Improvement in sensitivity with delayed imaging of pulmonary lesions with FDG-PET

R. Núñez, A. Kalapparambath and J. Varela

Abstract.—Purpose. This study was undertaken to determine the value of using dual-time point ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging to distinguish malignant from benign pulmonary lesions after lesion detection by conventional computed tomography chest imaging.

Methods. Patients referred for characterization of lung lesions were included in this prospective study. Eighty-three patients had histopathologic confirmation of disease. Patients underwnt FDG-PET coincidence imaging, performed with a dual-headed gamma camera at 1 h (“early” scan) and 3 h (“late” scan) after injection of 185 MBq of FDG. Studies were read independently by 2 physicians who had knowledge of the lesion location but not the final diagnosis. For both early and late images, readers graded FDG lesion uptake intensity on a scale of 1 (definitively benign) to 5 (definitively malignant) and classified studies dichotomously for malignancy. Tumor-to-background (T:B) ratios were computed using contralateral lung sites as controls.

Results. Sixty one lesions (74 %) were non-small cell lung cancer, and 10 (12 %) were other primary tumors or metastases. Twelve lesions (14 %) were benign. T:B ratios were significantly higher for early versus late scans (+ 5.1 ± 4.9 versus + 8.2 ± 8.7, p = 0.01, n = 71) for malignancies but not for benign lesions (+ 3.1 ± 3.4 versus + 2.6 ± 2.2, n = 12). The percent change of T:B ratios was higher for malignant than benign lesions (+ 48.3 ± 40.2 % versus + 7.2 ± 22.8 %, p = 0.0009). No malignant lesion of any type demonstrated a time decrease in FDG T:B ratios. The accuracy and sensitivity of lesion characterization were significantly higher for late scans than early scans for dichotomous visual readings. Quantitative analysis was found to provide significantly higher sensitivity and accuracy than visual analysis for lesion characterization, with no significant difference in test specificity.

Conclusions. In malignant pulmonary nodules, there is a progressive, although variable, increase in FDG uptake over time. Increasing FDG uptake is nonspecific finding, as some benign lesions also demonstrate increasing uptake, particularly those associated with granulomas. The use of late PET images increases the accuracy and sensitivity of visual detection of malignancy.

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Correspondence:

R. Núñez
Department of Nuclear Medicine, Unit 1264
The University of Texas M. D. Anderson Cancer Center
1515 Holcombe Boulevard, PO Box 301439
Houston, TX 77030-1439
E-mail: rodolfo.nunez@mdanderson.org

KEY WORDS: pulmonary lesions, PET, FDG, dual time point imaging.

MEJORA EN SENSIBILIDAD CON IMAGEN TARDÍA DE LESIONES PULMONARES CON FDG-PET

Resumen.—Objetivo. Determinar cuál es el valor del estudio en dos fases en la tomografía por emisión de positrones con ¹⁸F-fluorodesoxiglucosa (FDG-PET), a la hora de diferenciar lesiones pulmonares entre benignas y malignas, detectadas por tomografía axial computarizada.

Material y métodos. Estudio prospectivo de 83 pacientes remitidos a nuestro centro para la caracterización de lesiones pulmonares, en los que se obtuvo la confirmación histopatológica de la lesión. Se realizó FDG-PET con gammamáquina en detección de coincidencia a la hora (estudio inicial) y a las tres horas (estudio tardío) de la inyección de 185 MBq de FDG. Dos médicos nucleares que sólo conocían la localización de la lesión, pero no el diagnóstico final, interpretaron de forma independiente los estudios. Tanto el estudio inicial como el tardío fueron calificados de acuerdo a la intensidad de la lesión, usando una escala visual de 1 (definitivamente benigno) a 5 (definitivamente maligno). Además, para obtener una dicotomía se determinó si se consideraba el estudio maligno o benigno. Se calcularon los índices tumor/背景 (T:B) usando el pulmón contralateral como control.

Resultados. Sesenta y una lesiones (74 %) fueron carcinomas pulmonares no microcíticos, y 10 (12 %) fueron otros tumores primarios o metástasis. Doce lesiones (14 %) fueron benignas. Los índices T:B fueron significativamente más elevados para los estudios tardíos que para los iniciales en lesiones malignas, pero no en las benignas. El porcentaje de cambios en los índices T:B fue mayor para las lesiones malignas que para las benignas. Ninguna lesión maligna mostró una disminución del índice T:B entre los dos estudios. Con la interpretación dicotómica, se obtuvo una mayor precisión y sensibilidad en la caracterización de las lesiones en los estudios tardíos que en los iniciales. El análisis cuantitativo proporcionó una mayor sensibilidad y precisión en la caracterización de las lesiones en comparación con el análisis visual, sin diferencias significativas en la especificidad.

