Probability of Malignancy in Solitary Pulmonary Nodules Using Fluorine-18-FDG and PET

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Nearly one-third of solitary pulmonary nodules are radiographically indeterminate for the presence of malignancy. **Methods:** FDG-PET imaging was used to differentiate benign and malignant solitary pulmonary nodules in 61 patients with radiographically indeterminate nodules. After confirmation of the histological diagnosis, the probability for cancer was established for positive and negative PET scans and compared to the risk estimates calculated using other patient variables. **Results:** FDG-PET had a sensitivity, specificity and positive predictive value of 93%, 88% and 92%, respectively, for detecting malignancy in indeterminate solitary pulmonary nodules. The probability of malignancy with a positive PET scan is 83%, which increases with the patient's age (90% in >60 yr) and the size of the nodule. A negative PET scan is associated with only a 4.7% risk of malignancy. FDG-PET also accurately characterized hilar/mediastinal lymphadenopathy in 12 patients with associated lymph node lesions. **Conclusion:** FDG-PET imaging can be a useful noninvasive test to determine the risk estimate or probability of cancer as well as preoperative staging in patients with radiographically indeterminate solitary pulmonary nodules.

Key Words: solitary pulmonary nodules; fluorine-18-FDG; PET

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Solitary pulmonary nodules are parenchymal lung lesions that are well defined and less than 3 or 4 cm in diameter. A solitary nodule may represent a diverse benign and malignant conditions. The American Cancer Society estimates that 172,000 lung cancer cases will be reported each year in the U.S. (*1*). Many of these would present as one of the 130,000 solitary nodules found each year. It is estimated that 52 of every 100,000 people will have a solitary pulmonary nodule. Clinical features, including symptoms, physical examination and laboratory results, are usually nonspecific and may not be able to differentiate the variety of benign and malignant diseases (*2*). Several diagnostic procedures, including chest radiography and CT, are used to differentiate benign from malignant nodules. A large proportion of solitary pulmonary nodules are, however, radiographically indeterminate (*3*). The only definite criteria for benign solitary pulmonary nodules are the presence of characteristic calcification (central, concentric or stippled) on chest radiographs or CT and stable nodule size after more than 2 yr of follow-up (*4*).

Treatment of radiographically indeterminate solitary pulmonary nodules remains controversial (*5*). Many investigators advise immediate thoracotomy or a transthoracic percutaneous needle biopsy. Ideally, the best regimen for any new patient would depend greatly on the probability of malignancy in the particular surgical nodule (*6*). Data from surgical series indicate that as many as 60% of the nodules resected could in fact be benign.

PET is useful in detecting malignant cells by exploiting the fundamental biochemical differences between benign and malignant cells (*7*). Fluorine-18-fluorodeoxyglucose (FDG) when used with PET scanning has provided encouraging results for detecting the increased glucose metabolism characteristic of malignant cells (*8*). FDG is a D-glucose analog labeled with a positron emitter ^{18}F behaving like D-glucose in its transport through the cell membrane and phosphorylation by hexokinase in the normal glycolytic pathway. The increased uptake and accumulation of FDG is seen and occurs within the abnormally metabolizing tumor cells (*9*). Recent in vitro and in vivo studies of lung cancer with FDG-PET have demonstrated increased glucose metabolism in the malignant cells (*8,10*). In a recent study, we also reported that the FDG-PET imaging is highly accurate in differentiating benign from malignant nodules up to 3 cm in size (*11*).

Several factors have been found to be associated strongly with the probability of malignancy in lung nodules: patient's age, nodule size, appearance of the nodule and the patient's smoking history (*5,6*). In the present study, we examine the diagnostic efficacy of FDG-PET imaging in the evaluation of 61 patients with radiographically indeterminate solitary pulmonary nodules 0.6–3 cm in size. We have analyzed our data to develop a simple method for estimating the probability of malignancy in a nodule. We compared methods for computing the probability of malignancy in solitary pulmonary nodule based on FDG-PET imaging alone to computing the probability of malignancy based on several risk factors.

