The Utility of a Somatostatin-Type Receptor Binding Peptide Radiopharmaceutical (P829) in the Evaluation of Solitary Pulmonary Nodules*

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**Objective:** Many neoplasms including small cell cancers more densely express somatostatin-type receptors or more avidly bind somatostatin than granulomatous and other nonmalignant processes. While non-small cell neoplasms of the lung have not yet been shown to demonstrate this receptor expression, previous studies have documented non-small cell lung cancer detection with somatostatin analog scintigraphy. This phenomenon can be conceivably exploited utilizing technetium Tc-99m P829 (P829), a unique low molecular weight somatostatin-type receptor binding polypeptide radiopharmaceutical. The objective of this study was to determine the ability of P829 scintigraphy to noninvasively differentiate malignant and nonmalignant solitary pulmonary nodules (SPNs).

**Methods:** The radiopharmaceutical technetium ⁹⁹ᵐTc-P829 was utilized for scintigraphy including single photon emission computed tomography. Thirty individuals with indeterminate SPNs of ≥ 1 cm and significant risk factors for primary lung cancer were identified and underwent P829 scintigraphy. Tissue diagnosis was then established by transthoracic needle biopsy specimens.

**Results:** Fourteen subjects demonstrated abnormal P829 scans in the region of the radiographic abnormality. Twelve of this group had biopsy specimens revealing neoplasia. Two subjects with necrotizing granuloma on biopsy specimen had abnormal P829 scans in the region of the nodule. Sixteen subjects had no abnormal P829 tracer uptake in the region of the nodule. Fourteen subjects had benign diagnoses on biopsy specimens. One member of this group with a non-diagnostic biopsy specimen refused thoracotomy and remains radiographically stable at 24 months of follow-up. One subject with a squamous cell carcinoma demonstrated no P829 activity in the region of the nodule. The specificity of P829 scintigraphy based on transthoracic needle biopsy specimen was 88%. The sensitivity was 93%. P829 scintigraphy correctly identified or excluded malignancy in 27 of 30 subjects.

**Conclusions:** P829 scintigraphy reliably identified or excluded malignancy in radiographically indeterminate solitary pulmonary nodules. The sensitivity and specificity compared favorably with the reported results of F-18 fluorodeoxyglucose positron emission tomographic imaging.

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**Key words:** granulomas; lung cancer; radionuclide imaging; scintigraphy; solitary pulmonary nodules; somatostatin receptors

**Abbreviations:** FDG = F-18 fluorodeoxyglucose; GSRMC = Good Samaritan Regional Medical Center; PET = positron emission tomography; P829 = technetium ⁹⁹ᵐTc P829; SPECT = single photon emission computed tomography; SPN = solitary pulmonary nodule; SSTR = somatostatin type receptors

The socioeconomic impact of lung cancer is underscored by the fact that it is the leading cause of cancer mortality for both sexes in the United States and worldwide.¹² In 1995, there were an estimated 170,000 new lung cancer cases in the United States alone with 157,400 lung cancer deaths.³

Approximately 130,000 new solitary pulmonary nodules (SPNs) are discovered each year and are found in approximately 1 in 500 routine chest radiographs.⁴⁵ In various series, 28 to 39% of resected SPNs were malignant, accounting for approximately 20% of newly diagnosed lung cancer.⁶⁻⁹ This suggests that SPNs are of serious concern and require evaluation. Invasive methods such as bronchoscopy are inadequate while others, including thoracotomy or needle biopsy, are associated with significant morbidity and cost.¹⁰⁻¹³

Current noninvasive methods for evaluating patients with SPNs include chest radiograph, CT,
positron emission tomography (PET), and sputum cytology. With the exception of PET, all of these methods, including the use of iodinated contrast and dynamic CT studies, result in a significant number of indeterminate diagnoses.\textsuperscript{7,10,14–19} Mathematical approaches including Bayesian analysis of diagnostic criteria such as smoking history, nodule size, patient age, and history of malignancy will misdiagnose or be indeterminate in up to 15\% of SPNs.\textsuperscript{20–23} Although such statistical analysis has been shown to be less accurate than PET,\textsuperscript{14,24} expense and lack of availability greatly limit the utility of PET.

