

The Solitary Pulmonary Nodule¹

Helen T. Winer-Muram, MD

The imaging evaluation of a solitary pulmonary nodule is complex. Management decisions are based on clinical history, size and appearance of the nodule, and feasibility of obtaining a tissue diagnosis. The most reliable imaging features are those that are indicative of benignancy, such as a benign pattern of calcification and periodic follow-up with computed tomography for 2 years showing no growth. Fine-needle aspiration biopsy and core biopsy are important procedures that may obviate surgery if there is a specific benign diagnosis from the procedure. In using the various imaging and diagnostic modalities described in this review, one should strive to not only identify small malignant tumors—where resection results in high survival rates—but also spare patients with benign disease from undergoing unnecessary surgery.

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¹ From the Department of Radiology, Indiana University, Indianapolis, Ind. Received February 28, 2005; revision requested April 22; revision received April 28; accepted June 13; final version accepted August 11; final review and update by the author October 31. Address correspondence to the author, 11224 Clarkston Rd, Zionsville, IN 46077 (e-mail: *hwinermu@iupui.edu*).

As solitary pulmonary nodule (SPN) is a round or oval opacity smaller than 3 cm in diameter that is completely surrounded by pulmonary parenchyma and is not associated with lymphadenopathy, atelectasis, or pneumonia (1) (Fig 1a). Larger lesions are not included in this definition because many of these lesions are malignant (2–4). An SPN is noted on up to 0.2% of chest radiographs (5,6) (Fig 2a). While the differential diagnosis for SPN is extensive (Figs 3, 4), most lesions are found to be granulomas, lung cancers, or hamartomas (7,8) (Fig 5). Detection and work-up of SPNs are critical because SPNs may be malignant and lung cancer has an overall mortality rate of up to 85% (3,9). Early detection of small nodules may potentially reduce lung cancer-specific mortality; in time, data from the National Lung Screening Trial may be used to prove this hypothesis.

While one may not be able to establish a diagnosis based solely on the im-

aging features, the radiologist often plays a major role in the care of patients with SPNs. In this article, some of the clinical and radiographic features that are important to consider when determining the likelihood of malignancy of an SPN will be reviewed, and an algorithm will be proposed for the care of patients with indeterminate nodules.

Risk of SPN Malignancy

To understand the rationale underlying clinical and imaging work-up when an SPN is discovered, one must first recognize the clinical factors that make lung cancer a more likely cause of SPN (Table). The likelihood of lung cancer increases if a patient has a smoking history, and it is directly proportional to the number of pack-years as a smoker (12). While many physicians have believed that smoking cessation produces a progressive reduction in lung cancer incidence, this concept has been challenged (13). The incidence of lung cancer does not increase after smoking cessation, but it never equals that for individuals who have never smoked. Consequently, one commonly sees patients with newly diagnosed lung cancer who stopped smoking years or even decades earlier (14).

Lung cancer risk also increases if the patient has a history of primary pulmonary or extrapulmonary cancer or pulmonary fibrosis (eg, idiopathic fibrosis or fibrosis due to asbestos exposure, collagen vascular disease, adult respiratory distress syndrome, or radiation) (10,15) (Fig 6). An SPN is unlikely to be a metastasis in the absence of a known prior malignancy, and a routine search for an extrathoracic primary tumor is not cost-effective (16) (Fig 7). In patients with melanoma, sarcoma, or testicular carcinoma, a malignant SPN is 2.5 times more likely to be a metastasis than a primary lung cancer; however, in patients with head and neck squamous cell carcinoma, a malignant SPN is eight times more likely to be a primary lung cancer (17).

Onset of lung cancer before the age of 40 years is rare; however, its incidence increases steadily between 40

and 80 years of age (18). Patients with the human immunodeficiency virus have an increased risk for lung cancer and may develop cancer at a younger age (19). Lung cancer was once far more common in men than women, but increased smoking rates among women during the 1960s and 1970s have led to an increased incidence of lung cancer in women (20). The American Cancer Society estimated that there would be about 172 570 new cases of lung cancer in 2005 (93 010 in men and 79 560 in women). The chance of developing lung cancer is one in 13 in men and one in 18 in women. This incidence includes all people, and it does not take into account whether they smoke (21).