METHODS

Patients

The study was preapproved by the Institutional Review Board of Creighton University and all patients gave informed consent. Sixty-one patients (16 women, 45 men; aged 24–89 yr; mean age 65 yr) presenting to the primary physician or thoracic surgeon for evaluation of indeterminate solitary pulmonary nodules 0.6–3 cm in size. All patients had chest radiographs and thoracic CT scans which were interpreted independently before the PET study. With the exception of one patient who had eccentric calcification, all solitary pulmonary nodules were noncalcified and considered indeterminate on the bases of chest radiographs and CT scans. The final diagnoses were established by obtaining tissue from thoracotomy (n = 43), percutaneous transthoracic needle aspiration biopsy (n = 13) or bronchoscopy (n = 4). One subject who showed no change in the nodule size for a period of 2 yr was presumed to have a benign nodule.

PET

All subjects fasted for at least 4 hr prior to PET imaging. Diabetic patients (6/61) were included, but no special dietary precautions were taken. Serum glucose levels could not be obtained for all patients. PET imaging was performed on a tomograph that produces 15 slices of 8-mm thickness and has a reconstructed in-plane resolution of approximately 5–7 mm. The imaging device

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has a 12-cm longitudinal field of view. Transmission scanning was also performed in all subjects (by using a ^{68}Ge ring source) before FDG administration for attenuation correction. Transmission scans were acquired for 10–15 min for a minimum of 10 million counts per direct plane and a total of 220 million counts. Image acquisition was started 1 hr after intravenous administration of 10 mCi of [^{18}F]FDG. All subjects underwent two acquisitions to include the entire lung in the field of view.

Image processing was performed on the Sun 4/110 work station (SUN Microsystems, Mountain View, CA), and image reconstruction was performed on a Microvax computer (Digital Equipment, Marlboro, MA). Images were analyzed qualitatively using visual analysis for focal areas of increased FDG uptake in both lungs' fields and mediastinum by two experienced observers. Images in the transverse, coronal and sagittal views were reviewed for the presence of focal abnormalities. The emission images were also superimposed over transmission scans for anatomic correlation. The focal areas in suspected nodules or lymph nodes with uptake greater than background mediastinal activity were considered abnormal.

Semiquantitative analysis, to compute the differential uptake ratios (DUR), was performed in all patients by drawing a region of interest (ROI) (0.8 cm^2 size) over the solitary pulmonary nodule on transaxial images. The interobserver variability to calculate DUR by drawing the ROI was calculated to be <5%. Areas of decreased or absent FDG uptake within the nodule were not included in the ROI. Average counts per pixel in the ROI were used to compute the DUR values. The ROI was drawn over the hottest region in the nodule. In some patients, no nodules could be detected on the PET or transmission scan. In these patients, the ROI was drawn in its location as extrapolated from chest radiographs and CT scans. The radiotracer counts were corrected for radioactive decay from the time of injection. These counts were normalized for the patient's body mass and the injected dose. DUR was thus computed as follows:

$$\frac{\text{Mean PET counts/pixel/sec} \times \text{calibration factor}}{\text{Injected dose } (\mu\text{Ci})/\text{body weight (kg)}},$$

where calibration factor = (microcuries/ml)/(counts/pixel/sec)

Data Analysis

PET findings were compared to the final histologic diagnoses obtained from tissue specimens. Sensitivity, specificity, accuracy as well as positive and negative predictive values of PET imaging for detecting malignancy in solitary pulmonary nodules were calculated by comparison to the final histologic diagnosis. Semiquantitative DUR indices were also compared to the final diagnoses and the differences between the malignant and benign nodules were statistically analyzed.

Statistical Analysis

The diagnostic efficacy of FDG-PET imaging in differentiating benign from malignant nodules was calculated using Bayes' theorem. When the nodule had increased FDG uptake, it was regarded as a positive PET scan for calculating the probability of cancer.

Likelihood Ratio. Several earlier studies have estimated the probability of cancer in pulmonary nodules based on characteristics of the patients and nodules. We used Bayes' theorem to calculate post-test odds of nodule malignancy. Let M and N denote the presence of malignant and nonmalignant nodules, respectively. We denote the probabilities for a nodule being malignant or nonmalignant by P(M) and P(N), respectively. If the prevalence of malignancy in all solitary pulmonary nodules is 40% (*1*), then the probability of benign disease is 60%. The odds of malignancy must therefore be O(M) = 0.40/0.60 = 0.67. With Bayes' theorem, it can be shown that post-test odds O(M|E) and the pretest odds O(M) for presence of cancer are related as follows:

$$\text{O(M|E) (post-test odds)} = L_E \cdot \text{O(M) (pretest odds)},$$

where E is an experimental or observational outcome. The mathematical likelihood ratio is represented as:

$$L_E = \frac{P(E|M)}{P(E|N)},$$

where LR is the likelihood ratio or Bayes' factor (especially in statistical literature). In other words, the likelihood ratio is simply

$$\frac{\text{True-positive rate}}{\text{False-positive rate}}$$

and post-test odds for malignancy is:

pretest odds for malignancy

$\times$ likelihood ratio for diagnostic test.