\textit{In vitro} presence of somatostatin receptors in a variety of human malignancies, including small cell lung cancer, has been well documented.\textsuperscript{1,24} While \textit{in vitro} demonstration of somatostatin receptor expression by non-small cell lung cancer has not yet been shown (to our knowledge), detection of non-small cell lung tumors of the lung with somatostatin analog scintigraphy ([\textsuperscript{111}In-DTPA-D-Phe\textsubscript{1}]-octreotide) has been well documented.\textsuperscript{1,25,26} These encouraging early reports of lung cancer imaging with somatostatin-type receptor (SSTR) analog peptide radiopharmaceuticals\textsuperscript{25–28} led to our initial experience as part of a phase IIB clinical trial with a new somatostatin analog, technetium \textsuperscript{99m}Tc-P829 (P829).\textsuperscript{29}

The current study was conducted to assess the safety and efficacy of this new radiopharmaceutical, P829, in the noninvasive differentiation of benign and malignant etiologies of SPNs.

P829 is a new SSTR binding synthetic peptide with a cyclic portion composed of a six amino acid sequence and a molecular weight of 1,358 (Fig 1). When labeled with the radioactive isotope, technetium \textsuperscript{99m}Tc (half-life = 6 h), the resultant radiopharmaceutical, P829, is characterized by rapid clearance from the bloodstream after IV injection and produces high contrast resolution single photon emission computed tomography (SPECT) images with little normal pulmonary uptake.\textsuperscript{29,30} Previous preclinical and phase IIB clinical studies have documented the safety of this radiopharmaceutical.\textsuperscript{29}

Materials and Methods

In the setting of an outpatient pulmonary medicine practice of a large health maintenance organization (200,000 covered lives) in Phoenix, AZ, individuals found by the primary care base of physicians to have nodular or mass abnormalities on plain chest radiographs were randomly referred to two of the investigators (J.B. and N.R.). Patients with SPNs of $\geq$ 1 cm were evaluated for possible entrance into the study. All patients unable to demonstrate chest radiograph stability for a preceding 2-year period, which would otherwise have suggested benignity,\textsuperscript{7,8,10} underwent a CT scan of the thorax utilizing a scanner (9800 HiLite Advantage Scanner CT; General Electric, Milwaukee, WI). Within this group, patients without a characteristic benign pattern of calcification on CT scan of the thorax were considered to have indeterminate nodules.\textsuperscript{10,31–33} Within the group of patients with indeterminate nodules, those of age $\geq$ 35 years with a tobacco abuse history of $\geq$ 20 pack-years were considered to be at high risk for primary lung cancer,\textsuperscript{34–36} and they were offered entrance in the study. No gender, age, or other selection bias was
exerted and all referrals were evaluated until 30 individuals fulfilling the criteria for an indeterminate SPN at high risk for primary lung cancer were identified. The nodule size reported is based on the maximum lesion diameter found on CT scanning.

The purpose of this study was to attempt noninvasive differentiation of benign and malignant SPNs. Somatostatin receptor distribution is ubiquitous throughout many normal tissues in the respiratory tract and the significance of this has not yet been clarified. For this reason, only the regions of the nodules in question were interrogated for P829 uptake. P829 uptake in other structures, such as in the mediastinum, was disregarded for purposes of this study.

Study Design

Following institutional review board approval, written informed consent was obtained from the patients. All eligible patients underwent P829 planar and SPECT imaging.

Vials of a lyophilized formulation containing 50 mcg of P829 peptide kits for the preparation of the P829 were provided by the manufacturer [Diatide, Inc; Londonderry, NH]. P829 was prepared by reconstituting a kit with up to 50 mCi (1,850 MBq) technetium 99m Tc pertechnetate injection and heating the resulting solution in a boiling water bath for 10 min. After cooling to room temperature (10 to 15 min), the P829 solution was visually inspected for clarity and particulates and chromatographic quality control testing was performed. Using an instant thin layer chromatography method, the radiochemical purity of P829 was not less than 90%. Within 6 h of kit preparation, 15 to 20 mCi (550 to 740 MBq) of P829 containing approximately 50 mcg of peptide was injected IV into each patient.