SPN Size

At chest radiography, an SPN is seldom evident until it is at least 9 mm in diameter (22). Moreover, even larger nodules may be missed with radiography, unless prior chest radiographs are available for comparison. SPNs are frequently detected because they are either absent on previously obtained radiographs or present and not recognized until the current radiographs show enlargement. Nearly 90% of newly discovered SPNs on chest radiographs may be visible in retrospect on prior radiographs (23). Failure to detect an SPN is directly related to obscuration of the nodule by overlying structures, failure to compare the current radiograph with prior radiographs, or use of a faulty search pattern (24). Prior chest radiographs are also needed because a nodule that is unchanged on chest radiographs for 2 years is almost certainly benign and requires no further imaging.

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Abbreviations:

FDG = fluorine 18 fluorodeoxyglucose
FNAB = fine-needle aspiration biopsy
SPN = solitary pulmonary nodule

Key Point

Always compare current radiographs with previous radiographs (if available).

The size of the SPN is not a reliable predictor of benignity (4); however, the

larger the nodule (approaching 3 cm in diameter), the more likely it is to be malignant. More than 90% of nodules that are smaller than 2 cm in diameter are benign (10,25).

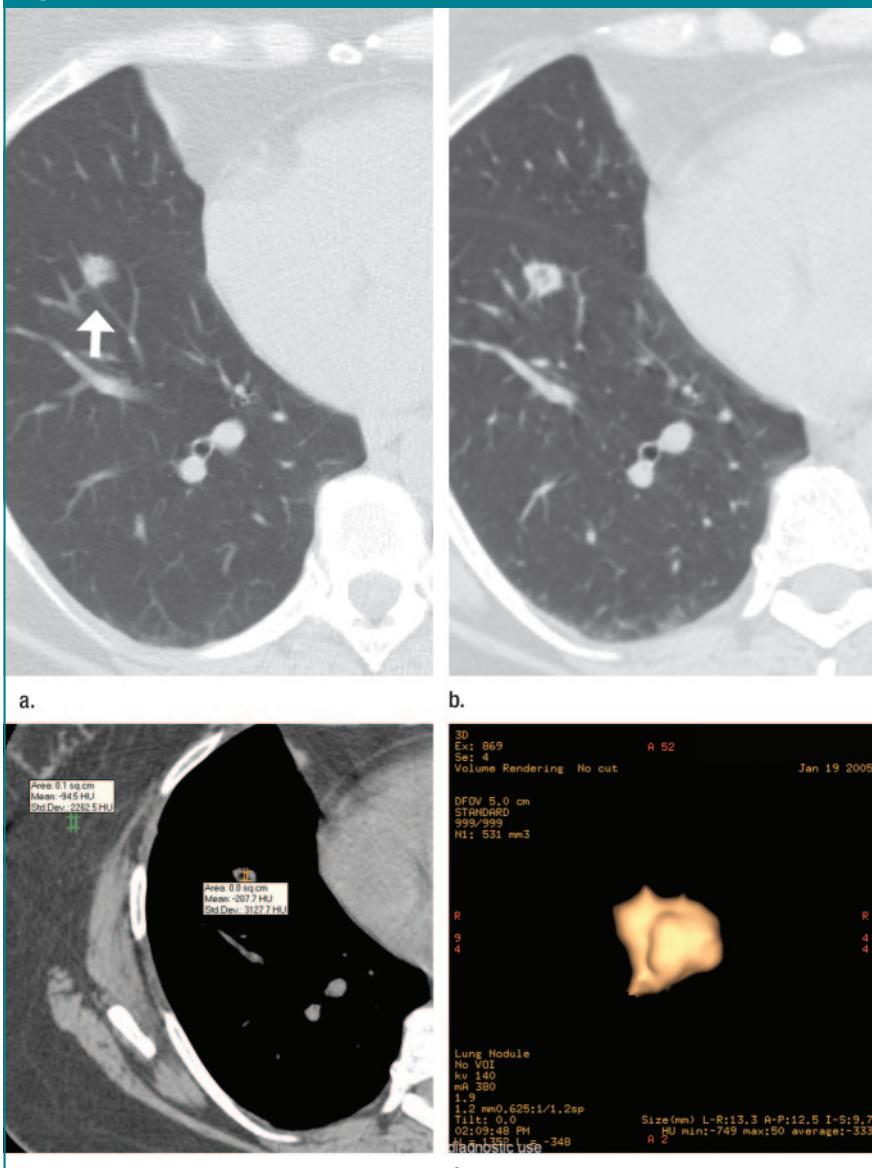
Figure 1

Figure 1: Chest CT scans (5-mm section width) in a female 48-year-old former smoker (9 pack-years) with a history of remote purified protein derivative conversion. (a) Transverse cardiac screening scan shows a 10-mm solid nodule (arrow) in the right lower lobe. (b) Transverse thin-section (1.25-mm section width) scan shows irregular margins and central lucency. (c) Thin-section scan shows central lucency (-208 HU), which indicates air bronchograms or early cavitation. (d) Three-dimensional CT scan obtained with volume rendering shows the nodule volume to be 531 mm³. FNAB was performed, and atypical cells were seen. Because of the nonspecific diagnosis, repeat FNAB was performed, and no malignant cells were seen. The nodule will be observed with serial CT during the next 24 months. If the nodule remains stable for 24 months, no further intervention will be performed.

The prevalence of cancer in SPNs smaller than 1 cm in diameter is unknown. Of noncalcified nodules smaller than 1 cm, 42%–92% have been found to be benign (3,4,26). The large variability reflects selection bias, and reports from surgical series tend to show higher prevalence of malignant lesions than do reports

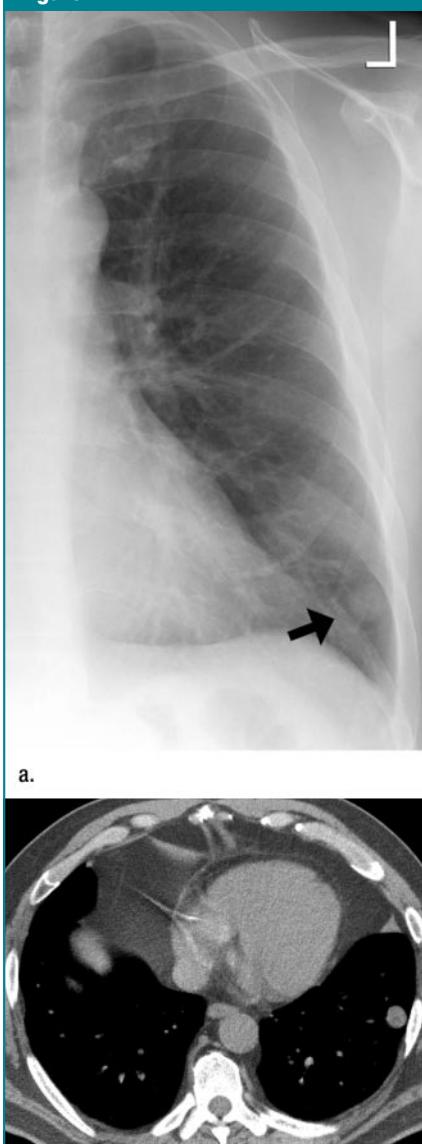
Figure 2

Figure 2: (a) Chest radiograph shows an incidental small nodule (arrow) at the left costophrenic angle. (b) Thin-section CT scan shows central fat attenuation (-43 HU) in the nodule. Hamartoma was diagnosed.

from screening studies. In 64 patients with SPNs 1 cm or smaller in diameter who were referred for video-assisted thoracoscopic surgery, 58% of SPNs, including six that were smaller than 5 mm in diameter, were malignant (27). Other series have found a similar frequency of malignancy (26–29). In comparison, the Early Lung Cancer Action Project screening study showed that only 8% of lesions

Figure 3

Figure 3: CT scan shows a markedly enhancing right lower lobe nodule with a feeding artery and draining vein (not shown). Pulmonary arteriovenous malformation was diagnosed.