Conclusiones. Los nódulos pulmonares malignos muestran un incremento progresivo, aunque variable en la captación de FDG, con el transcurso del tiempo. Sin embargo, este aumento de FDG no es específico, ya que algunas lesiones benignas también pueden comportar de manera similar, especialmente las granulomas. El uso de las imágenes tardías en la FDG-PET incrementa la sensibilidad y la precisión en el análisis visual de estos estudios.

PALABRAS CLAVE: lesiones pulmonares, PET, FDG, estudio en dos fases.

INTRODUCTION

Pulmonary nodules affect 0.1 % to 0.2 % of the general adult population. In the United States, approximately 130,000 new pulmonary nodules are diagnosed each year, and with the increasing popularity of lung cancer screening with helical and multislice computed tomography (CT), the number will likely rise. Approximately 20 % to 50 % of these nodules are malignant, varying according to factors such as patient age, smoking history, or previous malignancy.

Conventional evaluation of pulmonary nodules has limitations. Most pulmonary nodules remain indeterminate on repeated CT scans. Because a watch-and-wait policy is not advocated unless the likelihood of malignancy is less than 10 %, an invasive procedure to obtain samples for histopathologic examination is the main evaluation method.

Bronchoscopy, including bronchial washings, has a sensitivity of 20 % to 80 %, depending on the size of the nodule, its proximity to the bronchial tree, and the prevalence of cancer in the study population. For nodules less than 1.5 cm in diameter, the sensitivity drops to 10 %; therefore, negative findings on bronchoscopy do not exclude malignancy.

Another nonsurgical approach to diagnosis is transthoracic fine needle aspiration biopsy, with most studies reporting sensitivities of 75 % to 86 %. Even for lesions that are less than 2 cm in diameter, transthoracic fine needle aspiration biopsy has a sensitivity of no more than 60 % for detecting malignant processes, but the false-negative rate is 3 % to 29 %.

In addition, complication rates are higher for this technique than for bronchoscopy, with an incidence of pneumothorax of up to 30 %, requiring chest tube placement in up to 26 % of patients in some series.

A relatively new noninvasive procedure that has widespread applications for the evaluation of pulmonary nodules is 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging. Kubota et al first described the value of this technique for characterizing pulmonary nodules and differentiating between benign and malignant lesions. Since then, other investigators have reported the utility of FDG-PET for imaging pulmonary nodules. In a meta-analysis, the sensitivity for identifying a malignant process in the lungs with FDG-PET were reported to be 96.8 % and its specificity 77.8 %.

Standardized uptake values (SUVs) above 2.5 are used as a semiquantitative index to aid in differentiating benign and malignant pulmonary nodules with PET imaging. However, the use of SUVs has limitations because some malignant lesions such as bronchoalveolar cell carcinoma and bronchial carcinoid are known to poorly concentrate FDG. In small (subcentimeter) lesions, FDG uptake is underestimated because of partial volume effects. Moreover, inflammatory and infectious lesions may demonstrate increased and sometimes prominent FDG uptake above the cut-off SUV value of 2.5, limiting the specificity of the method.

Hustinx et al reported the results of dual-time-point FDG-PET imaging in the evaluation of 18 patients with head and neck cancer and 9 patients with inflammatory lesions. They found that in the tumors, there was a mean 12 % increase in FDG uptake between the first and second scans, but in the inflammatory lesions, FDG uptake was stable over time or declined slightly. Since then, several other investigators have reported similar results with dual-time point FDG-PET imaging.

The purpose of this prospective study was to determine the value of dual-time-point imaging in distinguishing malignant from benign pulmonary lesions in patients referred for FDG-PET imaging after lesion detection by conventional CT chest imaging.

PATIENTS AND METHODS

Patient population

Patients were referred to us for FDG-PET imaging for characterization and differentiation of suspicious pulmonary densities found on conventional CT scans of the chest. All patients who presented to our department between December 2001 and December 2003 with pulmonary densities of at least 1 cm in diameter and who had histopathologically characterized lesions were included in the study. Eighty-three patients (46 women and 37 men; mean age, 69 ± 11 years; range, 38-88 years) were included in the analysis.

