Characterization of the Solitary Pulmonary Nodule: ^{18}F-FDG PET Versus Nodule-Enhancement CT

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OBJECTIVE. The purpose of this study was to directly compare nodule-enhancement CT and ^{18}F-FDG PET in the characterization of indeterminate solitary pulmonary nodules (SPNs) greater than 7 mm in size.

MATERIALS AND METHODS. Examinations from patients undergoing both nodule-enhancement CT and ^{18}F-FDG PET to characterize the same indeterminate SPN were reviewed. For nodule-enhancement CT, an SPN was considered malignant when it showed an unenhanced to peak contrast-enhanced increase in attenuation greater than 15 H. Fluourine-18-FDG PET studies were blindly reinterpreted by two qualified nuclear radiologists. SPNs qualitatively showing hypermetabolic activity greater than the mediastinal blood pool were interpreted as malignant. These interpretations were compared with the original prospective clinical readings and to semiquantitative standardized uptake value (SUV) analysis. Results were compared with pathologic and clinical follow-up.

RESULTS. Forty-two pulmonary nodules were examined. Twenty-five (60%) were malignant, and 17 (40%) were benign. Nodule-enhancement CT was positive in all 25 malignant nodules and in 12 benign nodules, with sensitivity and specificity of 100% and 29%, respectively, and with a positive predictive value (PPV) and negative predictive value (NPV) of 68% and 100%, respectively. Qualitative ^{18}F-FDG PET interpretations were positive in 24 of the 25 malignant nodules and in four benign nodules. Fluourine-18-FDG PET was considered negative in one malignant nodule and in 13 of the 17 benign nodules. This correlates with a sensitivity and specificity of 96% and 76%, respectively, and with a PPV and NPV of 86% and 93%, respectively. Original prospective ^{18}F-FDG PET and semiquantitative SUV analysis showed sensitivity, specificity, PPV, and NPV of 88%, 76%, 85%, and 81% and 84%, 82%, 88%, and 78%, respectively.

CONCLUSION. Due to its much higher specificity and only slightly reduced sensitivity, ^{18}F-FDG PET is preferable to nodule-enhancement CT in evaluating indeterminate pulmonary nodules. However, nodule-enhancement CT remains useful due to its high NPV, convenience, and lower cost. Qualitative ^{18}F-FDG PET interpretation provided the best balance of sensitivity and specificity when compared with original prospective interpretation or SUV analysis.

T he accurate characterization as benign or malignant of a solitary pulmonary nodule (SPN) found on routine chest imaging is a diagnostic dilemma that has perplexed clinicians for several decades. This dilemma is becoming more pronounced today as the volume of diagnostic imaging performed continues to increase. In the United States, more than 150,000 new SPNs are identified each year by conventional chest radiography [1]. A considerably greater number of indeterminate pulmonary nodules will be detected annually by low-dose screening chest CT as this technique becomes more widely used in certain patient populations. In a recent Mayo Clinic study, 69% of patients screened using low-dose CT exhibited indeterminate pulmonary nodules [2]. Clinicians must be able to accurately characterize an SPN as benign or malignant not only to avoid missing a potentially life-threatening disease, but also to avoid unnecessary and costly invasive procedures with the accompanying postoperative morbidity and mortality. Numerous studies have been performed comparing the ability of various imaging techniques to adequately characterize SPNs as benign or malignant [3–9].