The odds of having a malignant nodule with a positive PET scan O(M|E) is equal to L_E O(M), where E is the observed data (i.e., the PET scan results). The likelihood ratio is defined as a ratio of two probabilities—the probability of finding an experimental outcome among those with malignancy (true-positive rate) to the probability of the same finding among those who are free of malignancy (false-positive rate). The L_E or likelihood ratio measures the amount of data supporting malignancy provided by the observed result E. By using this ratio, we are able to calculate the likelihood of malignancy from the given data:

$$\text{L Positive PET} = \frac{\text{Probability of a positive PET scan in a malignant nodule (TP)}}{\text{Probability of a positive PET scan in a benign nodule (FP)}}$$

$$\text{L Negative PET} = \frac{\text{Probability of a negative PET scan in a malignant nodule (FN)}}{\text{Probability of a negative PET scan in a benign nodule (TN)}},$$

where TP = true-positive, FP = false-positive, FN = false-negative and TN = true-negative. If L_E is greater than 1, then E provides evidence in favor of malignancy. If $0 \leq L_E \leq 1$, then E provides evidence against malignancy and if $L_E = 1$, then E does not differentiate between M and N.

After observing E, the uncertainty about malignancy is now expressed by the post-test probability:

$$P(M|E) = \frac{0(M) \cdot L_E}{1 + 0(M) \cdot L_E},$$

that is, we start with 0(M) before observing E, then after observing E, we find L_E and by using the above formula, we arrive at the revised probability of malignancy in view of the evidence provided by E (in this case, the PET scan).

Previous investigators have also used the likelihood ratio form of Bayes' theorem to combine individual odds into an overall estimate of the odds favoring malignancy (*5,6*).

RESULTS

Histologic Findings

Sixty of 61 patients had histologic diagnoses based on review of tissue specimens obtained by thoracotomy (n = 43), transthoracic needle aspiration (n = 13) and bronchoscopic biopsy (n = 4). One patient who did not undergo biopsy had no change

in nodule size during the past 2 yr. Diagnosis of malignancy was established in 45 patients.

Forty-two of 45 patients had a diagnosis of bronchogenic carcinoma, which included adenocarcinoma (n = 22), squamous-cell carcinoma (n = 9), non-small-cell carcinoma (n = 7) and small-cell carcinoma (n = 4). Three patients had other forms of malignancy (melanoma: 2, teratoma: 1). Six of 61 patients had histories of previous malignancy [breast (n = 2), melanoma (n = 2), prostate (n = 1) and lung (n = 1)]. Five of these six patients also had malignant solitary pulmonary nodules.

The patient who had showed no change in nodule size over 2 yr did not have a biopsy and was considered benign. Histologic examination revealed benign lesions in 15 patients: granuloma (n = 6), histoplasmosis (n = 4), nonspecific inflammation (n = 2), hamartoma (n = 1), carcinoid (n = 1), pneumonia (n = 1). The carcinoid nodule is included in the benign group, although bronchial carcinoid tumors may metastasize in 10% of cases. On follow-up, the clinical behavior of the carcinoid nodule in this patient was benign.

Semiquantitative DUR indices ranged from 0.12 to 3.38 in benign nodules as compared with 0.9–13.11 in malignant nodules. The mean DUR value in benign nodules was 1.15 ± 0.957 as compared to 6.28 ± 3.247 in malignant nodules. Using the Wilcoxon rank sum test, the DUR value was significantly higher in the group with malignant nodules as compared with the group with benign nodules. In our study, visual analysis was used as the interpretative criteria. Based on this visual analysis, there were two false-positive lesions that had DUR values of 3.38 and 1.92. All benign nodules had DUR values of <2.62. There were three false-negative PET studies with DUR values of 0.9, 1.67 and 2.29. The other true-positive malignant nodules had DUR values greater than 2.4. Forty of the 45 (89%) malignant nodules had DUR values greater than 2.6.