Imaging protocol

Details of the study were explained to patients by a physician, and informed consent was obtained. The study was approved by the institutional IRB. Patients underwent imaging twice on the same day using a dual-detector gamma camera operating in coinci-
quired at 57 ± 12 min after intravenous injection of 
18F-FDG, imaging the neck, chest, abdomen, and upper 
third of the pelvis.

The second PET scan ("late" scan) was performed 
at 3 h and 17 min ± 13 min after the initial injection, 
imaging the lower neck, chest and upper abdomen. 
All patients fasted a minimum of 6 h prior to the in-
jection of 18F-FDG and during the interval between 
early and late scans.

Coincidence-PET imaging

The early PET scan consisted of 2 bed positions, 
and the late PET scan, only 1 bed position. The axial 
field of view was 38 cm when 1 bed position was 
used and 57 cm with 2 bed positions. All patients 
were imaged for 32 stops through a rotation of 180° 
per detector at 40 s/frame for the early scan. To com-
penstate for decay of 18F-FDG, the late scan was ac-
quired at 60 s/frame. Data were acquired in 3-dimen-
sional mode, and decay correction was performed 
during the acquisition. Images were corrected for 
photon attenuation with a transmission scan using 137-Cs point sources. The total acquisition time of 
emission and transmission scans was approximately 
30 min per bed position.

Energy windows were set at 511 keV/30 % for the 
18F-FDG photopeak, 310 KeV/30 % for the Compton 
events in the NaI crystal, and 662 keV/30 % for the 
137Cs photopeak. The coincidence mode of acquisition 
used all photopeak-photopeak events and photo-
peak-Compton scatter events. The detectors provided a 
timing resolution of 6 ns, and a 15-ns timing window 
was used to acquire coincidence events. The spatial 
resolution in axial and transaxial directions (full-width 
half maximum) for this type of scanner has been doc-
umented to be 0.5 cm by National Electrical Manufac-
turers Association standards15. All data were rebinned 
using single-slice rebinning and reconstructed using an 
ordered subset expectation maximization iterative al-
gorithm provided by the scanner’s manufacturer.

Visual assessment

All images were read independently by 2 nuclear 
medicine physicians who had knowledge of the loca-
tion of the pulmonary nodule but not of the final di-
agnosis. For both early and late PET scans from each 
patient, readers were asked to classify the lesions as 
either malignant or benign (dichotomous score) on 
the basis of their visual perception of the greater local 
tracer uptake by the lung lesion compared with the 
uptake by the mediastinum. The likelihood of malign-
nancy of each lesion was also graded on a scale of 1 
(definitively benign) to 5 (definitively malignant) on 
the paired early and late images using the same crite-
ria of relative tracer uptake.

In addition, the early and late scans were compared 
together, and readers judged whether uptake of FDG 
by the lesions increased, decreased, or remained sta-
ble over time. Finally, visual readings were compared 
between the 2 observers.

Quantitative analysis

Quantitative analysis of the lesions was performed 
using the attenuation-corrected coronal images. For 
all patients, square regions of interest (ROIs) of the 
same size (5 pixels × 5 pixels) were drawn manually 
by an observer over perceived lung lesions. Mean 
FDG counts per pixel were measured within each 
ROI. For each patient, regions of identical size were 
also drawn over the contralateral lung, which served 
as the control region. The same locations were used 
for target and background ROIs for early and late 
scans. For lesions with no uptake of FDG, an ROI 
was drawn in the area where the lesion was supposed 
to be located on the basis of the anatomic information 
obtained from the CT scan. Tumor target-to-back-
ground (T:B) ratios were generated by dividing the 
mean ROI counts of the lesions by the mean ROI 
counts of the contralateral lung background areas. 
The percentage change of the T:B ratios was defined 
as 100 % × (late T:B – early T:B)/early T:B.

Subanalysis by physical lesion size

To facilitate analysis by lesion size, no lesion was 
excluded because of size. By CT, the median lesion 
size was 2.5 cm. Subjects were divided into those 
with lesions smaller than 2.5 cm versus those with 
larger lesions, including both benign and malignant 
lesions. Accuracy, sensitivity, specificity, positive 
predictive value (PPV), and negative predictive value 
(NPV) were calculated separately for the T:B quanti-
tative analysis and dichotomous visual scores, for each of these two groups.