Two techniques currently used to characterize indeterminate SPNs are nodule-enhancement CT and ^{18}F-FDG PET. Nodule-enhancement CT is performed under the
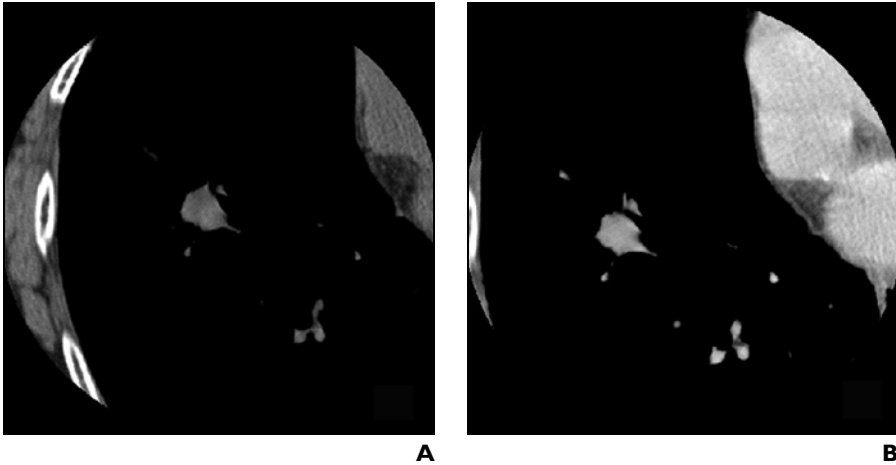
Fig. 1—69-year-old man with indeterminate right lower lobe pulmonary nodule.
A, Axial nodule-enhancement CT unenhanced image shows irregular 18 × 13 mm nodule in right lower lobe.
B, Axial nodule-enhancement CT contrast-enhanced image shows peak nodule enhancement of 53 H. Histology of resected nodule showed grade 2 squamous cell lung carcinoma, confirming nodule-enhancement CT result as true-positive for malignancy.
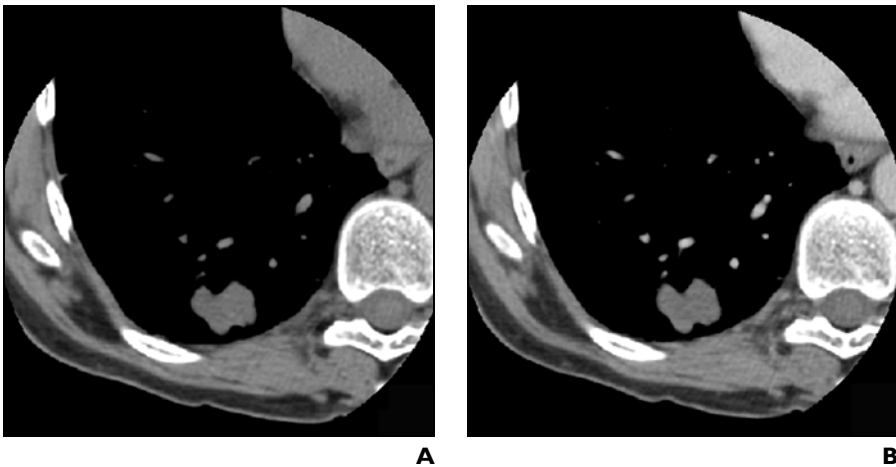

Fig. 2—61-year-old woman with indeterminate right lower lobe pulmonary nodule.
A, Axial nodule-enhancement CT unenhanced image shows lobulated 22 × 18 mm nodule in right lower lobe.
B, Axial nodule-enhancement CT contrast-enhanced image shows peak nodule enhancement of 10 H, supporting benign cause for this nodule. Histology of resected nodule showed hamartoma, confirming nodule-enhancement CT result as true-negative for malignancy.
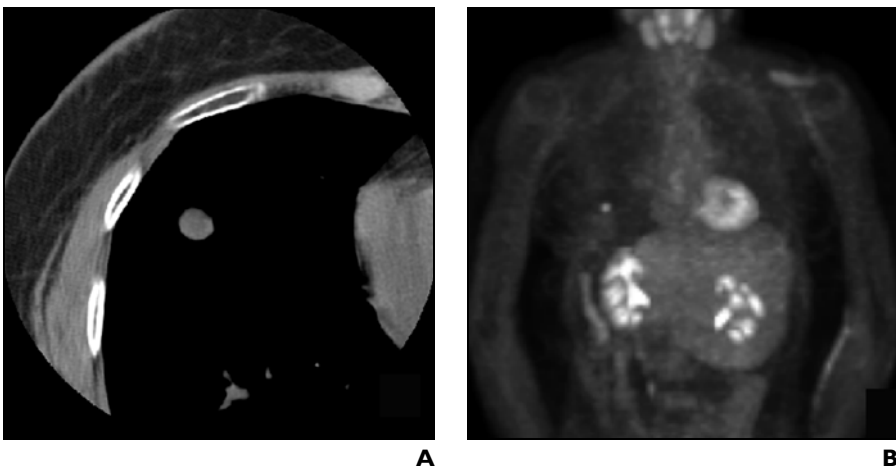

Fig. 3—57-year-old woman with history of breast carcinoma and new right middle lobe pulmonary nodule.
A, Axial unenhanced CT image shows 12-mm nodule in right middle lobe.
B, Anterior maximum-intensity-projection image from whole-body ^{18}F-FDG PET shows focus of intense hypermetabolism in inferior right lung that correlates with right middle lobe nodule and was, therefore, highly suspicious for malignancy. Histology of resected nodule showed metastatic grade 4 breast carcinoma, confirming ^{18}F-FDG PET result as true-positive for malignancy.

premise that a neoplastic lesion, with its increased vascularity, will enhance when imaged with IV contrast material. Lesions that enhance greater than 15 H from the unenhanced level to peak contrast-enhancement are considered likely malignant, whereas those that enhance less than 15 H are considered likely benign. A recent multicenter analysis of nodule-enhancement CT using these criteria showed a sensitivity of 98% and a specificity of 58% [10]. Fluourine-18-FDG PET uses ^{18}F-FDG as a marker of metabolism

TABLE 1: Interpretation Values for Each Technique

Interpretation Value	Nodule-Enhancement CT (Prospective)	Prospective ^{18}F-FDG PET	Retrospective Qualitative ^{18}F-FDG PET	Semiquantitative ^{18}F-FDG PET (SUV)
Sensitivity	100	88	96	84
Specificity	29	76	76	82
Positive predictive value	68	85	86	88
Negative predictive value	100	81	93	78