Thus, PET imaging accurately identified 56 of the 61 solitary pulmonary nodules based on qualitative analysis. The diagnostic accuracy of PET for differentiating benign from malignant solitary pulmonary nodules was 92%, with a sensitivity and specificity of 93% and 88%, respectively. Positive and negative predictive values of PET imaging for detecting malignancy in solitary pulmonary nodules were 95% and 82%, respectively.

All three malignant solitary pulmonary nodules missed on PET imaging had histological diagnoses of adenocarcinoma, two of which were identified as scar adenocarcinoma. These three nodules with false-negative PET were 0.8, 1 and 3 cm in size, respectively. The two benign nodules (2 cm in diameter) with false-positive PET findings had histologic diagnoses of granuloma with histoplasmosis. Two other patients with histoplasmosis (though not with caseating granuloma) showed negative PET findings.

All benign nodules were less than 2.5 cm in size and 14 of 16 benign nodules were less than 2 cm in size. Eleven of the 45 malignant nodules were less than 2 cm in size. The smallest nodule (histologically graded as non-small-cell carcinoma) with positive PET findings was 0.6 cm. The predictive accuracy of PET in the group of solitary pulmonary nodules 1–2 cm in size was 91% and 96% in those sized 2–3 cm. Both nodules sized <1 cm were accurately detected on PET.

Correlation of DUR indices with the histologic type of malignancy showed no relationship between DUR indices and histological subtypes.

Hilar/Mediastinal/Lymphadenopathy

Twelve of the 61 patients with indeterminate solitary pulmonary nodules also had hilar/mediastinal lymphadenopathy which was confirmed histologically. In five of these patients lymph node involvement was not suspected prior to PET, but PET accurately identified benign or malignant lesions in all 12 lymph node abnormalities. Another five patients also had benign histologies including: histoplasmosis (n = 2), granuloma (n = 1), anthracosis (n = 1) and fibrosis (n = 1). These benign lymph node lesions were 1–3 cm in size. No increased FDG uptake was seen at the site of any of these five nodal lesions. There were also seven malignant lymph node lesions varying in size from 1 to 3.5 cm. These included perihilar lymph nodes (n = 2), peribronchial (n = 3) or mediastinal lymph nodes (n = 2). PET imaging showed increased FDG uptake in all seven lymph node lesions (Fig. 1). Three of the seven malignant lesions were not detected on the plain film or CT scan.