All imaging was performed on an iX-40 all-digital single rectangular head gamma camera (SMV; Twinsburg, OH) and processed (on an SMV Vision Power Station at Papago Imaging, Phoenix, AZ). All patients underwent four-phase imaging, including immediate flow, blood pool, and static planar images, consisting of 1 million counts each, in 128 × 128 or 256 × 256 matrices. Subsequent static planar images were obtained at 5- to 15-min and 3- to 4-h time intervals. SPECT was also performed within 4 h of injection, centered at the thorax, and acquired in a 64 × 64 matrix, with 360° “step-and-shoot” acquisition, each stop consisting of 20 to 30 s. SPECT images were reconstructed in conventional axial, sagittal, and coronal projections. All P829 imaging was completed within 6 h. No special bowel or dietary preparation was employed. All P829 images were interpreted by an experienced nuclear radiologist (H.H.). These interpretations were conducted in conjunction with the subject’s current chest radiograph and CT scan to direct the area of interrogation, and all interpretations preceded biopsy procedures and pathology reporting.

Within 10 days of, and in all instances, after P829 scanning, all patient participants had CT-guided transthoracic needle biopsy of the radiographic abnormality, using an 18-gauge biopsy needle (ASAP; Meditech; Watertown, MA), in the Radiology Department of Good Samaritan Regional Medical Center (GSRMC) in Phoenix, AZ. The specimens were examined histopathologically by GSRMC pathologists and some specimens were cultured for mycobacteria and fungi.

The resultant data were analyzed for positive and negative predictive values, and sensitivity and specificity. P829 SPECT study results were compared with final surgical pathology reports. Mean and SD for nodule size and patient age were also determined.

Results

Forty-five patients were referred for evaluation; 30 individuals fulfilled criteria for study admission. The study group consisted of 16 women and 14 men with a mean age of 59 years (SD = 13) and mean nodule size of 2.4 cm (SD = 0.9). The results are summarized in Table 1. Representative P829 SPECT and corresponding CT images of true negative and true positive scintigraphy patients are shown in Figures 2 and 3.

Fourteen patients demonstrated abnormal P829 scans in the region of the radiographic abnormality (4 men and 10 women, mean age 64 years, and mean nodule size 3.0 cm). Twelve patients had biopsy specimens revealing neoplasia: 10 compatible with adenocarcinoma of the lung, 1 compatible with squamous cell carcinoma of the lung, and 1 patient had a malignant carcinoid tumor on biopsy specimen. No revision of biopsy diagnosis was necessary in the group who ultimately underwent thoracotomy.

Two patients with abnormal P829 scans were diagnosed as having necrotizing granuloma on biopsy specimen. Mycobacterium avium complex was grown in tissue culture from one of these patients and the other demonstrated hyphae on periodic acid-Schiff staining of the biopsy specimen consistent with coccidioidomycosis.

Sixteen study patients had no abnormal tracer uptake on P829 scintigraphy in the region of the radiographic abnormality. Thirteen of these patients had necrotizing granulomatous inflammation on histologic examination of the biopsy specimens, 8 with coccidioidal spherules on periodic acid-Schiff staining. One patient had a biopsy specimen diagnosed hamartoma. One patient with no P829 uptake in the area of the SPN and an indeterminate biopsy specimen refused thoracotomy. The lesion in question remains radiographically stable after 24 months of follow-up. One patient with no uptake in the region of the SPN had a biopsy specimen compatible with squamous cell carcinoma. The initial P829 scintigraphic study was determined to be technically unsatisfactory by one of the investigators based on unusual high background distribution of activity and was “negative” for P829 uptake in the region of the SPN, but was positive in the region of the SPN on the repeat study. The reason for this singular occurrence is unclear. The subject, therefore, is reported in this series as the only false negative study.