Figure 4

Figure 4: CT scan in a 90-year-old woman with chronic congestive heart failure shows a tiny nodule adjacent to the right major fissure that is likely to represent a congested intrapulmonary lymph node (arrow). Follow-up CT was not performed because of the patient's advanced age.

smaller than 1 cm in diameter were malignant (26).

Key Point

Nodules approaching 3 cm in diameter are more likely to be malignant, while nodules smaller than 1 cm in diameter are more likely to be benign.

SPN Location

Lung cancer is 1.5 times more likely to occur in the right lung than in the left lung (30). Studies have shown that 70% of lung cancers are located in the upper lobes and occur most frequently in the right lung (31,32). Thus, one should carefully scrutinize the upper lobes when re-

viewing chest images, as most missed lung cancers are located in the right upper lobe (24). As benign nodules are equally distributed throughout the upper and lower lobes, location alone cannot be used as an independent predictor of malignancy (16). In patients with idiopathic pulmonary fibrosis, lung cancers more commonly involve the periphery of the lower lobe, a site in which fibrosis is most likely to occur (15). Approximately half of primary pulmonary adenocarcinomas manifest as isolated peripheral SPNs, while squamous cell carcinomas that manifest as SPNs are more likely to be centrally located (33).

Increasing use of low-tar and filtered cigarettes in the United States has been

Figure 5

Type of Cause	Disease Entity
Neoplastic	
Malignant	Primary pulmonary carcinoma Adenocarcinoma, squamous cell carcinoma, bronchioalveolar cell carcinoma, small cell carcinoma Primary pulmonary lymphoma Primary pulmonary carcinoid Solitary metastasis Melanoma, osteosarcoma, testicular cancer, breast, prostate, colon, renal cell carcinoma
Benign	Hamartoma, chondroma Arteriovenous malformation Fibroma Neural tumor (schwannoma, neurofibroma) Sclerosing hemangioma
Infectious	Granuloma <i>Mycobacterium tuberculosis</i> Fungal (<i>Histoplasmosis</i> , <i>Coccidioidomycosis</i> , <i>Blastomycosis</i> , <i>Cryptococcosis</i> , <i>Aspergillosis</i>) <i>Dirofilaria immitis</i> Bacterial (<i>Nocardia</i> , <i>Actinomycosis</i> , round pneumonia) Measles Abscess Septic embolus
Noninfectious	Sarcoidosis Lipoid pneumonia Amyloid Subpleural lymph nodule Rheumatoid arthritis Wegener granulomatosis Pulmonary scar Infarct
Congenital	Bronchogenic cyst Bronchial atresia with mucoid impaction Sequestration
Other	Skin nodule Rib fracture Pleural thickening, mass or fluid

Figure 5: Chart shows differential diagnosis of SPN.

Figure 6

Figure 6: Transverse CT scan in a 75-year-old man with idiopathic pulmonary fibrosis shows a solid left lower lobe nodule (arrow). FNAB of the nodule revealed squamous cell carcinoma.

associated with changes in the histologic type and anatomic distribution of lung cancer, such as decreasing incidence of small-cell carcinoma (the cell type most closely associated with cigarette smoking) and increasing incidence of adenocarcinoma (34). Adenocarcinomas are frequently peripheral lung tumors rather than central lung tumors because people who smoke low-tar filtered cigarettes inhale deeply and distribute smoke to the lung periphery. People who smoke high-tar unfiltered cigarettes do not inhale as deeply and are more likely to develop tumors associated with central lesions, such as squamous cell carcinomas (34).

Key Point

The right upper lobe is the most common location of lung cancer.