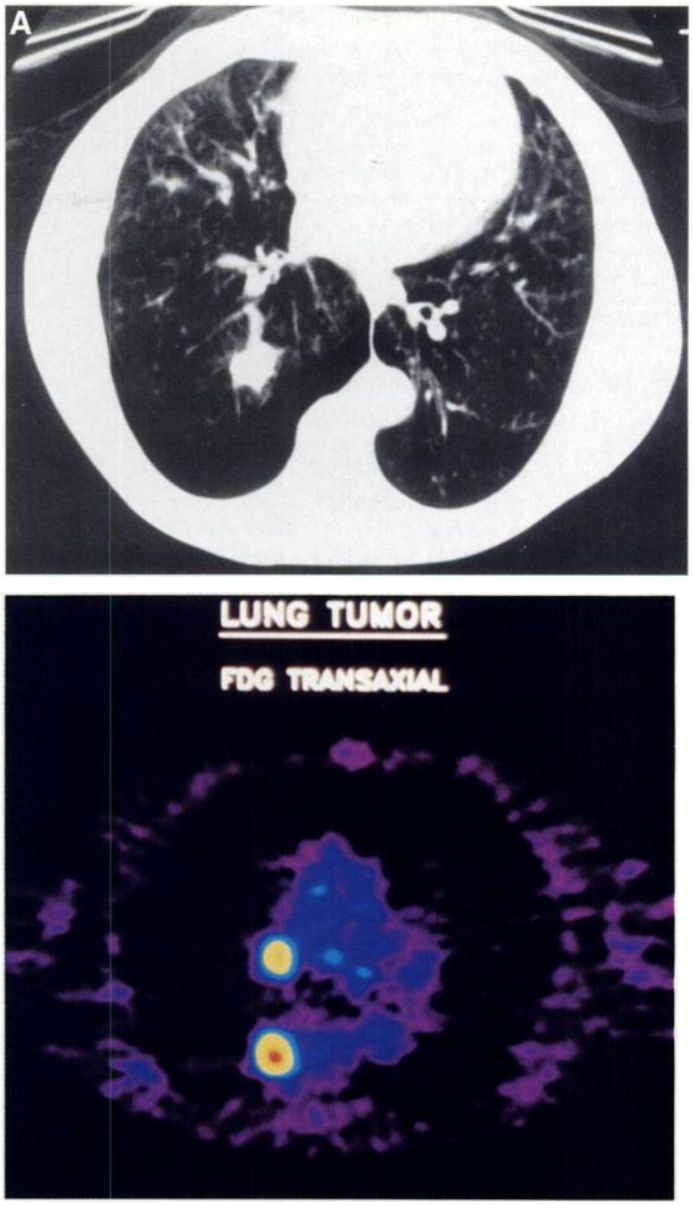


FIGURE 1. CT scan (A) from a 73-yr-old man shows a 2-cm noncalcified nodule in the right lower lobe. FDG-PET (B) study clearly shows enhanced glucose metabolism in this solitary pulmonary nodule and additionally detected a small right hilar lymph node not seen on CT, which was malignant on needle biopsy. Note pneumothorax resulting from biopsy.

TABLE 1
Probability of Malignancy Based on PET Results

PET scan	P(PET scan|M)	P(PET scan|N)	$L_{PET\ scan}$	Probability of malignant nodule
Positive (n = 45)	0.933	0.125	7.464	0.833
Negative (n = 16)	0.066	0.875	0.075	0.047

M = malignant nodule; N = nonmalignant nodule.

Statistical Analysis

In our data, the probability of a positive PET scan in a malignant nodule is 93%; the probability of positive PET scan in a nonmalignant nodule is 12.5%. Therefore, L Positive PET scan = 7.5. That is, the probability of observing a positive PET scan in a malignant nodule is 7.5 times greater than observing a positive PET scan in a benign nodule. The probability of malignancy with a positive PET is 83.3%. Similarly, probability of malignancy with a negative PET scan is only 4.7%, with a likelihood ratio of 0.075 (Table 1).

Table 2 shows the likelihood of observing malignancy in our patients on the basis of age. As expected, Table 2 shows an increase in the probability of cancer with increasing age of the patient. In the group aged <60 yr, the probability of cancer is 21.3%. In the patient group aged 70–89 yr, the probability of cancer is 69.3%. In patients aged 60–69 yr, the probability of cancer is 38%.

Table 3 shows the likelihood of malignancy based on nodule diameter. The results indicate increasing probability of cancer with increasing nodule size. The probability of finding a larger nodule (>2.0 cm) in the malignant group is 64.5% and that of finding a <1 cm nodule is 20%. The probability of a benign nodule being smaller than 1 cm is 50%, compared to a 31.2% probability that its size would be >2 cm. Overall, the probability of malignancy increases from 21.1% (with nodule size ≤1 cm) to 58.0% (with nodule size >2 cm).

If we assume the statistical independence of PET scan results, patient age and the nodule diameter, then we have P(M|PET scan, age, diameter) =

$$\frac{0(M)\, L_{PET\ scan} \cdot L_{age} \cdot L_{diameter}}{1 + 0(M)\, L_{PET\ scan} \cdot L_{age} \cdot L_{diameter}}.$$

Table 4 shows the probability of diagnosing malignancy given the PET scan result, patient's age and nodule diameter. There is an increasing probability of malignancy with increasing size in the same age group as well as with increasing age with the same nodule size. The highest probability of cancer is in nodules greater than 2 cm in patients aged 70–89 yr. Similarly, the lowest probability of cancer is in the patient group age <59 yr or younger with nodules less than 1 cm. The probability of malignancy with a positive test is 83.3%. Perhaps, even more importantly, the probability of malignancy is <5% with a negative test result.