The sensitivity of P829 SPECT scanning based on a final tissue diagnosis was 93% in this series with one false negative result, as previously described. Normal SPECT scans correctly excluded neoplasia in all but this one patient. The specificity of this method based on transthoracic needle biopsy specimen was 88%. The positive and negative predictive
values of this study in evaluating SPN were 87% and 93%, respectively. The false positive rate was 12% and the false negative rate was 7%.

There were no adverse clinical reactions associated with P829 imaging and patients were discharged from the imaging facility immediately following the SPECT examination. Five patients developed a pneumothorax following CT-guided needle biopsy requiring chest tube placement and hospital observation, a 12% incidence rate.

**Discussion**

Somatostatin is a peptide hormone found in a variety of neuroendocrine tissues, primarily with a down regulatory function.\(^1\)\(^{-1}3\)\(^7\) SSTRs are ubiquitous, being found in many tissue and blood cell types.\(^3\)\(^8\)\(^{-4}0\) At least five receptor subtypes have been described.\(^40\) The specific role of each subtype has not yet been clarified and *in vitro* expression of the various subtypes for different tumors varies between research groups.\(^41\) Despite the ubiquity of somatostatin receptors in the respiratory tract, many neoplasms, including small cell cancers, more strongly express SSTRs or more avidly bind somatostatin than do granulomas and nonneoplastic tissue.\(^42\)\(^{-4}5\) This phenomenon can be exploited conceivably for diagnostic purposes.\(^27\)\(^39\)\(^46\) Our experience and the experience of others\(^25\) suggests that non-small cell cancers can similarly be imaged scintigraphically despite the absence, to date, of the demonstration of specific receptor subtypes *in vitro*.

Octreotide, a synthetic analog of somatostatin, was first synthesized by Bauer and associates\(^47\) in 1982. In 1994, following successful clinical trials,\(^26\)\(^28\)\(^48\) the labeled peptide indium In 111 pentetreotide was approved by the Food and Drug Administration as the radiopharmaceutical, OctreoScan (Mallinckrodt Medical Inc; St. Louis, MO), for imaging neuroendocrine tumors. The expense of the $^{111}$In isotope related to cyclotron production, its relatively poor imaging characteristics, and a relatively long half-life (2.8 days) limiting the amount of tracer that can be administered, have thus far diminished the usefulness of OctreoScan in evaluating nonneuroendocrine tumors.

**Table 1—Results**

<table>
<thead>
<tr>
<th>Age, yr/Sex</th>
<th>Histology</th>
<th>P829 Results</th>
<th>Location</th>
<th>SPN Size, cm</th>
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<tbody>
<tr>
<td>64/M</td>
<td>Bronchoalveolar carcinoma</td>
<td>Positive</td>
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<td>Nondiagnostic</td>
<td>Negative</td>
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<td>57/F</td>
<td>Adenocarcinoma</td>
<td>Positive</td>
<td>RUL</td>
<td>4</td>
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<td>79/F</td>
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<td>Positive</td>
<td>LUL</td>
<td>1.5</td>
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<tr>
<td>52/M</td>
<td>Granuloma (cocci)</td>
<td>Negative</td>
<td>LUL</td>
<td>1.8</td>
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<td>72/M</td>
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<td>Negative</td>
<td>LUL</td>
<td>2.5</td>
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<tr>
<td>73/F</td>
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<td>Positive</td>
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<tr>
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<td>Granuloma (MAC)</td>
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<td>RUL</td>
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<td>Negative</td>
<td>RUL</td>
<td>2.5</td>
</tr>
<tr>
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<td>RUL</td>
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<td>1.8</td>
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<td>3</td>
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<td>LUL</td>
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<tr>
<td>62/F</td>
<td>Hamartoma</td>
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<td>RLL</td>
<td>2</td>
</tr>
<tr>
<td>53/F</td>
<td>Squamous cell</td>
<td>Negative</td>
<td>RUL</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Mean age = 59 years (SD = 13). Mean nodule size = 2.4 (SD = 0.9). RUL = right upper lobe; LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; MAC = *Mycobacterium avium* complex.
Figure 2. A 57-year-old female smoker with history of chronic bronchitis and newly discovered SPN, right upper lobe. Top (A): chest radiograph demonstrating the SPN (arrow). Center (B): P829 planar and SPECT images demonstrating intense focal P829 tracer uptake corresponding to the SPN seen on chest radiograph and CT scan. Bottom (C): transaxial biopsy localized CT scan and P829 transaxial SPECT image demonstrating the intense corresponding tracer uptake. Final diagnosis: adenocarcinoma.
Figure 3. A 42-year-old male smoker with occupational exposure to asbestos. Top (A): chest radiograph demonstrating the newly discovered left upper lobe SPN. Center (B): P829 planar and SPECT images demonstrating normal P829 biodistribution with no abnormal uptake in the region of the SPN seen on chest radiograph and CT scan. Bottom (C): transaxial CT scan and corresponding P829 transaxial SPECT image demonstrating no abnormal uptake in the region of the SPN. Final diagnosis: coccidioidomycosis.
P829 is a new SSTR binding synthetic peptide with a molecular weight of 1,358. This study along with previous investigations suggest P829 is a safe and convenient radiopharmaceutical with rapid clearance from the bloodstream after IV injection and capable of producing high-contrast resolution SPECT images with little normal pulmonary uptake. These images can be conveniently correlated with chest radiographs and CT images. The absence of adverse clinical events in subjects repeatedly tested suggests the absence of significant immunogenicity. While a direct comparison with OctreoScan was not made as part of this study, the superiority of P829 scintigraphy is suggested because of the convenience and improved imaging characteristics resulting from the kit preparation and well-known imaging advantages of the $^{99m}$Tc label compared with the cyclotron production, multiple and higher-energy photopeaks of the emissions, and longer half-life of the $^{111}$In required to produce OctreoScan.