Statistical analysis

All values are reported as means ± 1 standard deviation. Analysis of the interpretations of the early and late PET scans by each reader was performed using biopsy results as the standard of truth. The ability of T:B ratios to discriminate malignant from benign lesions was assessed by optimizing the accuracy of lesion characterization on imaging versus that on histopathologic evaluation. The degree of agreement between readers was assessed using Kendall statistics, and agreement between observers of 5-point-scale readings was assessed by Spearman’s rank correlation. Receiver operating characteristic (ROC) curves were generated for the readings from the scores assigned by the visual estimation of FDG uptake by pulmonary lesions. The visual readings from the 2 physicians were also combined into a single set of readings, for a total of 166 visual judgments (83 readings per observer), and compared with the biopsy results for the 83 patients.

Accuracy, sensitivity, specificity, PPV, and NPV were calculated separately for the T:B quantitative analysis, dichotomous visual scores, and 5-point-scale visual scores. McNemar’s test was used to compare the pairs of tests of dichotomous readings. An analysis of proportions was used to compare the results among all discrimination methods in this investigation and to compare this study’s results with those of previous investigators. For all tests, a probability (p) value of < 0.05 was defined as statistically significant.

RESULTS

Characterization of patients’ pulmonary lesions

Eighty-three lesions (1 lesion per patient) were evaluated in this study. Sixty one lesions (74 %) were non-small cell lung cancer, and 10 (12 %) were other primary tumors or metastases (table 1). Twelve lesions (14 %) were benign, of which 7 (8 %) were sites of granulomatous disease, including tuberculosis (caseating granuloma), and five (6 %) were non-granulomatous lesions.

<table>
<thead>
<tr>
<th>Cell type</th>
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<tr>
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<tr>
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<td>Large cell carcinoma</td>
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<td>Fibrous tumor with malignant transfor-</td>
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<tr>
<td>mations</td>
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<tr>
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<tr>
<td>Focal inflammation</td>
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<tr>
<td>Fibrosis</td>
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<td>Hamartromas</td>
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<tr>
<td>Total</td>
<td>83</td>
</tr>
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</table>

Table 1

HISTOPATHOLOGIC LESION CHARACTERIZATION

Dichotomous visual readings

Agreement was excellent between the 2 readers for dichotomous readings of early scans (kappa = 0.89, p < 0.0001), late scans (kappa = 0.89, p < 0.0001), and changes between scans (kappa = 0.79, p < 0.0001). Because dichotomous readings for the 2 observers were similar for accuracy, sensitivity, specificity, PPV, and NPV, with no statistically significant differences between them, for subsequent analyses of dichotomous interpretation, their readings were combined into a single set, for a total of 166 visual judgments (83 readings per observer), and compared with the biopsy results for the 83 patients.

The accuracy was significantly lower for the early scans versus the late scans (72 % versus 78 %, p < 0.02). Sensitivity values were also significantly lower for the early scans versus the late scans (74 % versus 85 %, p < 0.001) and for changes in intensity (74 % versus 82 %, p < 0.01). However, the specificity values were not significantly different (table 2).

For the benign lesions, the visual interpretations were correct in 50 % of the readings of the early scans (14 of 24 readings for 12 lesions), and in 42 % of the readings of the late scans (10 of 24 readings for 12 lesions). There was no change between early and late
scan interpretation for nongranulomatous lesions, being correct 60% of the time (6 of 10 readings for 5 lesions) on both occasions. However, for granulomatous lesions, the interpretation was correct in 57% of the readings (8 of 14 readings for 7 lesions) for the early scans, dropping to 29% (4 of 14 readings for 7 lesions) for the late scans.

