Solitary Pulmonary Nodules: Part II. Evaluation of the Indeterminate Nodule[1]

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Various strategies may be used to evaluate indeterminate solitary pulmonary nodules. Growth rate assessment is an important and cost-effective step in the evaluation of these nodules. Clinical features (eg, patient age, history of prior malignancy, presenting symptoms, smoking history) can be useful in suggesting the diagnosis and aiding in management planning. Bayesian analysis allows more precise determination of the probability of malignancy (pCa). Decision analysis models suggest that the most cost-effective management strategy depends on the pCa for a given nodule. At contrast material–enhanced computed tomography, nodular enhancement of less than 15 HU is strongly predictive of a benign lesion, whereas enhancement of more than 20 HU typically indicates malignancy. At 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography, lesions with low FDG uptake are typically benign, whereas those with increased FDG uptake are typically malignant. Results of transthoracic needle aspiration biopsy influence management in approximately 50% of cases and, in indeterminate lesions with a pCa between 0.05 and 0.6, is the best initial diagnostic procedure. It is optimally used in peripheral nodules and has been reported to establish a benign diagnosis in up to 91% of cases. Although there is no one correct management approach, the ability to distinguish benign from malignant solitary pulmonary lesions has improved with the use of these strategies.

Abbreviations: FDG = 2-[fluorine-18]fluoro-2-deoxy-D-glucose, LR = likelihood ratio, pCa = probability of malignancy, PET = positron emission tomography

Index terms: Fluorine, radioactive, 60.12163 • Lung, CT, 60.1211 • Lung, diseases, 60.281, 60.332 • Lung, nodule, 60.11, 60.1211, 60.12163, 60.281, 60.332 • Lung, radionuclide studies, 60.12163

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See also the article by Erasmus et al (pp 43–58) in this issue.

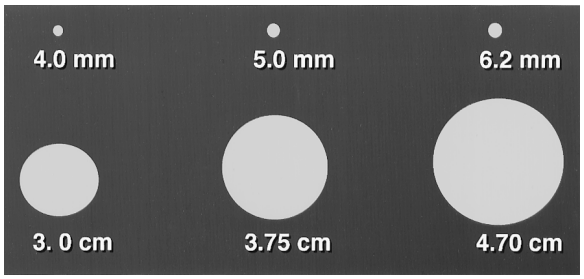


Figure 1. Effect of initial nodule size on perception of growth. Schematic illustrates two volume doublings of a 4-mm nodule and a 3-cm nodule. Because the eye perceives the arithmetic increase in diameter rather than the change in volume, the smaller nodule appears to be growing more slowly than the larger one, even though both are doubling in volume at the same rate.

Introduction

Although a number of clinical and radiologic features may suggest the diagnosis, many solitary pulmonary nodules remain indeterminate after conventional radiologic evaluation. If there are no definite benign morphologic findings, the solitary pulmonary nodule is classified as an indeterminate, possibly malignant lesion. Many solitary pulmonary nodules have similar features, and 25%–39% of malignant nodules are inaccurately classified as benign after radiologic assessment of size, margins, contour, and internal characteristics (1,2). As a result, a noninvasive diagnosis is often not possible. Indeterminate nodules may be treated with biopsy, resection, or simple observation depending on the radiologic appearance of the nodule, the patient's clinical history and current status, and the likelihood of malignancy. However, there are additional objective parameters that may aid in further stratifying indeterminate nodules.

In this article, we review the use of growth rate assessment and clinical data in evaluating solitary pulmonary nodules. In addition, we discuss developments in management strategies including Bayesian analysis, decision analysis, contrast material–enhanced computed tomography (CT), 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET), and transthoracic needle aspiration biopsy with emphasis on cost-effectiveness.