This study demonstrates that P829 SPECT scintigraphy is a highly reliable noninvasive technique for the confirmation or exclusion of malignancy in SPNs. The burden of thoracotomy must be estimated not only in the cost of the procedure and hospitalization, but also in terms of patient morbidity, discomfort, and recovery time. Transthoracic needle biopsy engenders a complication rate, primarily pneumothorax requiring chest tube placement, recently reported at 15% in an experienced center. Additionally, the procedure is very operator dependent. The nondiagnostic rate of CT-guided transthoracic biopsy in this series was only 3% (1 of 30 cases). However, false negative and nondiagnostic rates have been reported by others as problematic, frequently necessitating further invasive studies. While one recent study utilizing immediate cytologic evaluation following CT-guided biopsy demonstrated 99% diagnostic accuracy, 24% of patients in that series experienced pneumothorax and 6% required chest tube placement.

Four patients in our series with subsequent benign diagnoses developed a pneumothorax related to the CT-guided biopsy requiring chest tube insertion and hospital observation. P829 SPECT scintigraphy correctly excluded malignancy in all but one of these cases. It can be hypothesized that reliance on P829 imaging alone to exclude malignancy in these four patients would have obviated both the significant health-care costs incurred and the related burden on patient time and comfort.

Indeed, P829 scintigraphy correctly excluded malignancy in all 15 subjects proven to have a benign etiology for their SPN. This compares very favorably with the recently published retrospective and prospective analyses of F-18 fluorodeoxyglucose (FDG) PET imaging. False positive and negative results have been reported previously with FDG-PET. Further, the specificity of P829 scintigraphy was equivalent to that widely reported with FDG-PET. In an effort to improve availability and decrease the cost of the PET technique, FDG coincidence detection utilizing dual-head SPECT cameras has been advocated. Recent investigation indicates that the sensitivity and specificity of this technique do not compare favorably with the conventional more expensive and less available PET imaging. The potential for wider availability and cost effectiveness of P829 scintigraphy compared with conventional FDG-PET is suggested by the kit production of P829 and the compatibility of $^{99m}$Tc with existing conventional nuclear medicine detector systems.

Since SSTR expression has not yet been demonstrated in non-small cell cancer (to our knowledge), the precise mechanism yielding positive OctreoScan and P829 scintigraphic imaging is unknown. As noted by Virgolini et al., the failure to demonstrate SSTR in non-small cell lung cancer could reflect the variation in methodology utilized in this regard. O’Byrne and Carney, using cell membrane preparations and autography, failed to detect SSTR in non-small cell lung tumors. Using SSTR messenger RNA, Fujita et al. found evidence for the presence of subtypes 1 and 2 in non-small cell lung cancer lines.