ROC analysis of visual readings

Agreement was strong between the readings of the 2 observers on a 5-point scale for the early scans (Spearman’s rho = 0.94, p < 0.0001; 95% confidence interval [CI] for rho = 0.91 to 0.96), late scans (rho = 0.94, p < 0.0001; 95% CI for rho = 0.90 to 0.96), and 3-point scale readings between scans (rho = 0.79, p < 0.0001; 95% CI for rho = 0.69 to 0.86). The accuracy, sensitivity, and specificity between both observers were not statistically significantly different for early scans (0.70 versus 0.68, 0.82 versus 0.82, and 0.50 versus 0.50, respectively), late scans (0.63 versus 0.64, 0.90 versus 0.93, and 0.42 versus 0.42, respectively), or changes between scans (0.57 versus 0.64, 0.79 versus 0.86, and 0.33 versus 0.42, respectively). The readings of the 2 observers analyzed separately by ROC analysis were not significantly different in accuracy between early and late scans for reader #1 (0.70 versus 0.63, p = 0.98) or for reader #2 (0.68 versus 0.64, p = 0.79). As with dichotomous readings, because there were no statistically significant differences between the ROC analyses of the 2 observers, for subsequent ROC analyses, the readings of the 2 observers were combined into a single set of readings, for a total of 166 visual judgments (83 readings per observer), and compared with the biopsy results for the 83 patients.

Figure 1 shows the ROC curves for the combined readings of the 2 observers for early scans, late scans, and time changes between scans.

Table 2

<table>
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<th>Characteristic</th>
<th>Early</th>
<th>Late</th>
<th>Change</th>
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<tbody>
<tr>
<td>Accuracy</td>
<td>72%</td>
<td>78%</td>
<td>75%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>74%</td>
<td>85%</td>
<td>82%</td>
</tr>
<tr>
<td>Specificity</td>
<td>58%</td>
<td>41%</td>
<td>37%</td>
</tr>
<tr>
<td>PPV</td>
<td>91%</td>
<td>89%</td>
<td>88%</td>
</tr>
<tr>
<td>NPV</td>
<td>28%</td>
<td>32%</td>
<td>26%</td>
</tr>
</tbody>
</table>

\( p < 0.05 \) for “early” versus “late”. \( p = 0.05 \) for “early” versus “change”. NPV: negative predictive value; PPV: positive predictive value.

Table 3

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early</th>
<th>Late</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>69%</td>
<td>64%</td>
<td>60%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>82%</td>
<td>90%</td>
<td>82%</td>
</tr>
<tr>
<td>Specificity</td>
<td>50%</td>
<td>42%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Quantitative analysis of T:B ratios

For the 12 benign lesions, early versus late T:B ratios were not significantly different (2.6 ± 2.2 versus 3.1 ± 3.4). However, for the 71 malignant lesions, early versus late T:B ratios were significantly lower (5.1 ± 4.9 versus 8.2 ± 8.7, \( p = 0.01 \) (table 4). In addition, there were significantly different percent
be benign by T:B time change
tics of the 9 malignant lesions incorrectly declared to
of benign nongranulomatous lesions.
7) of benign granulomatous lesions and 60 % (3 of 5)
respectively) (table 5).

between early and late scans (25 %, 33 %, and 66 %, re-
for early scans, late scans, or percentage change be-
ficity values were not statistically significantly higher
(92 %, 95 %, and 87 %, respectively) (table 5). Speci-
86 %, and 84 %, respectively), as was sensitivity
nate malignant from benign lesions was nearly iden-
tive of malignancy.
increases with time of at least 10 % were all indica-
tors benign lesions, (fig. 5), and –45 % to
change values for all malignant lesions versus all be-
ign lesions (+ 48.3 ± 40.2 % versus + 7.2 ± 22.8 %, 
p = 0.004) and for malignant versus nongranulomatous
benign lesions (+ 48.3 ± 40.2 % versus –4.1 ± 21.0 %, 
p = 0.02) but not for malignant versus granuloma-
tous benign lesions (table 4; fig. 2A-C). The range of
changes in T:B ratios was 0 % to + 144 % for malignant
lesions (fig. 3 y 4), 0 % to + 54 % for granulomatous
benign lesions, (fig. 5), and –45 % to + 17 % for non-
granulomatous benign lesions (fig. 2C). No mali-
gnant lesion demonstrated a time decrease in FDG T:B
ratios.
T:B ratios for early and late scans and for time
changes between scans were analyzed for their ability
to discriminate malignant from benign lesions. The
T:B threshold values that maximized accuracy were
1.1 for early scans and independently determined to
also be 1.1 for late scans. The threshold for the per-
centage change in T:B ratios with time was ≥ 10 %.
Thus, tumor counts 10 % higher than background
counts, whether for early or late scans, and for further
increases with time of at least 10 % were all indica-
tive of malignancy.
The accuracy of the use of T:B values to discrimi-
nate malignant from benign lesions was nearly iden-
tical for early, late, and time-difference values (83 %, 86 %,
and 84 %, respectively), as was specificity (92 %, 95 %,
and 97 %, respectively) (table 5). Specificity values were not statistically significantly higher
for early scans, late scans, or percentage change be-
tween early and late scans (25 %, 33 %, and 66 %, re-
spectively) (table 5).
T:B time change criteria were correct in 57 % (4 of
7) of benign granulomatous lesions and 60 % (3 of 5)
of benign nongranulomatous lesions.
There were no obvious distinguishing characteris-
tics of the 9 malignant lesions incorrectly declared to
be benign by T:B time change < 10 % criterion, as
their size of 3.0 ± 3.5 cm (range, 0.8 cm to 12.0 cm)
was not different from that of all other lesions. These
mischaracterized lesions consisted of a variety of cell
types (2 bronchoalveolar, 3 adenocarcinoma, 2 squa-
mos cell, 1 spindle cell, and 1 carcinoid).