Growth Rate Assessment

An important and cost-effective step in the evaluation of a solitary pulmonary nodule is determining its growth rate by comparing its size on a current image with that on prior images. Doubling time (ie, the time required for a nodule to double in volume) for most malignant nodules is between 30 and 400 days and results in a 26% increase in nodule diameter (3). Nodules that double either more rapidly or more slowly typically have a benign cause. Stability at chest radiography or CT over a 2-year period implies a doubling time of at least 730 days and is generally considered to be a reliable indicator of a benign cause (4–7). However, the assumption that stability over a 2-year period indicates benignity has recently come into question. Recalculation from the original data shows that the predictive value for benign disease is only 65% if the nodule is stable in size for a period of 2 years (5,8,9). Furthermore, it can be difficult to reliably detect growth in small (<1-cm) nodules. For example, a 5-mm nodule can double in volume over a 6-month period (malignant growth rate), but its diameter will increase by only 1.25 mm to 6.25 mm. This 1.25-mm change in diameter cannot be reliably detected with either radiography or CT. Thus, small lung malignancies can double in volume and yet ap-

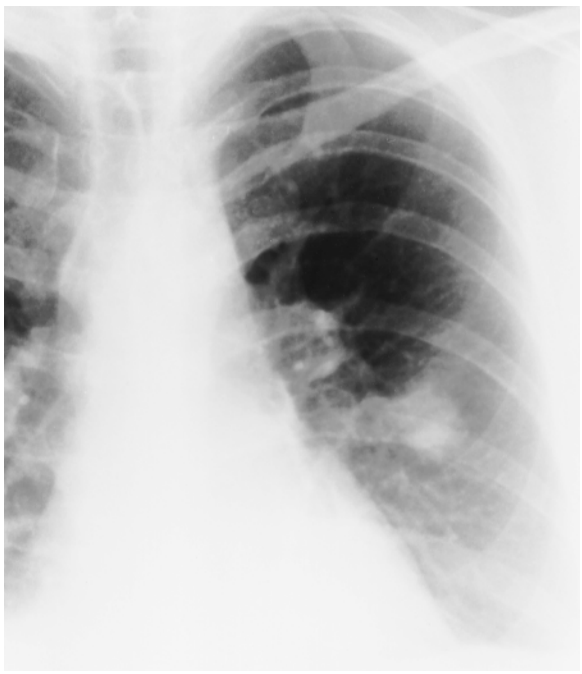
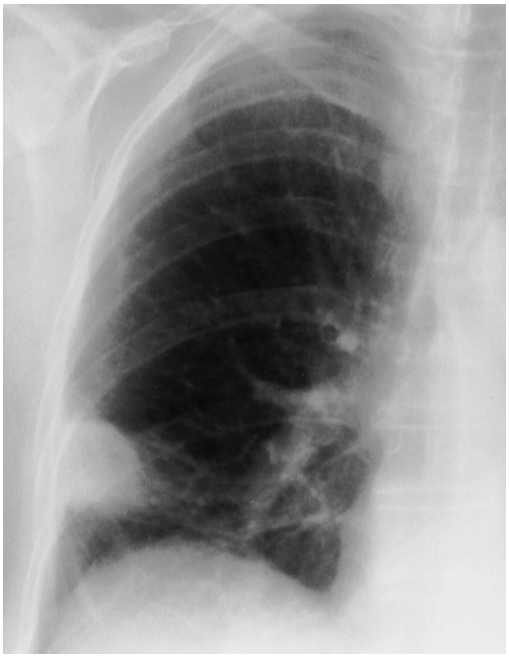


Figure 3. Round pneumonia in a 23-year-old woman who presented with cough and fever. Close-up posteroanterior radiograph of the left lung shows a poorly marginated nodule in the midlung. Because of clinical symptoms, the patient was treated for community-acquired pneumonia. Follow-up radiography performed 2 weeks later demonstrated complete resolution of the nodular area of increased opacity.