Note—Data are percentages. SUV = standardized uptake value.
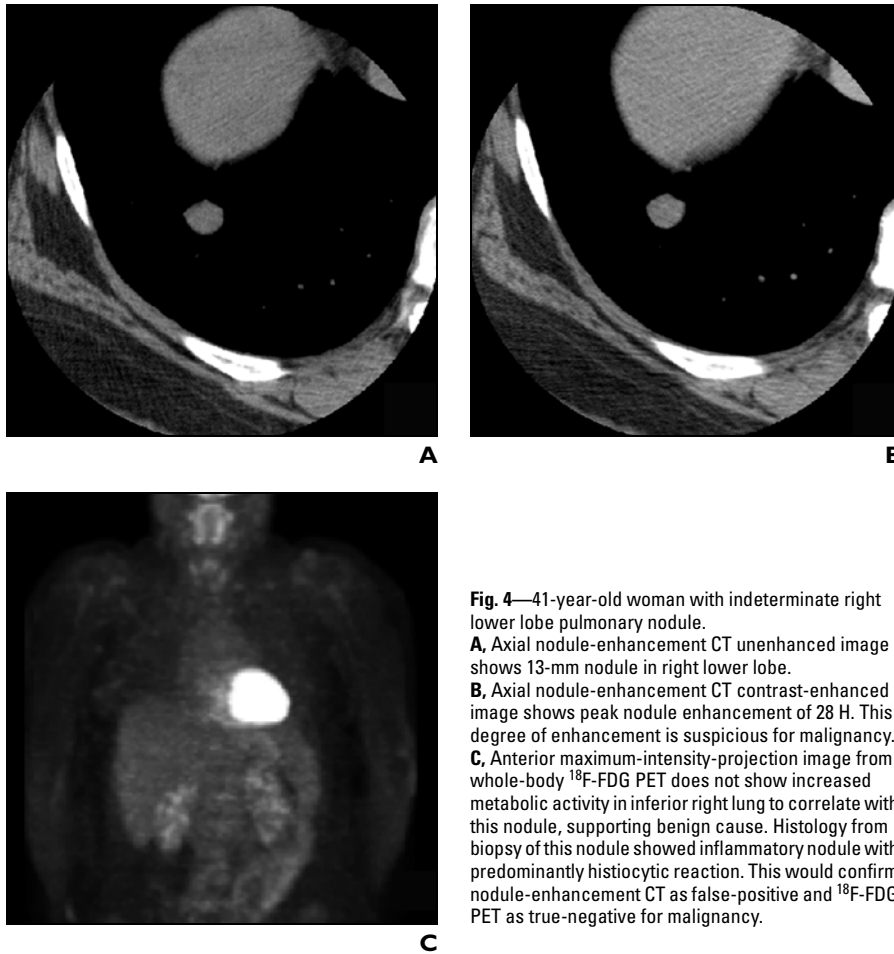

A

B

C

Fig. 4—41-year-old woman with indeterminate right lower lobe pulmonary nodule.
A, Axial nodule-enhancement CT unenhanced image shows 13-mm nodule in right lower lobe.
B, Axial nodule-enhancement CT contrast-enhanced image shows peak nodule enhancement of 28 H. This degree of enhancement is suspicious for malignancy.
C, Anterior maximum-intensity-projection image from whole-body ^{18}F-FDG PET does not show increased metabolic activity in inferior right lung to correlate with this nodule, supporting benign cause. Histology from biopsy of this nodule showed inflammatory nodule with predominantly histiocytic reaction. This would confirm nodule-enhancement CT as false-positive and ^{18}F-FDG PET as true-negative for malignancy.

with lesions localizing ^{18}F-FDG proportionate to their metabolic activity. SPNs with hypermetabolism greater than the mediastinal blood pool are likely malignant. To further quantify metabolism in individual nodules, a standardized uptake value (SUV) can be calculated [11]. An SUV greater than 2.5 defines the SPN as malignant with a relatively high degree of sensitivity and specificity [11]. Using these criteria, recent studies have shown a sensitivity of 92–96% and a specificity of 77–90% using ^{18}F-FDG PET [11, 12].

An informal and indirect comparison of nodule-enhancement CT and ^{18}F-FDG PET seems to show that ^{18}F-FDG PET, with its slightly lower sensitivity yet much higher specificity, would perhaps be the technique of choice in the characterization of an indeterminate SPN. However, there has not yet been a direct comparison of nodule-enhancement CT and ^{18}F-FDG PET to determine the relative sensitivity and specificity on a nodule-by-nodule basis. We have designed and completed this study to directly compare nodule-enhance-

ment CT and ^{18}F-FDG PET in their respective abilities to accurately characterize indeterminate SPNs as benign or malignant.