TABLE 2
Probability of Malignancy Based on Patient's Age

Patient's age (yr)	P(Age|M)	P(Age|N)	L_{Age}	Probability of malignant nodule
<60 (n = 15)	0.177	0.437	0.405	0.213
60–69 (n = 25)	0.400	0.437	0.915	0.380
70–89 (n = 21)	0.422	0.125	3.376	0.693

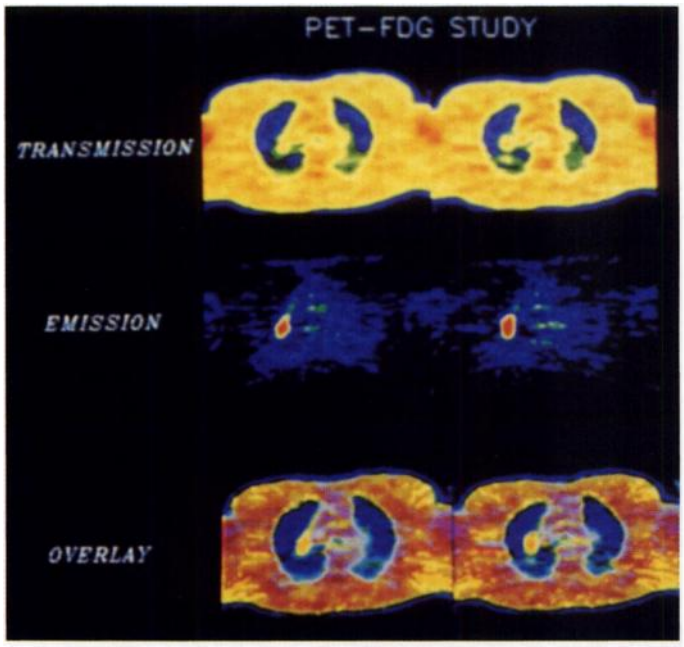
TABLE 3
Probability of Malignancy Based on Nodule Size

Nodule diameter (cm)	P(diameter|M)	P(diameter|N)	L diameter	Probability of malignancy
≤1.0 (n = 17)	0.200	0.500	0.400	0.211
1.1–1.9 (n = 10)	0.155	0.187	0.828	0.356
≥2.0 (n = 34)	0.644	0.312	2.064	0.580

DISCUSSION

A solitary pulmonary nodule is a single spheroid lesion in the lung. Lesions up to 6 cm in diameter were classified as nodules, but there appears to be an agreement that an upper limit of 3 cm may be more useful (*2,10,12*). In general, all malignant solitary nodules should be removed if there is no evidence of metastatic disease. In current clinical practice, 40%–50% of clinically observed solitary nodules are malignant (*5*). However, resection of a benign lung nodule exposes the patient to the risk of thoracotomy without any benefit in most instances (*13*).

The widely accepted treatment for solitary pulmonary nodules is exploratory thoracotomy unless benignity can be estab-



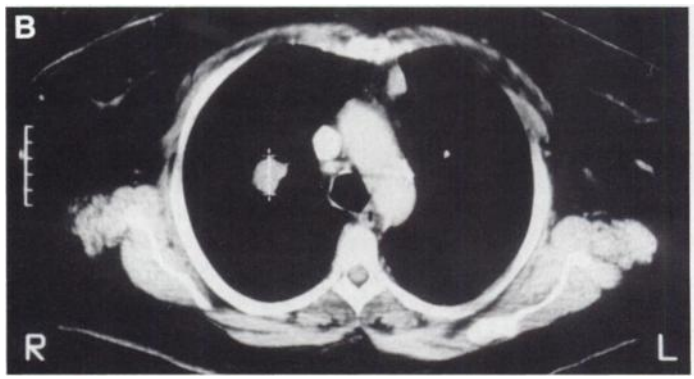


FIGURE 2. FDG-PET (A) and CT (B) scans (transverse views) in a 50-yr-old woman with a 2.0 × 1.5-cm right lung nodule (adenocarcinoma at thoracotomy). There is intense FDG uptake in the nodule seen on emission images.

TABLE 4
Probability of Malignancy Based on PET Result, Patient Age and Nodule Size

PET scan	Age (yr)	Nodule diameter (cm)	Probability of malignancy
Positive	≤59	≤1	0.447
Positive	≤59	1.1–1.9	0.626
Positive	≤59	≥2	0.806
Positive	60–69	≤1	0.646
Positive	60–69	1.1–1.9	0.791
Positive	60–69	≥2	0.904
Positive	70–89	≤1	0.871
Positive	70–89	1.1–1.9	0.933
Positive	70–89	≥2	0.972
Negative	≤59	≤1	0.008
Negative	≤59	1.1–1.9	0.016
Negative	≤59	≥2	0.040
Negative	60–69	≤1	0.018
Negative	60–69	1.1–1.9	0.036
Negative	60–69	≥2	0.086
Negative	70–89	≤1	0.063
Negative	70–89	1.1–1.9	0.123
Negative	70–89	≥2	0.259

lished in other clinical or diagnostic criteria (*14*). The only definite criteria for diagnosing a benign nodule appears to be detection of a specific pattern of calcification characteristic of a benign nodule (*4*).

