TAC pattern. In contrast, the non-granuloma benign nodules all showed a type II TAC pattern.

**Fig. 3.** The ROCs of SUV$_{\text{max}}$ (○), SUV$_{\text{mean}}$ (◇), $K_i$ (●), MRGlu (□), and TAC slope (△) are compared from the 34 SPNs. The AUCs along with 95% confidence intervals (CIs) distinguishing benign from malignant nodules for SUV$_{\text{max}}$, SUV$_{\text{mean}}$, $K_i$, MRGlu, and TAC slope. The $K_i$ value had greatest AUC, although the difference did not reach statistical significance as compared with SUV$_{\text{max}}$ or SUV$_{\text{mean}}$ ($P = 0.17$ and 0.15, respectively).
lesions, including granulomas and reactive inflammations, had a TAC pattern with an initial rise followed by a rapid down slope, though the percentage of mycobacterial infections in the study population was not mentioned. Our study suggests that $K_i$ and TAC slope from dynamic F-18 FDG PET imaging are valuable to differentiate granulomas from malignant nodules.

Dynamic F-18 FDG PET imaging had higher specificity for diagnosing SPNs than conventional SUV analysis. We found 30% (3/10) of the benign nodules had SUV values over the threshold to be considered malignant by SUV analysis. When we considered both $K_i$ and MRGlu values, we could correctly diagnose two of the three cases as benign nodules, and ultimately correctly classify nine of the 10 (90%) benign nodules. An overlapping distribution between SUV values of benign and malignant lesions has been noted by other researchers. Since the tracer concentration has plateaued when SUVs are measured, SUVs are considered related to the metabolic rate. The F-18 FDG concentration in lung cancer has been found to take several hours after injection to plateau. Therefore, calculating SUVs at a single time point, which is usually 50–60 minutes after the F-18 FDG injection, may not accurately reflect tumor metabolism and may introduce a high degree of variability. In contrast, dynamic study informs us about F-18 FDG metabolism and may introduce a high degree of variability.

Increased F-18 FDG accumulation has been reported in active granulomatous diseases, including infectious diseases such as tuberculosis, aspergillosis, and histoplasmosis and non-infectious diseases such as sarcoidosis. These entities can be intensely hypermetabolic and indistinguishable from lung cancer on F-18 FDG PET imaging. Taiwan has a high (0.1%) prevalence of active pulmonary tuberculosis, and an incidence (64.8/100,000) that is approximately 10 times higher than in the United States. We found that granulomas and malignant SPNs did not have significantly different SUV values. Granulomas in our study had a SUV$_{max}$ value (4.93 ± 1.69) similar to the SUV$_{max}$ value (4.2 ± 2.2) of tuberculosis reported in a previous study. Our results indicate also that differentiating granulomas from malignant SPNs based on SUV analysis in a tuberculosis-endemic region is difficult, and suggest that dynamic F-18 FDG PET imaging is helpful for this differentiation.

The thresholds of 5.05 for SUV$_{max}$ and 3.35 for SUV$_{mean}$ that characterized SPNs by ROC analysis in our study were higher than previously reported values of 2.5 to 3.8. We found that the granuloma group had higher SUV$_{max}$ and SUV$_{mean}$ values than the non-granuloma benign SPN group. Of the benign SPNs in our study, 60% were granulomatous diseases, and 50% of these granulomatous disease cases were mycobacterial or fungal infections. The high percentage of granulomatous disease in the benign nodules may explain our higher SUV cut-off values. The malignancy rate of SPNs (71%) in this series was higher than in previous studies, which may be because we selected patients with pathologic proof of pulmonary nodule.

Since this study included only 34 patients, the statistical relevance of the reported results is limited. The lack of partial volume effects (PVE) correction is another shortcoming. When the lesion has a size that is two to three times smaller than the spatial resolution of the scanner, the PVE causes the activity around the structure to appear smeared over a larger area than it actually occupies in the reconstructed image. This ultimately causes the object to appear to have a lower activity concentration than it actually has. The effects of PVE underestimate SUV, and especially SUV$_{mean}$. For FDG kinetic analysis, the PVE will affect both the image-derived input function and the measured tissue activities, and PVE has been reported to result in underestimated $K_i$ of various tissues. The accuracies of the SUV values and the dynamic parameters of the small lesions in our study would be affected by the SUV. We do not know how the effect of incongruent lesion position between PET and CT that is caused by respiratory motion when using a combined PET/CT scanner would change our results.

**SUMMARY STATEMENT**

Dynamic F-18 FDG PET imaging is valuable in differentiating benign from malignant SPNs, since combining $K_i$ and MRGlu data generates high specificity, and since the $K_i$ and TAC slope values generated have the potential to differentiate malignant SPNs from granulomatous disease.

**ACKNOWLEDGMENTS**

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