Materials and Methods

With the approval of our institutional review board, a retrospective review of all patients who underwent both nodule-enhancement CT and ^{18}F-FDG PET in the evaluation of an SPN greater than or equal to 7 mm in size (the resolution limit of the scanners used) from April 2000 to April 2004 inclusive was performed. Patients with adequate imaging follow-up or definitive pathologic diagnosis of the nodule in question were included in the final analysis. To include the greatest number of patients possible, we defined adequate imaging follow-up as having at least 18 months (instead of the customary 24 months) of nodule stability or regression on interval radiologic imaging.

Nodule-enhancement CT was performed on each patient using HiSpeed Advantage, HiSpeed CT/i, or LightSpeed Qx/i helical scanners (GE Healthcare). A standardized protocol was used in the imaging of each patient using a collimation of 3 mm with a narrow field of view including the nodule. Images were obtained before and after administration of IV contrast material (420 mg I/kg injected at 300 mg/mL) at 1, 2, 3, and 4 minutes. The original prospective nodule-enhancement CT examination reports were retrospectively reviewed. Examination reports that did not state the attenuation difference were reviewed and the attenuation difference was measured by an experienced radiologist. An increase in attenuation within the nodule from unenhanced to peak contrast enhancement greater than 15 H was considered to be malignant. An increase from unenhanced to peak contrast enhancement less than 15 H was interpreted as benign (Figs. 1 and 2).

Fluourine-18-FDG PET was performed using an Advance PET or a Discovery LS PET/CT scanner (GE Healthcare). Whole-body attenuation-corrected images were obtained from the base of the skull through the symphysis pubis after administering a standard dose of 15 mCi of ^{18}F-FDG IV and allowing for a 60-minute equilibration. Each patient had been fasting at least 4 hours when imaged.

Fluourine-18-FDG PET examinations were interpreted three ways to test for differences in sensitivity and specificity using both qualitative and semiquantitative interpretations. First, the original ^{18}F-FDG PET reports were reviewed to determine the original prospective characterization of each SPN as benign or malignant. Second, a blinded qualitative reinterpretation of each ^{18}F-FDG PET examination was performed independently by two experienced nuclear radiologists. In this qualitative reinterpretation, a nodule was defined as malignant if it had hyper-
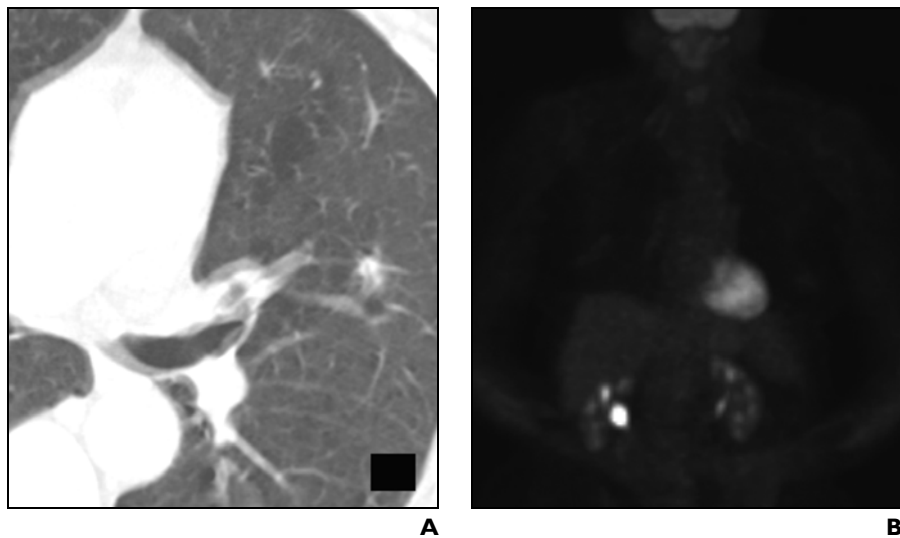
Fig. 5—71-year-old woman with indeterminate left lower lobe pulmonary nodule.
A, Axial lung-window CT image shows somewhat spiculated 8 × 5 mm nodule in left lower lobe. Nodule-enhancement CT showed peak nodule enhancement of 55 H.
B, Anterior maximum-intensity-projection image from whole-body ^{18}F-FDG PET fails to show increased metabolic activity within this nodule. Histology of resected nodule revealed grade 2 lung adenocarcinoma. This would confirm nodule-enhancement CT result as true-positive and ^{18}F-FDG PET as false-negative for malignancy.

metabolic activity greater than the metabolic activity of the adjacent mediastinal blood pool (Fig. 3). Nodules with no activity or activity less than that of the adjacent mediastinal blood pool were identified as benign. Last, a semiquantitative measure of metabolism was performed for each SPN. A region of interest was placed over each nodule and average SUVs were determined using body-weight normalization. Nodules with an SUV greater than or equal to 2.5 were considered malignant. Nodules with an SUV less than 2.5 were considered benign.

Sensitivity, specificity, and negative and positive predictive values from each examination technique including the three different methods of ^{18}F-FDG PET interpretation were calculated and are presented in Table 1.