Figure 2. Pulmonary infarct in 65-year-old woman who presented with pleuritic chest pain. **(a)** Close-up posteroanterior radiograph of the right lung shows a poorly marginated nodule peripherally in the lower lobe. Because of symptoms suggestive of pulmonary embolism, technetium-99m microaggregated albumin perfusion scintigraphy was performed. **(b)** Tc-99m microaggregated albumin perfusion scintigram shows multiple segmental perfusion defects, findings consistent with pulmonary embolism. Results of a ventilation scan (not shown) were normal. *ANT* = anterior, *LAO* = left anterior oblique, *LPO* = left posterior oblique, *POST* = posterior, *RAO* = right anterior oblique, *RPO* = right posterior oblique. **(c)** Follow-up radiograph obtained 2 weeks after **a** demonstrates resolution of the infarct.



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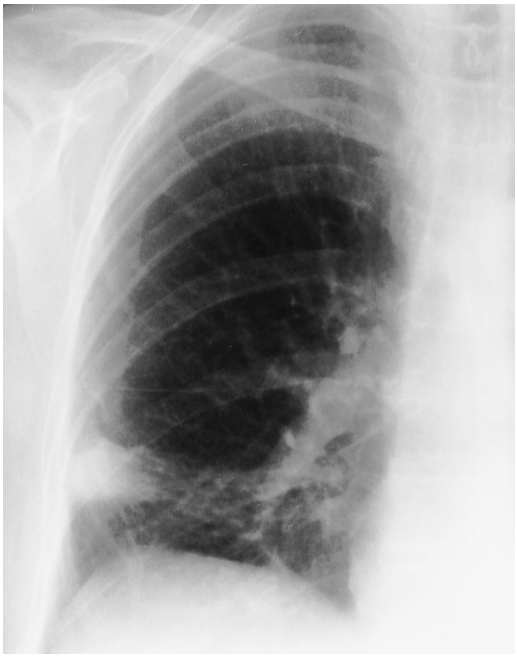

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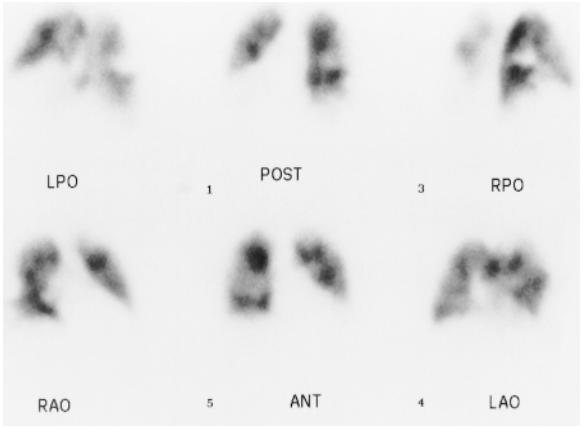
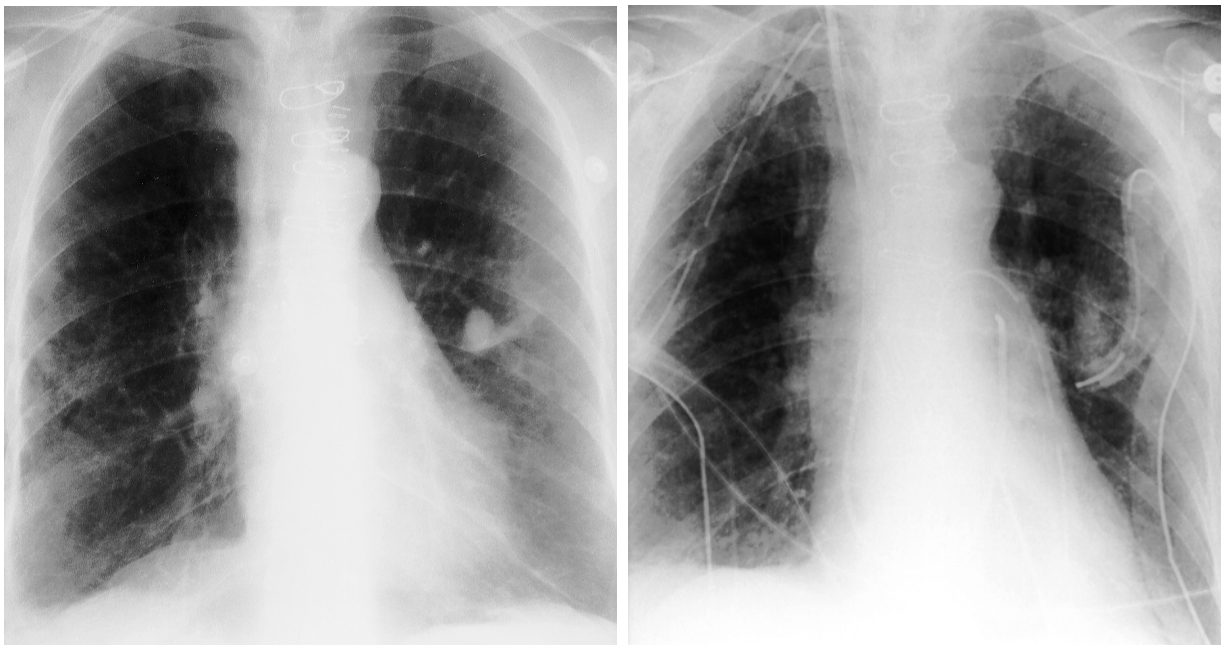