Standard chest roentgenograms detect most solitary nodules as well as provide an assessment of the characteristic of the edge of the nodule, detect the calcification and provide guidance for a needle biopsy (*2*). Computed tomography may also reveal the presence of additional nodules not seen on chest radiographs. High-resolution CT may reveal the internal characteristics of the nodule (*3*). The use of a phantom with CT may also enhance the diagnostic accuracy (*15*). However, 30%–40% of the solitary nodules may still remain radiographically indeterminate after chest radiography and CT examinations (*5,6,12*) (Fig. 2). Bronchoscopy has limited usefulness in the patient with solitary nodules. In nodules <2 cm in diameter, sensitivity for bronchogenic carcinoma is only 10%–30% (*16*). Transthoracic needle aspiration biopsy under fluoroscopic CT or ultrasound guidance is diagnostic in 80%–95% of the malignant nodules (*17*). An indeterminate biopsy report, however, does not exclude malignancy (*18*). All of the solitary pulmonary nodules are usually resectable on thoracotomy.

The survival rate after resection is dependent on the size of the lesion and the presence of lymph node involvement. In patients with solitary nodules and no lymph node metastases, prompt resection could lead to a 5-yr survival rate of up to 80% of patients (*19*). Resection of pulmonary nodules, however, has a surgical mortality rate of 3%–7%. The objective of PET scanning before exploratory thoracotomy in patients with benign solitary nodules is to determine appropriateness for surgery as well as prevent the unnecessary complications that occur in a significant fraction of patients. So far, a test that reliably identifies benign solitary nodules is not available. An estimated 25,000 thoracotomies are currently performed on patients with benign solitary pulmonary nodules. In the present study, we have utilized Bayes' technique to calculate the probability of malignancy in patients with solitary pulmonary nodules. Several previous studies have calculated the likelihood ratios for a range of values for various predictor variables in predicting malignancy. Clinical variables that have correlated with the probability of malignancy include baseline incidence of malignancy, nodule size, patient age, smoking history, characteristics of the edge of the nodule and presence or absence of occult calcification on CT densitometry. In our study, the likelihood ratios for the probability for malignancy for clinical variables were compared to the likelihood ratios for PET scanning using [^{18}F]FDG. The likelihood ratios for positive PET scans in the presence of malignancy appear to provide a significantly more precise estimate than any of the predictor variables stated. Similarly, the likelihood ratio for the probability of malignancy based on the semiquantitative PET analysis (DUR) ratio is also more accurate than the clinical variables.

The sensitivity of FDG-PET in detecting malignancy in indeterminate solitary pulmonary nodules is 93% in our study. Hypothetically, the two false-negative PET scans may be due to the very small size of those nodules (0.8 cm, 1 cm), because no partial volume correction was applied. It is also possible, because blood glucose levels were not available, that the competitive effect of hyperglycemia on FDG uptake could potentially decrease the sensitivity.

The likelihood of malignancy increases with increasing nodule size. In solitary pulmonary nodules >2 cm, the probability of cancer was 58% but was only 21% in solitary pulmonary nodules <1 cm. The somewhat higher likelihood of malignancy in solitary pulmonary nodules <1 cm in our study could be due to patient selection bias. Patients with negative PET scans and low risk were not forced to undergo biopsy and were conservatively treated. Patients with solitary pulmonary nodules <3 cm have a more optimistic 5-yr survival rate (60%–90%) in the early stages of disease (T_1 N_0M_0 or T_2 N_0M_0). Even when there is a calcification pattern characteristic of malignancy (spiculated, irregular), mediastinal staging is useful prior to surgery. Unlike PET, CT has a sensitivity of only 52% for distinguishing N_1, N_2 or N_3 involvement from N_0. It is estimated that 33% of primary lung cancer patients with negative mediastinoscopy may harbor disease in mediastinal lymph nodes found on thoracotomy (*20*). By identifying early disease in these involved lymph nodes, PET can significantly enhance surgical outcome.