Results

A total of 42 pulmonary nodules in 41 patients were identified and examined using both nodule-enhancement CT and ^{18}F-FDG PET. Twenty women and 21 men were included in the study. The average patient age was 66 years (age range, 36–84 years). Twenty-eight patients (67%) had a previous smoking history (average, 48 pack-years; range, 5–120 pack-years). Nine patients (21%) had a history of a prior malignancy (3 colon; 2 breast; 1 each of lung, thyroid, bladder, and renal). The average nodule size was 15 mm in greatest dimension (range, 7–27 mm). Nodules were distributed as follows: 10, right upper lobe; 10, right middle lobe; nine, right lower lobe; six, left upper lobe; and seven, left lower lobe. Scans were performed a mean of 42 days (range, 0–601 days) from one another. Twenty-five (60%) of the 42 nodules were defined histologically as malignant by biopsy or open surgical resection. The

remaining 17 nodules were considered benign based on the following criteria: nine of the 17 were confirmed histologically as benign by biopsy or open surgical resection; the remaining eight nodules were considered benign due to nodule stability or regression on radiologic follow-up of greater than 18 months.

Nodule-enhancement CT was interpreted as positive (enhancement > 15 H) in all 25 malignant nodules and in 12 of the benign nodules. Five nodules were interpreted as negative (enhancement < 15 H) on nodule-enhancement CT. All five of these nodules were benign. These numbers represent a cumulative sensitivity of 100% and a specificity of 29%, with a positive predictive value (PPV) and negative predictive value (NPV) of 68% and 100%, respectively. The 12 false-positive SPNs for malignancy on nodule-enhancement CT were as follows: five nodules exhibited radiologic stability or regression (two by follow-up chest X-ray and three by CT). The other seven nodules showed benign histology after open resection or biopsy: one nodule each as histoplasmosis, chondroid hamartoma, sarcoidosis, foreign body reaction to talc, and caseating granuloma; and two nodules were interpreted as benign histology not otherwise specified (Fig. 4).

Prospective ^{18}F-FDG PET was interpreted as positive (original report interpreted as positive for malignancy by the primary interpreting radiologist) in 22 of the 25 malignant nodules and in four benign nodules. Sixteen nodules were considered benign on prospective ^{18}F-FDG PET. Thirteen of these were benign. This represents a sensitivity of 88% and a specificity of 76%, with a PPV and NPV of

85% and 81%, respectively. The four false-positive SPNs were one each of histoplasmosis, sarcoidosis, foreign body reaction to talc, and caseating granuloma. Two small grade 2 adenocarcinomas (13 × 8 × 7 mm in the right lower lobe and 7 × 7 × 5 mm in the left upper lobe) and one atypical carcinoid were the three malignant nodules initially interpreted as negative for malignancy by the primary radiologist (Fig. 5).

Blinded, qualitative retrospective ^{18}F-FDG PET interpretation (using visual analysis: metabolic activity in the nodule greater than the metabolic activity of the adjacent mediastinal blood pool) was positive in 24 of the 25 malignant nodules and in four benign nodules. Fourteen nodules were interpreted as benign on ^{18}F-FDG PET. Thirteen of these were defined as benign by imaging follow-up or pathology. This represents a sensitivity of 96% and a specificity of 76%, with a PPV and NPV of 86% and 93%, respectively. The four false-positive nodules were one each of histoplasmosis, sarcoidosis, foreign body reaction to talc, and benign histology not otherwise specified. The single false-negative nodule was one of the same grade 2 adenocarcinomas interpreted as false-negative by the prospective clinical ^{18}F-FDG PET interpretation (7 × 7 × 5 mm in the left upper lobe). There was no interobserver variability between the two blinded, independent ^{18}F-FDG PET reviewers.

Semiquantitative ^{18}F-FDG PET was interpreted as positive (SUV ≥ 2.5) in 21 of the 25 malignant nodules and in three of the benign nodules. Eighteen nodules were considered benign by SUV criteria (SUV < 2.5). Fourteen of

Fig. 6—Proposed algorithm for evaluation of newly found solitary pulmonary nodules. SUV = standardized uptake value.