b.

pear radiologically stable, resulting in a delay in diagnosis (Fig 1). To overcome this limitation, it has been proposed that the growth rate of small nodules be assessed with serial measurements of volume rather than diameter (10). Although measurement of volume (which increases proportionally faster than diameter) may be more accurate in growth rate assessment for small nodules, experience suggests that most nodules greater than 1 cm in diameter that are stable in size for at least 2 years are benign.

Clinical Data

Clinical features such as patient age, history of prior malignancy, presenting symptoms, and smoking history can be useful in suggesting the diagnosis and aiding in management planning (Figs 2–4). For example, a new lung nodule that is detected in a young adult patient with a peripheral sarcoma is more likely to be a solitary metastasis than a primary lung tumor. Similarly, in a patient in whom infection or infarction is



a. **b.**

Figure 4. Pulmonary hematoma in a 65-year-old woman. **(a)** Posteroanterior radiograph obtained 1 week after the patient underwent aortic valve replacement shows a well-marginated nodule in the middle of the left lung. **(b)** Initial postoperative anteroposterior radiograph shows bilateral pleural tubes and an area of increased opacity adjacent to the tip of the left pleural tube, a finding that is consistent with intrapulmonary hematoma. Follow-up radiography demonstrated resolution of the nodule.

strongly suspected clinically, follow-up radiography performed 1–2 weeks later may suffice for further evaluation.

Management Strategies

Bayesian Analysis

Bayesian analysis can be useful in the evaluation of indeterminate solitary pulmonary nodules by allowing more precise determination of the probability of malignancy (pCa) (11,12). Bayesian analysis uses likelihood ratios (LRs) for numerous radiologic findings and clinical features associated with solitary pulmonary nodules to estimate pCa (11). The LR for a given characteristic is derived as follows:

$$LR = \frac{\text{number of malignant nodules with feature.}}{\text{number of benign nodules with feature}} \quad (1)$$

An LR of 1.0 indicates a 50% chance of malignancy. LRs less than 1.0 typically indicate benign lesions, whereas LRs greater than 1.0 typically indicate malignancy. LRs for selected radiologic features of nodules and patient characteristics are shown in Table 1. The odds of malignancy are calculated as

$$Odds_{ca} = LR_{prior}\, LR_{size}\, LR_{sh}\, LR_{edge}\, LR_{calcif}, \quad (2)$$

where LR_{prior} is the likelihood of malignancy in all

Table 1
LRs for Selected Radiologic Features of Nodules and Patient Characteristics