SPN Internal Attenuation Characteristics

Calcification

The most important imaging feature that can be used to distinguish benign

Hierarchy of Likelihood Ratios for Malignancy

Characteristic	Likelihood Ratio
Cavity wall thickness (mm)	
>16	37.97
>4–16	0.72
≤4	0.07
Size (cm)	
>3.0	5.23
2.1–3.0	3.67
1.1–2.0	0.74
≤1.0	0.52
PET standardized uptake value	
>2.5	4.30
≤2.5	0.04
Age (y)	
>70	4.16
50–70	1.90
30–39	0.24
20–29	0.05
Growth rate (d)	
>465	0.01
7–465	3.40
<7	0
Enhancement (HU)	
>15	2.32
≤15	0.04
Irregular spiculated edge	5.54
History of malignancy	4.95
Current smoker	2.27
Never smoked	0.19
Indeterminate calcification at CT	2.20
Upper and/or middle lobe location	1.22
Smooth nodule at CT	0.30
Benign calcification at CT	0.01

Source.—References 10 and 11.

SPNs from malignant SPNs is calcification. Benign nodules can be diagnosed confidently if the lesion is smaller than 3 cm in diameter and exhibits one of the following patterns of calcification: central nidus, laminated, popcorn, or diffuse. When one of these patterns is seen, the likelihood of benignity approaches 100% (3,4). Popcorn calcifications are observed in one-third of hamartomas (7), and the other patterns are seen with histoplasmosis and tuberculosis (Fig 8).

SPNs smaller than 9 mm in diameter are rarely visible on chest radiographs; therefore, a nodule of that size

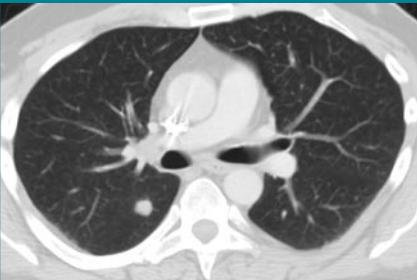
Figure 7

Figure 7: Transverse CT scan of the chest shows a solitary right lower lobe nodule. FNAB of the nodule revealed renal cell carcinoma metastasis.

Figure 8

Figure 8: Transverse CT scan shows a 1-cm-diameter left lower lobe nodule with central nidus calcification. This finding is indicative of benign disease.

that is clearly seen is likely to be diffusely calcified and benign. For larger SPNs, however, detection of calcification with radiography is less certain. In a study where the mean SPN diameter was 13 mm, sensitivity and specificity of radiography in the detection of calcification were 50% and 87%, respectively (35) (Fig 9). When computed tomography (CT) was used, 7% of these definitely calcified nodules were not calcified and were, therefore, potentially malignant.

While low-voltage radiography and

dual-energy computed radiography (and perhaps in the future, tomosynthesis) can be used to show calcification within SPNs (36,37), CT has largely replaced radiography for this purpose. Assessing calcification with CT requires the use of sequential thin “cuts” through

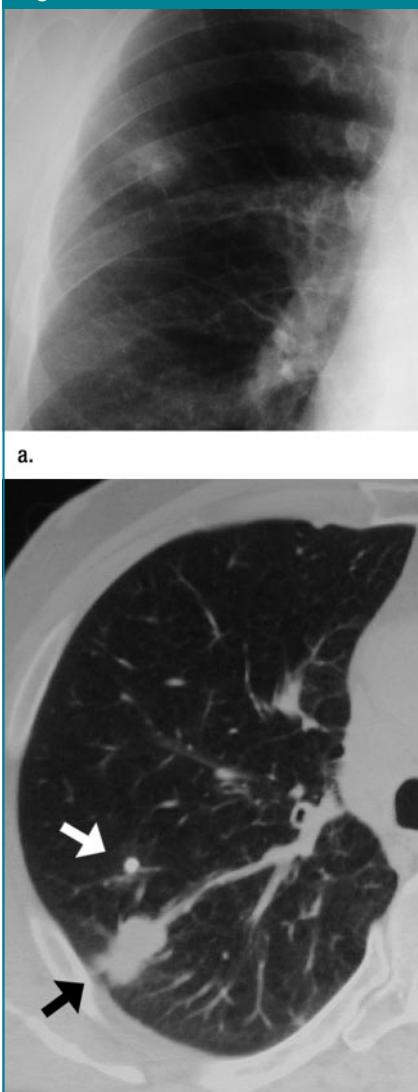
Figure 9

Figure 9: (a) Chest radiograph shows a right upper lobe nodule with central calcification. The margins are irregular. (b) CT scan shows a right upper lobe nodule with irregular margins that represents pulmonary carcinoma (black arrow). The calcification seen on the radiograph is caused by a calcified granuloma anterior to the tumor (white arrow).