Solitary Pulmonary Nodule Discovered

Thin-section CT

Benign characteristics (fat, calcification, etc.) — Indeterminate

> 7 mm — < 7 mm

Nodule enhancement

< 15-H Enhancement — > 15-H Enhancement

^{18}F-FDG PET

> Mediastinal blood pool — < Mediastinal blood pool

SUV > 2.5 — SUV < 2.5

Benign — Malignant — Likely benign

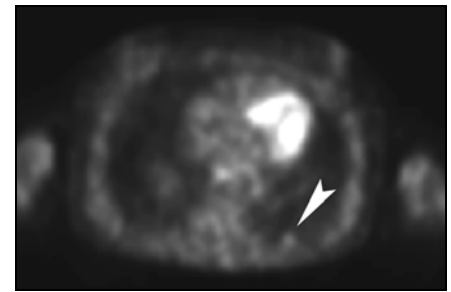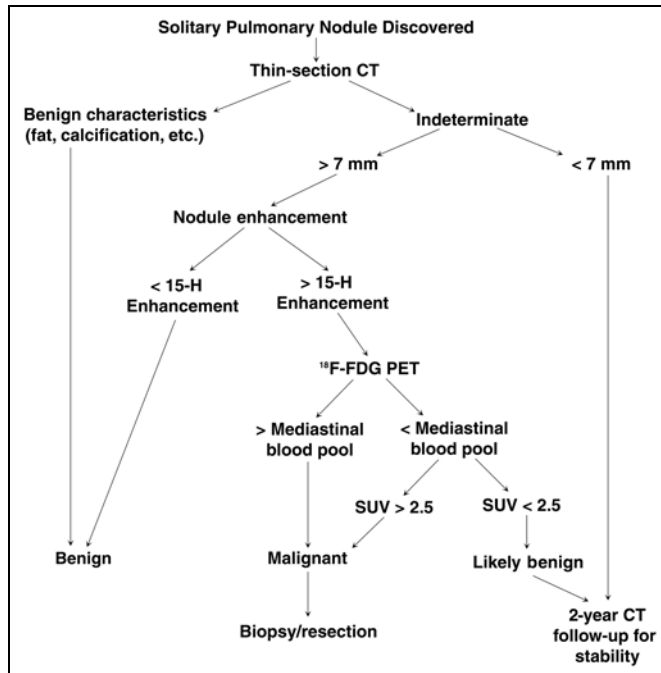Biopsy/resection — 2-year CT follow-up for stability

Fig. 7—67-year-old woman with enlarging 8 × 7 mm left lower lobe pulmonary nodule first detected on low-dose screening chest CT. Axial ^{18}F-FDG PET image shows focus of increased metabolic activity in posterior left lung base (*arrowhead*) correlating with location of nodule. During blinded, qualitative review, two experienced nuclear radiologists independently interpreted this nodule as malignant; however, measured standardized uptake value maximum was 1.7, below 2.5 threshold for malignancy and favoring benign cause. Histology of resected nodule revealed grade 2 adenocarcinoma.

these were truly benign. This represents a sensitivity of 84% and a specificity of 82%, with a PPV and NPV of 88% and 78%, respectively. The three false-positives included one each of histoplasmosis, sarcoidosis, and foreign body reaction to talc. Three of the four nodules interpreted as false-negative for malignancy were the same atypical carcinoid and the same two grade 2 adenocarcinomas interpreted as negative by the prospective radiologist. The remaining false-negative nodule was a 10 × 15 mm grade 2 adenocarcinoma interpreted as malignant by both prospective and blinded qualitative ^{18}F-FDG PET.

Thirty-eight of the 42 nodules were examined with nodule-enhancement CT first, followed by ^{18}F-FDG PET. Thirty-four of the nodules initially imaged with nodule-enhancement CT exhibited enhancement greater than 15 H and were interpreted as likely malignant. All 25 malignant nodules were correctly identified by nodule-enhancement CT. However, nine benign nodules (24% of those imaged initially with nodule-enhancement CT) were false-positive. Eight of these were correctly identified as benign on the subsequent ^{18}F-FDG PET examination. The remaining benign nodule interpreted as malignant on both initial nodule-enhancement CT and subsequent ^{18}F-FDG PET was identified pathologically after open biopsy as histoplasmosis. The four nodules initially imaged with nodule-enhancement CT and inter-

preted as benign were also interpreted as benign on subsequent ^{18}F-FDG PET examination. Three of these nodules exhibited radiologic stability or regression. The fourth was resected and pathologically identified as a hamartoma.

Four nodules were imaged initially with ^{18}F-FDG PET, followed by nodule-enhancement CT. All of these nodules were benign. Three had positive results on the initial prospective ^{18}F-FDG PET examination. One of these three nodules was negative on subsequent nodule-enhancement CT. This nodule was also negative and interpreted as benign on retrospective qualitative and semiquantitative ^{18}F-FDG PET interpretation. The benign nodule that was interpreted as negative on initial prospective ^{18}F-FDG PET was also interpreted as negative on retrospective qualitative and semiquantitative ^{18}F-FDG PET but was interpreted as positive on subsequent nodule-enhancement CT.

Discussion

A large number of indeterminate SPNs are discovered each year on routine chest imaging. This number is rapidly increasing, precipitated mainly by the increased use of MDCT and low-dose chest CT screening protocols [2, 13]. To avoid costly and invasive procedures in patients without malignant disease, it is imperative to characterize these pulmonary nodules as benign or malignant with

a high degree of accuracy. Numerous studies to date have reported the efficacy of various imaging techniques and protocols in accurately diagnosing the nature of newly found pulmonary nodules.

Nodule-enhancement CT is one such technique. A multicenter study performed by Swensen et al. [10] showed a sensitivity of 98% and a 96% NPV. The same study, however, also showed a relatively low specificity of only 58% and a PPV of 68%. The high sensitivity and high NPV of nodule-enhancement CT coupled with its relatively low cost and high general availability render it a useful examination in SPN characterization. However, the poor specificity of this examination can lead to increased overall costs and greater morbidity due to unnecessary biopsies and other thoracic surgical interventions.