Feature or Characteristic	LR
Spiculated margin	5.54
>3 cm	5.23
>70 years of age	4.16
Malignant growth rate	3.40
Smoker	2.27
Upper lobe location	1.22
<1 cm	0.52
Smooth margins	0.30
30–39 years of age	0.24
Never smoked	0.19
20–29 years of age	0.05
Benign calcification	0.01
Benign growth rate	0.01

Table 2
Odds and Probability of Cancer in Four Hypothetical Situations

Patient Age	Patient Smoking History	LR_{prior}	LR_{size}	LR_{sh}	LR_{edge}	LR_{age}	$Odds_{ca}$	pCa*
35	Nonsmoking	0.40/0.60	0.52	0.19	0.30	0.24	0.01	0.01 (1)
35	Current smoker	0.40/0.60	0.52	2.27	0.30	0.24	0.06	0.05 (5)
70	Nonsmoking	0.40./0.60	0.52	0.19	0.30	4.16	0.08	0.07 (7)
70	Current smoker	0.40./0.60	0.52	2.27	0.30	4.16	0.99	0.50 (50)

*Numbers in parentheses are percentages.

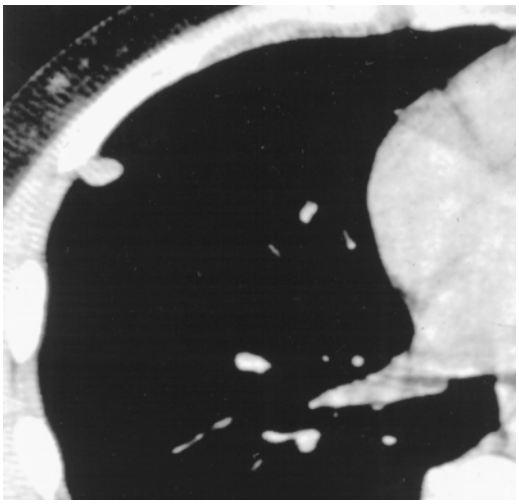


Figure 5. Effect of age and smoking history on pCa in an indeterminate pulmonary nodule. Close-up chest CT scan of the right lung shows a 7-mm, smoothly marginated, noncalcified nodule in the middle lobe. On the basis of decision analysis, observation would be the most cost-effective management strategy in a 35-year-old nonsmoker (pCa = 0.01) or current smoker (pCa = 0.05), and biopsy would be the most cost-effective management strategy in a 70-year-old nonsmoker (pCa = 0.07) or current smoker (pCa = 0.50) (cf Table 2).

nodules based on local prevalence of malignancy and LR_{size}, LR_{sh} ($LR_{smoking\ history}$), and so on are possible additional variables. pCa is calculated as

$$\frac{Odds_{ca}}{(1 + Odds_{ca})}. \quad (3)$$

Bayesian analysis has been shown to be superior to evaluation by experienced radiologists in the stratification of benign and malignant nodules and can be useful in determining treatment options. pCa for any nodule can be calculated with Bayesian analysis on Dr J. Gurney's Internet Web site at *www.chestx-ray.com*.

Table 2 demonstrates evaluation of solitary pulmonary nodules with Bayesian analysis. Four clinical scenarios involving hypothetical male patients with a smoothly marginated 7-mm nodule in the right middle lobe (Fig 5) are evaluated with published LRs (11) and an estimated prior pCa of 40%.