Likelihood of malignancy in solitary pulmonary nodules increases with age. In our series, 69% of solitary pulmonary nodules in patients >70 yr of age but only 21% of solitary pulmonary nodules <60 yr of age were malignant. This is similar to the direct relationship (of probability of cancer to age) reported in literature. However patients in the higher age group (>70 yr) with a negative PET scan though showed only 14% probability of cancer and there was only a 2% probability of cancer in the <60 yr patient group.

The probabilistic approach in decision making in the management of solitary pulmonary nodules is useful. Calculating the probability of malignancy can help in selecting the most appropriate diagnostic test. If the probability is low (negative PET scan), a "wait and watch" strategy could be a possible option. If the probability is high (positive PET scan) needle biopsy or immediate thoracotomy could be selected, depending on the individual patient. In patients with intermediate estimation of malignancy clinically, FDG-PET may offer the greatest benefit by estimating the probability for cancer based on the PET scan results. Simultaneous preoperative staging for hilar/mediastinal lymph nodes is an additional advantage for FDG-PET in patients with malignant lung nodules. The real value of PET scans, however, would be in avoiding unnecessary thoracotomies in patients with benign nodules. This is mainly due to a low false-negative rate (7%) with FDG-PET scanning in our study, which also accounts for a low likelihood or probability of malignancy with a negative scan result. Based on our results

with a negative PET scan, there is only ≤5% probability of malignancy. Therefore, it may be economical to postpone or avoid surgery in this probable benign group.

CONCLUSION

FDG-PET is highly accurate in differentiating malignant from benign solitary pulmonary nodules (0.6–3 cm) when radiographic findings are indeterminate. The projected risk estimate for probability of cancer as well as detection of any involved lymph nodes could be very useful in the treatment of patients with solitary pulmonary nodules.

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EDITORIAL

Is PET Ready for Prime Time?

The practices for establishing medical insurance coverage policies include certain technology assessment steps and standards for evaluating the quality of supporting evidence from the medical literature. If we look at the standards for accepting evidence from the medical literature of some of the major insurance companies we find that they define the quality of the evidence. The Technology Evaluation Committee (TEC Committee) of Blue Cross/Blue Shield, for example, has very well-defined standards:

1. The study must be prospective.
2. There must be more than 10 patients in each study.
3. There must be a representative patient sample.
4. The imaging technique must be clearly specified.
5. The observers or independent readers must be blinded—not only to the reference standard but the alternative test.
6. There must be a clear and consistent use of the reference standard, e.g., either tissue sampling or biopsy.
7. There must be a within subject comparison between the imaging test and the alternative test.

Abstracts will not meet these criteria and only peer-reviewed publications are acceptable. Are these standards reasonable? Sackett and others from the Evidence-Based Medicine Working Group have established and published similar yet more rigorous guidelines for determining the quality of evidence for a diagnostic procedure (*1,2*). Table 1 is adapted from Jaeschke et al. (*1*) and presents their criteria for evaluating and applying the results of studies of diagnostic tests. An inspection of Table 1 and the primary guides for assessing validity reveals that they are quite similar, but more detailed than described above.

Unfortunately, many payers, including Blue Cross and Aetna, have not deemed PET oncologic studies as acceptable for payment and have not established policies for coverage of these studies. Their stated major reason for this decision relates to the lack of articles in the peer-review literature that meets their criteria for satisfactory quality of evidence.

In this issue of *JNM,* Gupta et al. (*3*) present their experience in the use of FDG-PET studies in 61 patients with solitary pulmonary nodules. The results show PET to have a sensitivity of 93%, specificity of 88%, for detection of malignancy in solitary pulmonary nodules. This indeed sounds very

TABLE 1
Evaluating and Applying Results of Diagnostic Tests

Are the results of the study valid?
Primary Guides:
• Was there an independent, blind comparison with a reference standard?
• Did patient sample include appropriate spectrum of patients to whom diagnostic test will be applied in clinical practice?
Secondary Guides:
• Did the results of the test being evaluated influence the decision to perform the reference standard?
• Were the methods for performing the test described in sufficient detail to permit replication?
• If the test requires observer interpretation, was there a measure of observer variability.
What were the results?
• Are likelihood ratios for the test results presented or data necessary for their calculation provided?
Will the results help me in caring for my patients?
• Are the results applicable to my patients?
• Will the results change my management?
• Will patients be better off as a result of the test?

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