Fluorine-18-FDG PET has also been widely studied for its use in the accurate characterization of SPNs. A multicenter study by Lowe et al. [11] showed sensitivities of 100% and 80% and specificities of 74% and 95% for visual and SUV analyses of SPNs, respectively. A recent meta-analysis of studies using ^{18}F-FDG PET for SPN evaluation showed a sensitivity of 96.8% and a specificity of 77.8% [12]. Although a more costly examination than nodule-enhancement CT, the higher specificity of ^{18}F-FDG PET can ultimately lead to considerable cost savings by reducing the number of biopsies and surgical interventions. Prior limited access to ^{18}F-FDG PET is rapidly resolving because the number of both fixed and mobile ^{18}F-FDG PET units has in-

creased significantly during the past 5 years. However, one of the major limitations is the resolution of the scanners used. Currently, the resolving limit of ^{18}F-FDG PET scanners is nodules that are 6–8 mm in size. Nodules smaller than this are not adequately evaluated with ^{18}F-FDG PET.

Although studies have evaluated the individual potential of nodule-enhancement CT and ^{18}F-FDG PET to accurately characterize an SPN as benign or malignant, to date there has not been a study directly comparing the two techniques. The results from our comparison of ^{18}F-FDG PET and nodule-enhancement CT indicate that, in support of prior studies, nodule-enhancement CT shows a very high sensitivity and NPV (both 100%) but a very poor specificity (29%). Fluorine-18-FDG PET gives a slightly lower sensitivity yet much higher specificity and PPV than nodule-enhancement CT. In addition, our results show that the best balance of sensitivity and specificity for malignancy is obtained when ^{18}F-FDG PET images are interpreted by qualitatively comparing the metabolic activity within the SPN to the metabolic activity of the adjacent mediastinal blood pool. A degree of SPN activity greater than that of the mediastinal blood pool is highly suggestive of malignancy, with a sensitivity of 96% and a specificity of 76%. Our study showed a slightly higher specificity of 83% when semiquantitatively qualifying an SPN using an SUV threshold of 2.5. However, we found a lower sensitivity (88%) for malignancy when solely using SUV measurements. Overall, our study supports the use of ^{18}F-FDG PET over nodule-enhancement CT in the evaluation of indeterminate SPNs due to its high sensitivity and much better specificity.

The major limitation of our study is referral bias. The majority of SPNs (38 of 42 [90%]) were imaged with nodule-enhancement CT first. With a low pretest probability for malignancy, a positive nodule-enhancement CT for a given SPN may have been considered equivocal by the referring physician, dictating subsequent referral for ^{18}F-FDG PET and a higher incidence of malignancy in our study population. This would also certainly have the potential to increase the false-positive rate for nodule-enhancement CT and reduce its overall specificity. Also, due to the very high NPV of nodule-enhancement CT, many nodules not demonstrating enhancement on nodule-enhancement CT may have been considered benign and thus not referred for ^{18}F-FDG PET. This reduction in potential true-negative nod-

ule-enhancement CT cases from the study population could lead to a reduction in nodule-enhancement CT specificity and again, a higher incidence of malignancy in the study population. Despite these referral bias limitations, the difference in specificity between ^{18}F-FDG PET and nodule-enhancement CT in our study is so great that our data continue to support the preferential use of ^{18}F-FDG PET for evaluation of SPNs, particularly when there is a high index of suspicion for malignancy. In fact, the 76% specificity for qualitative ^{18}F-FDG PET interpretation is in line with multiple prior studies [8, 11, 12, 14, 15] and well above the 58% specificity established for nodule-enhancement CT in the large multicenter trial published by Swensen et al. [10].

Several nodules in our study were characterized erroneously by both techniques. In the nodule-enhancement CT group, there were no false-negative nodules. There were three false-negative nodules in the ^{18}F-FDG PET group. These occurred in two low-grade adenocarcinomas and in an atypical carcinoid. Encountering these false-negative nodules was not surprising, considering the reliance of ^{18}F-FDG PET on metabolic activity. It has previously been shown that ^{18}F-FDG PET can misdiagnose malignant lesions with low metabolic activity, such as is seen in low-grade neoplasms and, classically, in slow-growing carcinoid tumors [16, 17]. Our results are consistent with this. However, the majority of tumors are of higher metabolic activity, and ^{18}F-FDG PET, although misdiagnosing some low-grade malignant nodules, still performed quite well in our study, correctly diagnosing the majority of malignant nodules.