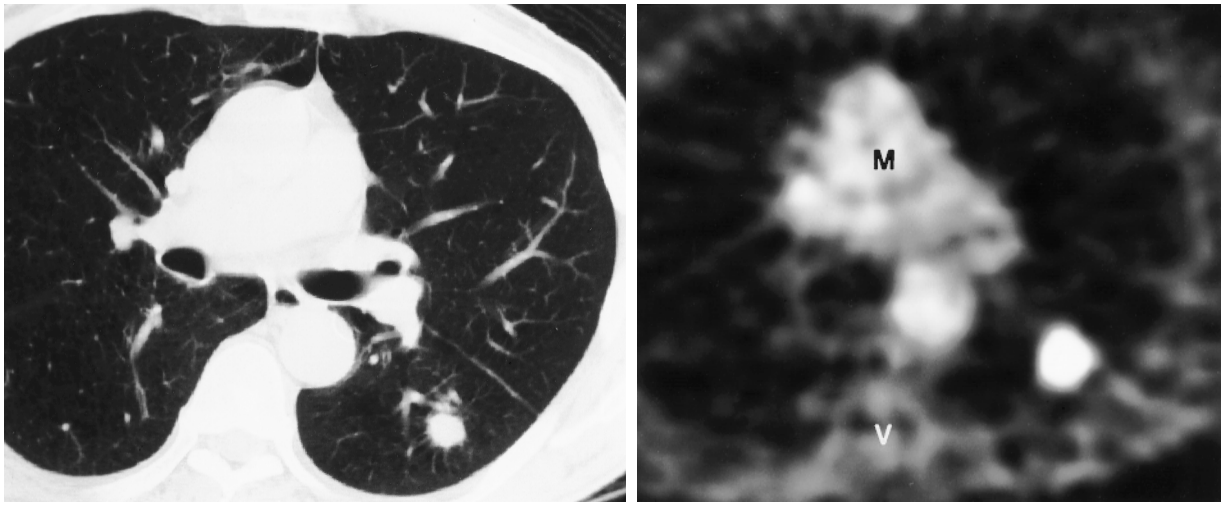
Decision Analysis

Decision analysis models suggest that the most cost-effective strategy for management of a solitary pulmonary nodule depends on the pCa for that nodule. Several studies from the mid-1980s suggest that the most cost-effective strategy is observation when pCa is low (<0.05), immediate surgical resection when pCa is high (≥0.60), and biopsy when pCa is between 0.05 and 0.60 (Fig 5) (3,13–15). These data suggest that the most cost-effective management strategy for the first two patients in Table 2 is observation, whereas the most cost-effective strategy for the third and fourth patients is biopsy.

Unfortunately, these studies did not include discussion of some of the more advanced imaging modalities (eg, contrast-enhanced CT, PET) that are useful in the preoperative stratification of benign and malignant nodules.

Contrast-enhanced CT

Contrast-enhanced CT allows accurate differentiation of benign and malignant nodules. It has been suggested that blood flow in malignant pulmonary nodules is qualitatively and quantitatively different from that in benign nodules (16,17). The degree of enhancement is directly related to the likelihood of malignancy and the vascularity of the nodule (17,18). Enhancement can be assessed by obtaining contiguous thin sections (1–3 mm) through the nodule before and after contrast material administration. Contrast material (iodine) is administered intravenously with power injection (300 mg/mL at 2 mL/sec; total dose, 420 mg/kg), and contiguous sections are obtained through the nodule every 30 seconds for 5



a. b.

Figure 7. Non–small cell lung cancer in a 65-year-old man. **(a)** Chest CT scan shows a small nodule in the left lower lobe. **(b)** Axial FDG PET scan shows marked FDG accumulation in the nodule, a finding that is suspicious for malignancy. Lung cancer was confirmed at resection. *M* = normal mediastinal uptake, *V* = vertebra.

minutes. Attenuation of the nodule is measured in a centrally placed region of interest prior to and at the peak of contrast enhancement. Nodular enhancement of less than 15 HU after contrast material administration is strongly predictive of a benign lesion, whereas enhancement of more than 20 HU typically indicates malignancy (sensitivity, 98%; specificity, 73%; accuracy, 85%) (Fig 6) (16).