Subanalysis by physical lesion size
By CT, the mean lesion size was 3.3 ± 2.2 cm, and
the median lesion size was 2.5 cm. Lesion sizes
were not different for benign lesions (2.3 ± 1.1 cm; 
range, 1.6 cm to 4.8 cm) versus malignant lesions
(3.4 ± 2.4 cm; range, 1 cm to 12 cm). Subjects were
divided into those with lesions smaller than 2.5 cm
(n = 43; size = 1.7 ± 0.5 cm) versus those with larger
lesions (n = 40; size = 4.9 ± 2.2 cm), including both
benign and malignant lesions.
For dichotomous visual analysis, larger lesions
were detected more accurately and sensitively than
smaller lesions for early scans (accuracy = 90 % ver-
sus 54 %, p = 0.0001; and sensitivity = 94 % versus
51 %, p = 0.03) and late scans (accuracy = 92 % ver-
sus 65 %, p = 0.0001; and sensitivity = 97 % versus
71 %, p = 0.0001) but not for changes between scans
(table 6A). For smaller lesions, percent change was
more sensitive than readings of early scans (74 % ver-
sus 51 %, p = 0.01) but not otherwise (table 6A).
By quantitative analysis, larger lesions were de-
tected with higher sensitivity than smaller lesions
for early scans only (100 % versus 84 %, p = 0.03)
(table 6B) but were not different for late scans or
changes between scans. By quantitative analysis, ac-
curacy and specificity were not different for larger
versus smaller lesions for any scans.
For larger lesions, linear regression analysis
demonstrated statistically significant correlations be-
tween T:B ratios and lesion size for both early scans
(t = 0.5b, p = 0.0002) and late scans (t = 0.50,
**DISCUSSION**

Delayed FDG-PET imaging is a technique that can facilitate the characterization of pulmonary lesions, especially when the size of the lesion is at the limit of resolution of the PET scanner or the malignancy shows poor FDG uptake. In our series, we achieved higher sensitivity and accuracy with the semiquantitative analysis of late images, with no statistically significant change in the specificity. Because, early FDG-PET imaging does not appear to provide better results or additional information than delayed imaging, it may be spared from the imaging protocol.

The usefulness of FDG-PET imaging in the evaluation of patients with pulmonary nodules is well documented in the scientific literature. Pulmonary nodules are not only one of the first clinical applications of this imaging technique but also a major indication for PET imaging in most PET centers. Since the first prospective evaluation of PET by Kubota et al., studies of more than 2,000 patients have provided favorable results, with sensitivities of 83% to 100% (overall sensitivity calculated from the pooled data of 95.9%) and specificities of approximately 52% to 100% (overall specificity from the pooled data of 78.1%). These data clearly show that FDG-PET is the most sensitive and specific imaging technique available today for the characterization of pulmonary nodules.

$p = 0.001$) but not for percent change in T:B. For smaller lesions, T:B ratios were not correlated with lesion size for early scans, late scans, or time changes between scans.
Fig. 3.—An example of a malignant lesion with intense lesion activity in early and late scans, with a large time-increase in lesion uptake. The patient was a 61-year-old woman with a 1.5-cm metastatic malignant melanoma to the right lower lobe. A) The chest x-ray (left and middle images) and the CT scan image (to the right) show the right lung nodule. B) Representative coronal, transverse and sagittal images of the early PET scan clearly show FDG uptake by the nodule. C) The same type of images B) as for the late PET scan, showing increased FDG uptake by the pulmonary nodule (132% increase in the T:B ratio from the early to late PET scan).