There were several false-positive results in the nodule-enhancement CT group, which lowered the overall specificity considerably. The false-positive results occurred in several nodules that were benign histologically or that proved to be benign after stability or regression on radiologic follow-up. These histologically confirmed false-positive nodules included histoplasmosis, chondroid hamartoma, sarcoidosis, foreign body reaction to talc, and necrotizing granuloma, all conditions with inflammatory components and thus increased vascularity. Nodules observed to be false-positive in the ^{18}F-FDG PET examinations included histoplasmosis, sarcoidosis, foreign body reaction to talc, caseating granuloma, and nonspecific benign abnormality at resection. The inflammation inherent to the majority of these false-positive nodules would certainly lead to increased metabolic

activity. It is understandable that the impact of these false-positive and false-negative nodule-enhancement CT and ^{18}F-FDG PET SPN examinations on patient management could be lessened by correlating the imaging findings with other important clinical parameters such as history, physical examination, risk factors, and laboratory studies.

Due to the high sensitivity and NPV of nodule-enhancement CT, nodules with a negative nodule-enhancement CT have an extremely low likelihood of being malignant. Patients with a negative nodule-enhancement CT thus would not benefit from further ^{18}F-FDG PET examination. However, nodule-enhancement CT generates a large number of false-positives owing to its low specificity. In cases where an SPN is positive on nodule-enhancement CT, subsequent ^{18}F-FDG PET examination would likely be helpful. In our study, nine of the 38 nodules (24%) examined initially with nodule-enhancement CT were erroneously interpreted as possibly malignant. Eight of these were subsequently interpreted as benign on ^{18}F-FDG PET. Relying on the nodule-enhancement CT results alone would have subjected these eight patients with benign nodules to costly interventions in which potential morbidity is relatively high, such as open thoracotomy, video-assisted thoracoscopic surgery, or transthoracic needle aspiration. Indeed, these results show the added value of performing ^{18}F-FDG PET after a positive nodule-enhancement CT study in an indeterminate SPN.

In conclusion, our recommendations for the use of nodule-enhancement CT and ^{18}F-FDG PET in the evaluation of an indeterminate SPN greater than 7 mm are summarized in algorithmic form in Figure 6. We believe that ^{18}F-FDG PET, with its high sensitivity and much higher specificity than nodule-enhancement CT, is the superior technique for accurately characterizing indeterminate SPNs. However, the lower sensitivity of ^{18}F-FDG PET does have the capacity of generating a greater number of false-negative results, especially in lower grade malignancies. The lower sensitivity of ^{18}F-FDG PET combined with the higher cost must be factored into the evaluation of any pulmonary nodule.

With its high sensitivity and NPV, widespread availability, and relatively low cost, nodule-enhancement CT could continue to be used as an integral part of the evaluation of indeterminate SPNs in patients with a low likelihood of malignancy. At the initial discovery of an SPN, all patients should un-

dergo a thin-section CT examination to accurately characterize the nodule. Nodules in patients with a low likelihood of malignancy could undergo nodule-enhancement CT, preferably during the same examination. Nodules with less than 15 H of enhancement on nodule-enhancement CT have a very low probability of malignancy and can be defined as benign, with no further imaging or follow-up needed. Nodules exhibiting greater than 15 H of enhancement on nodule-enhancement CT, however, should undergo subsequent ^{18}F-FDG PET examination. These patients benefit from the higher specificity of ^{18}F-FDG PET, eliminating the false-positive results generated from the low specificity of nodule-enhancement CT.

Patients with a moderate or high likelihood of malignancy should undergo ^{18}F-FDG PET evaluation. In our review, it appears that a nonbiased, qualitative interpretation of ^{18}F-FDG PET through comparison of SPN and mediastinal blood pool metabolic activity provides the best balance of sensitivity and specificity for the accurate diagnosis of malignant nodules. SUV analysis can then be reserved for those patients in whom the qualitative ^{18}F-FDG PET interpretation is equivocal. In our study, three malignant nodules interpreted as malignant by qualitative visual interpretation were considered negative by SUV analysis because the SUV fell below 2.5 (SUV of 1.7, 1.8, and 1.7) (Fig. 7). Nodules with metabolic activity greater than the mediastinal blood pool are likely malignant and should undergo further invasive resection or biopsy. Those with metabolic activity less than the mediastinal blood pool are likely benign. However, due to the imperfect sensitivity of ^{18}F-FDG PET, we would recommend that these nodules be examined with serial radiologic imaging for further workup of malignant conditions.

A recent study by Comber et al. [7] in an Australian setting supports these recommendations. This study showed a diagnostic strategy using both nodule-enhancement CT and ^{18}F-FDG PET to be more cost-effective than ^{18}F-FDG PET with conventional CT alone (incremental cost:accuracy ratio of Australian $12,059.18:Australian $12,636.36). This remained the case except in populations with a high disease prevalence, where the cost-effectiveness of both strategies was shown to be approximately equal [7]. By coupling the high sensitivity of nodule-enhancement CT with the much higher specificity and overall greater accuracy of ^{18}F-FDG PET, clinicians can accurately characterize indeterminate SPNs as benign or malignant, thereby reducing the number of invasive procedures required for diagnosis as well as providing for the early determination of malignancy while definitive surgical resection is still feasible and potentially curative.

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