FDG Positron Emission Tomography

PET is a physiologic imaging technique that uses metabolic substrates such as amino acids or glucose that are labeled with positron-emitting radioisotopes. Although several radionuclides are currently available, FDG, a D-glucose analog, is the most commonly used. Increased glucose metabolism in tumors results in increased uptake, trapping, and accumulation of FDG, permitting differentiation of benign and malignant nodules (Figs 7, 8). The sensitivity, specificity, and accuracy of FDG PET in the diagnosis of benign nodules are 96%, 88%, and 94%, respectively (20–25). The use of FDG PET alone has been reported to be a better predictor of malignancy than standard clinical and morphologic criteria used in Bayesian analysis (24,26).

The high specificity of FDG PET for the diagnosis of benign lesions has important clinical utility. Lesions with low FDG uptake may be considered benign. However, these lesions should be followed up radiologically because false-negative results, although rare, may be seen in primary pulmonary malignancies (eg, carcinoid tumors and bronchioloalveolar carcinoma may demonstrate lower FDG uptake than is expected for malignant tumors and PET can yield false-negative results in lesions less than 10 mm in diameter) (27–29).

Solitary pulmonary nodules with increased FDG uptake should be considered malignant, although false-positive results can be obtained in patients with infectious and inflammatory processes such as active tuberculosis, histoplasmosis, and rheumatoid nodules (4,20,30–32).

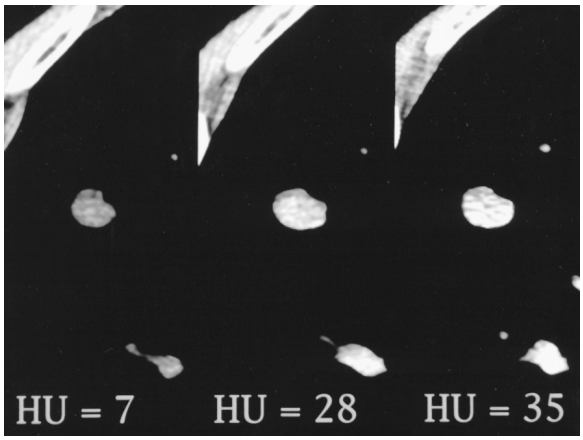
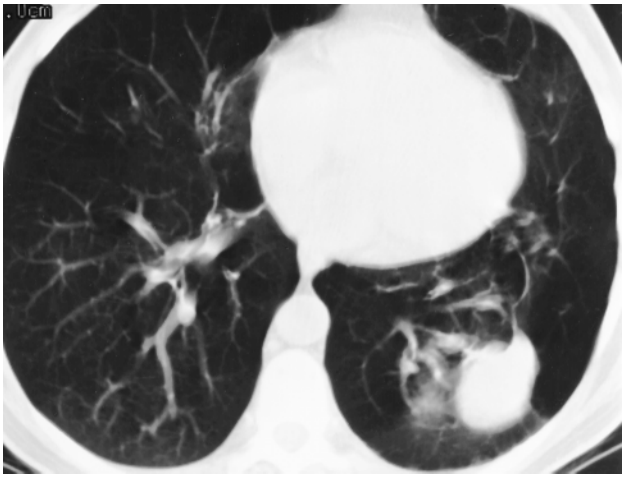


Figure 6. Metastatic melanoma in a 40-year-old man. Contrast-enhanced CT scan shows enhancement of 35 HU in a right lung nodule, a finding that is suggestive of malignancy. Metastatic melanoma was confirmed at resection.



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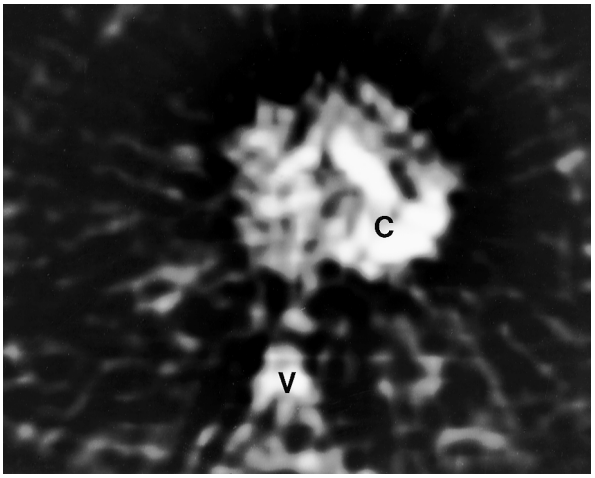