the nodule, with standard soft-tissue reconstruction. If a benign pattern of calcification involving more than 10% of the cross-sectional area of the nodule is present, malignancy is unlikely and observation is appropriate (38).

While CT studies have shown that up to 13% of lung cancers have some calcification (4,39,40), this is true of only 2% of lung cancers smaller than 3 cm in diameter (39). Eccentric calcification should not be considered a benign finding. It may represent a benign lesion that has calcified in an eccentric fashion or a malignant lesion that has dystrophic calcification or has engulfed a be-

nign calcified lesion (4) (Fig 10). Furthermore, central calcification in a spiculated SPN should prompt concern for malignancy, as most benign SPNs have smooth or minimally lobulated margins.

Calcification in lung cancers may appear amorphous, stippled, or diffuse (40). Some lung cancers can have dense foci of calcification or be entirely calcified, with a pattern resembling that of benign disease. Both of these patterns can be seen in carcinoids, metastatic osteosarcomas, and chondrosarcomas (Figs 11, 12). A stippled appearance or psammomatous calcification can be seen in SPNs that are metastases from mucin-secreting tumors, such as colon or ovarian cancers. In patients with a history of these tumors and a benign-appearing SPN, CT cannot be used to reliably determine benignity and biopsy may be necessary.

Unfortunately, calcification is often not useful, as about 45% of benign nodules are not calcified (4); thus, other imaging features associated with benignity must be sought.

Key Point

With the exception of SPNs in patients with a history of bone malignancy, SPNs with a benign pattern of calcification are indeed benign.

Fat

Demonstration of fat may be difficult if the nodule is small, as partial volume inclusion of the lung may interfere with attenuation measurements. However, if one can determine that fat is present, hamartoma or lipoma (albeit less likely) become the most likely causes (Fig 2b). Some malignancies, such as a metastasis from liposarcoma or renal cell carcinoma, may occasionally contain fat (41). In patients without prior malignancy, focal fat attenuation (-40 to -120 HU) is a reliable indicator of a hamartoma and is seen in over 50% of hamartomas at thin-section CT (42). In a series of 47 patients with hamartomas, both fat and calcium were seen in 10 and fat alone was seen in 18 (42).

Key Point

Demonstration of fat in an SPN in patients without a history of liposarcoma

Figure 10

Figure 10: CT scan in an 80-year-old man shows a 2.2-cm-diameter nodule in the left upper lobe with eccentric calcification. FNAB of the nodule revealed adenocarcinoma.

Figure 11

Figure 11: CT scan shows eccentric dense calcification in a right lower lobe carcinoid tumor. (Image courtesy of J. W. Gurney, MD, University of Nebraska, Omaha, Neb.)

or renal cell carcinoma suggests that the SPN is benign.

Nodule Attenuation

The advent of CT has led to improved recognition of the frequency with which nodules are nonsolid, partly solid, and solid. Aerated lung parenchyma is visible through a nonsolid (ground-glass) nodule, while a partly solid nodule contains solid regions that mask an aerated lung.

Approximately 34% of nonsolid nodules are due to malignancy (43). The risk of malignancy increases if the diameter of the SPN exceeds 1.5 cm or the nodule is round (43,44). Malignancies such as bronchioloalveolar carcinomas or invasive adenocarcinomas with bronchioloalveolar cell features may appear to be nonsolid nodules (Fig 13). Nonsolid nodules are often caused by benign conditions, such as inflammatory disease, and may contain premalignant lesions, such as atypical adenomatous hyperplasia or bronchoalveolar hyperplasia (45). Precursors of adenocarcinoma are believed to begin in regions of bronchoalveolar hyperplasia (46). Noguchi et al (47) devised a histopathologic classification system in which nodules are stratified according to their malignant potential and propensity for local and regional metastases.