Fig. 4.—An example of a malignant lesion with no lesion activity in the early scans but a notable time-increase in lesion uptake. The patient was a 70-year-old woman with a 2.2-cm bronchioloalveolar cell carcinoma of the right lower lobe. A) Representative coronal, transverse, and volume-rendered images of the early PET scan, in which there is no evidence of FDG uptake by the pulmonary nodule. B) Representative images for the late PET scan show uptake of FDG by the pulmonary nodule (arrows), which is only seen in this late set of images. The T:B ratio was 1.52.
While FDG-PET imaging has been increasingly used in patients with pulmonary nodules, we have gained more knowledge and a better understanding of the limitations of the technique. The clinical interpretation of PET scans by visual analysis and SUVs to determine the benign or malignant nature of pulmonary lesions is limited in small lesions (<1 cm), in which partial volume effects will produce an underestimation of true FDG uptake. In addition, it is well documented that several benign conditions, such as sarcoidosis, tuberculosis, histoplasmosis, and Wegener’s granulomatosis, can demonstrate increased FDG uptake above the accepted SUV cut-off value of 2.5. Moreover, well-differentiated malignancies may show little if any increase in metabolic activity compared with surrounding normal tissues and constitute causes for false-negative readings. In particular, bronchoalveolar cell carcinoma, carcinoids, and well-differentiated adenocarcinomas have been shown to poorly concentrate FDG.

Therefore, investigators have researched additional techniques to further improve the noninvasive characterization of pulmonary nodules. The use of conventional SPECT imaging with 201-thallium has not provided an additional advantage over FDG-PET imaging. Benign lung lesions can demonstrate uptake of 201-thallium in an imaging modality that has inherently lower resolution than PET. Other PET tracers, such as the radiolabeled amino acid 11C-methionine, have been found to have similar sensitivity but less or similar specificity to FDG. Studies with tyrosine, another amino acid, labeled with either 11C or 18F as 18F-fluoro-methyltyrosine, have shown that the sensitivity is lower than FDG for the detection of malignant lesions. None of these PET tracers

### Table 5
**LESION DISCRIMINATION OF MALIGNANT VERSUS ALL BENIGN LESIONS BY QUANTITATIVE ANALYSIS OF T:B COUNT RATIOS ABOVE OPTIMUM THRESHOLDS OF 10%**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early</th>
<th>Late</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>83%</td>
<td>86%</td>
<td>84%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>92%</td>
<td>95%</td>
<td>87%</td>
</tr>
<tr>
<td>Specificity</td>
<td>25%</td>
<td>33%</td>
<td>66%</td>
</tr>
<tr>
<td>PPV</td>
<td>88%</td>
<td>89%</td>
<td>93%</td>
</tr>
<tr>
<td>NPV</td>
<td>37%</td>
<td>57%</td>
<td>47%</td>
</tr>
</tbody>
</table>

NPV: negative predictive value; PPV: positive predictive value.

### Table 6A
**LESION DISCRIMINATION BY DICHOTOMOUS VISUAL INTERPRETATIONS ANALYZED ACCORDING TO CT-DETERMINED LESION SIZE**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lesion size &lt; 2.5 cm (n = 43)</th>
<th>Lesion size &gt; 2.5 cm (n = 40)</th>
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</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>54%†</td>
<td>90%∗</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>51%†</td>
<td>94%∗</td>
</tr>
<tr>
<td>Specificity</td>
<td>66%</td>
<td>33%</td>
</tr>
<tr>
<td>PPV</td>
<td>85%</td>
<td>94%</td>
</tr>
<tr>
<td>NPV</td>
<td>27%</td>
<td>33%</td>
</tr>
</tbody>
</table>

†p < 0.05 for lesions < 2.5 cm versus > 2.5 cm. ∗p < 0.05 for “early” versus “change” for lesions < 2.5 cm. NPV: negative predictive value; PPV: positive predictive value.