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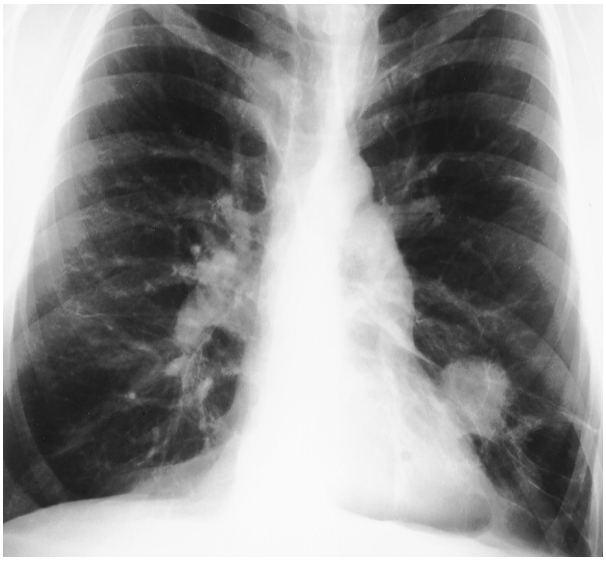

a.

Figure 8. Pulmonary cyst in a 42-year-old man with emphysema who was undergoing pre–lung transplantation evaluation. **(a)** Posteroanterior radiograph shows emphysema and a well-marginated nodule in the left lower lobe. **(b)** Chest CT scan helps confirm the homogeneous left lower lobe nodule. **(c)** Axial FDG PET scan obtained at the same level as **b** shows no increased metabolic activity in the region of the nodule. These findings are consistent with benignity, and hemorrhagic cyst was diagnosed at lung transplantation 18 months later. *C* = normal cardiac uptake, *V* = vertebra. (Fig 8 reprinted, with permission, from reference 19.)

Transthoracic Needle Aspiration Biopsy

When the radiologic features of a pulmonary nodule are not diagnostic, transthoracic needle aspiration biopsy, bronchoscopy, video-assisted thoracoscopic surgery, or thoracotomy may be performed. Transthoracic needle aspiration biopsy has been shown to influence management in approximately 50% of patients and, if the likelihood of malignancy is between 5% and 60% (ie, pCa is between 0.05 and 0.6), is the best initial diagnostic procedure (33,34). Transthoracic needle aspiration biopsy is optimally used in peripheral nodules, although this procedure can be performed in most radiographically visible lesions if it is clinically indicated (35–37). Transthoracic needle aspiration biopsy has a high sensitivity for the diagnosis of malignancy even in small nodules (95%–100% in nodules less than 10–15 mm in diameter) (35–37). It can be difficult to diagnose a specific benign entity with this procedure, although it has been reported to establish a benign diagnosis in up to 91% of patients (38). Complications, most notably pneumothorax and hemorrhage, occur in approximately 5%–30% of patients (35,39,40). Hemorrhage is almost always self-limiting, and only about 15% of patients with pneumothoraces will eventually require chest tube placement (35,39).

Conclusions

The solitary pulmonary nodule is a common radiologic finding that can require extensive evaluation to establish a benign or malignant diagnosis. There is no one correct management approach; rather, the objective is to use a logical, directed approach that takes into account both clinical history and radiologic findings to determine the cause cost-effectively. Morphologic evaluation of the size, margins, contour, and internal characteristics of a solitary pulmonary nodule with conventional imaging techniques is often unreliable in differentiating benign from malignant nodules. However, the ability to make this distinction has improved with the use of contrast-enhanced CT, PET, and Bayesian analysis.

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