Activated lymphocytes in the two infectious granulomatous processes that yielded falsely positive P829 scans in this study may have accounted for the “false positive” results. Conceivably, the mechanism producing somatostatin analog tracer activity, like FDG uptake in PET studies, can be correlated with metabolic activity. The two individuals in this group with histologic and culture findings consistent with coccidioidomycosis and Mycobacterium intracellulare, respectively, did show regression in nodule size with time, suggesting subclinical disease activity at the time of evaluation. Thus, P829 uptake may have been related to the activity of the diseases. The concept of increased somatostatin analog tracer uptake in activated lymphocytes has been suggested in a variety of settings with another peptide radiopharmaceutical (OctreoScan). Significant OctreoScan uptake has been demonstrated in patients with Grave’s disease, sarcoidosis, and tuberculosis.

Additionally, the one patient with squamous cell carcinoma and no activity on the first study in the region of the malignant nodule demonstrated multiple areas of parenchymal, hilar, and mediastinal activity without corresponding abnormalities on plain radiograph or CT scan. Although we have no
definitive explanation for this phenomenon, the repeat P829 scan revealed increased P829 activity in the region of the radiographic SPN without the other initially seen abnormalities. At thoracotomy, she was found to have both neoplastic involvement and coccidioidal inflammation in the lobar nodes. Conceivably, the initial study reflected subclinical, resolving acute intrapulmonary granulomatous disease, coccidioidomycosis.

Some P829 images in this series demonstrated increased nonparenchymal activity in mediastinal structures. This uptake could not be correlated with abnormalities on plain radiograph or CT scanning and at thoracotomy or in clinical follow-up, disease was not suggested in these regions. The variability of the distribution of neuroendocrine cells with SSTR in normal tissue may be responsible for this finding. The ubiquitous distribution of SSTR in the normal respiratory tract has been noted. Thus, P829 scintigraphic interpretation was confined to the nodules in question and this study did not address P829 uptake in other regions of the thorax. Variation in the defining size of SPN is based on the concept that nodules > 3 cm are commonly malignant. Experience in the Sonoran basin, including the desert southwest United States, reveals some lesions ≥ 3 cm to be coccidioidal granuloma, and coccidioidal granulomas have been reported to account for approximately 60% of SPNs in Arizona. For this reason, one patient with a 4.5-cm nodule was entered into this study. The mean nodule diameter, however, was 2.4 cm and the mean diameter for malignant nodules was 3.0 cm. Malignant nodules as small as 1.5 cm were correctly identified.

Patient selection was based on the fulfillment of criteria defining the characteristics of pulmonary nodules and risk factors for neoplasia. Consecutively referred patients were evaluated and no gender, age, or other bias was exerted. The unusual gender distribution for non-small cell cancer, including 11 women and 4 men, was a random occurrence. It does underscore the rising proportion of female subjects comprising the current lung cancer pool, and the increasing prevalence of adenocarcinoma in some populations.

CONCLUSIONS

P829 uptake on SPECT scintigraphy reliably excluded or correctly diagnosed malignancy in 27 of 30 patients with SPNs in this series. The specificity and sensitivity of this method in this study compared favorably with those reported with FDG-PET. The P829 radiopharmaceutical is safe, should be readily available to every nuclear medicine facility, and its kit preparation should make the procedure very cost effective when compared with more invasive methods of diagnosis. The ability of P829 imaging to be performed within existing nuclear medicine facilities and with conventional gamma camera detector systems suggests wider availability for patients and cost-effectiveness for payers when compared with FDG-PET. As the study group is expanded, smaller malignant nodules and patients at higher risk for granulomas such as tuberculosis will be evaluated to further substantiate the utility of this procedure. The clinical role of P829 SPECT scintigraphy awaits confirmation of this initial experience in larger series at our institutions and elsewhere.

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