### Table 6B
**LESION DISCRIMINATION BY QUANTITATIVE ANALYSIS OF T:B COUNT RATIOS, ANALYZED ACCORDING TO CT-DETERMINED LESION SIZE**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lesion size &lt; 2.5 cm (n = 43)</th>
<th>Lesion size &gt; 2.5 cm (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>73%</td>
<td>92%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>84%†</td>
<td>100%∗</td>
</tr>
<tr>
<td>Specificity</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>PPV</td>
<td>81%</td>
<td>92%</td>
</tr>
<tr>
<td>NPV</td>
<td>57%</td>
<td>–</td>
</tr>
</tbody>
</table>

†p < 0.05 for lesions < 2.5 cm versus > 2.5 cm. NPV: negative predictive value; PPV: positive predictive value.

**Núñez R et al. Improvement in sensitivity with delayed imaging of pulmonary lesions with FDG-PET**

are currently commercially available. Therefore, dual-time point imaging with FDG-PET has been used in different types of tumors in an attempt to overcome the limitations of the technique

The results of the present investigation show that with dual-time point FDG-PET imaging of pulmonary lesions, there is an increase in sensitivity in the interpretation of early to late images (fig. 5), varying slightly according to the method of analysis used. Using the combined visual dichotomous readings, the sensitivity improved from 74 % to 85 % ($p < 0.05$), and the accuracy improved from 72 % to 78 % ($p < 0.05$). However, there was a slight decrease in the specificity, from 58 % to 41 %, which nevertheless was not statistically significant. The results are similar for the semiquantitative analysis, in which there was an improvement in sensitivity from early to late imaging of 92 % to 95 % and in accuracy from 83 % to 86 %, respectively. It was interesting that there was a slight drop in the specificity from early to late imaging using the dichotomous interpretation (table 2), but this was not the case with the semiquantitative analysis, which increased minimally from early to late imaging and even more using the evaluation of time change in uptake, going from 25 % to 33 % and 66 %, respectively. Nevertheless, these differences were not statistically significant. These outcomes are similar to the ones obtained by Matthies et al$^{11}$ and Demura et al$^{13}$. However, the specificity in our study is on the lower side of the published range, probably because of the limited number of benign pulmonary nodules included in our series (12 [14 %]), which limits an accurate estimation of the true-negative and false-positive rates. Nevertheless, all lesions in our study, either benign or malignant, had histopathological confirmation.

The interpretation of the late images, either visually or semiquantitatively, provided higher sensitivity and accuracy than the early images, with no statistically significant change in the specificity. Therefore, it would be possible to spare the early image without affecting the sensitivity and accuracy of the study. Nevertheless, the semiquantitative analysis of T:B ratios above optimum thresholds of 10 % appears necessary to obtain better results.

One finding that is not surprising was that larger lesions are detected more accurately and with higher sensitivity than smaller lesions, either by visual dichotomy interpretation or by semiquantitative analysis (tables 6A and 6B). However, the improvement in accuracy and sensitivity with dual-time point imaging was seen only in smaller lesions.

Even though the total number of benign lesions ($n = 12$) was not very large, there was a tendency for better characterization of benign nongranulomatous lesions than benign granulomatous lesions, with visual analysis being correct in 60 % of cases for early and late imaging for the former and decreasing to 57 % and 29 %, respectively, for the latter. Similar findings have been seen by other investigators$^{13,15}$.\[Rev Esp Med Nucl. 2007;26(4):196-207\]
which is probably a reflection of different washout rates of these 2 lesion types. In fact, in our study, the percent change ratios of uptake from early to late PET imaging were not significantly different between malignant and benign granulomatous lesions; however, there was a statistically significant difference between malignant and benign nongranulomatous lesions (table 4).

The main limitation of our study is the rather small number of benign lesions included for analysis -12 of 83 lesions. A higher number of benign lesions would have been desirable to more accurately determine the true-negative and false-positive rates of the technique. However, the small number of patients was mainly because only lesions with histologic confirmation were included in the study. In addition, although our results are comparable to those of other investigators,6-13 they probably could have been improved with the use of a dedicated PET scanner instead of a coincidence gamma camera.

CONCLUSIONS

Our results show that in malignant pulmonary lesions, there is a progressive, although variable, increase in FDG uptake over time. Increasing FDG uptake is a nonspecific finding, as some benign lesions also demonstrate increasing uptake. The use of delayed PET imaging with semiquantitative analysis improves the sensitivity and accuracy of the characterization of pulmonary lesions, with no statistically significant change in the specificity. Therefore, appears to be possible to avoid the early image without affecting the results of the study.

REFERENCES