Partly solid nodules are more likely to be malignant than nonsolid nodules (Fig 14). Between 40% and 50% of partly solid nodules smaller than 1.5 cm in diameter are cancerous, and the risk of cancer increases with increasing nodule size, particularly if the solid component is in the center of the nodule (43,44). This solid component often contains invasive adenocarcinoma.

Although solid nodules are the most common type of nodule, they are less likely to be malignant than are partly solid or nonsolid nodules. Inflammatory diseases of the lung, particularly tuberculosis and mycoses, usually produce solid nodules that may eventually calcify and permit the designation of benign disease. Only 15% of solid nodules smaller than 1 cm in diameter contain malignant foci, but the proportion of nodules that contain such foci increases

Figure 12



Figure 12: CT scan shows calcified right lower lobe nodule that resembles a benign granuloma (arrow). The patient had a history of osteosarcoma. Open lung biopsy revealed metastatic disease.

Figure 13

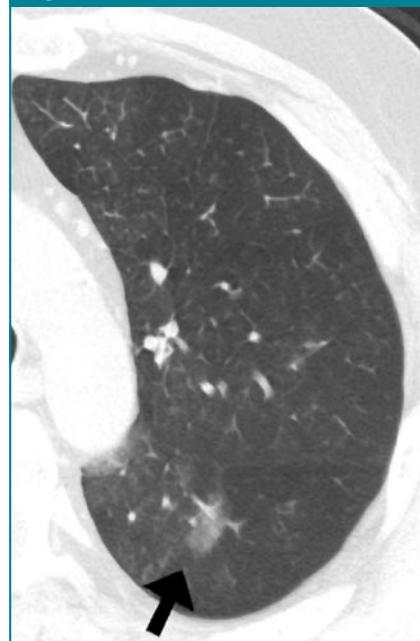


Figure 13: CT scan in a 64-year-old man shows an oval 2.1-cm left lower lobe nonsolid nodule (arrow). FNAB revealed adenocarcinoma.

with increasing diameter (48). While solid nodules are usually noncancerous (granulomas), most lung cancers are found in solid nodules (Fig 6). Histologic types of cancerous solid nodules include adenocarcinomas and squamous cell, large-cell anaplastic, neuroendocrine, carcinoid, and (rarely) small-cell carcinomas (48). In addition, most metastatic nodules are solid in appearance, with a partly solid appearance occurring less frequently.

Key Point

While most cancerous nodules are solid, partly solid nodules are most likely to be malignant.

Air Bronchograms

Air bronchograms and bronchiograms are seen more commonly in pulmonary carcinomas than in benign nodules (42) (Figs 1b, 1c, 15b). In one review, air bronchograms were seen in approximately 30% of malignant nodules but in only 6% of benign nodules (49). Air bronchiograms, also referred to as bubble-like lucencies or pseudocavitation, may simulate cavities and are seen in up to 55% of bronchioloalveolar cell

Figure 14

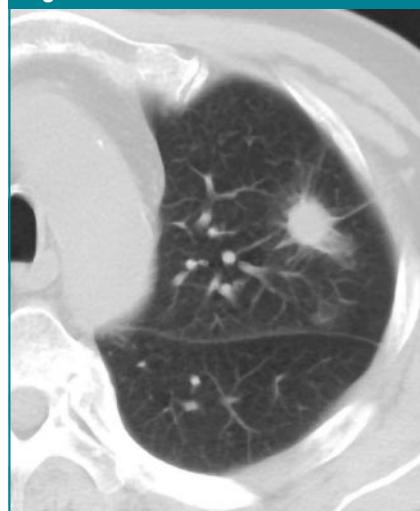


Figure 14: CT scan in an 81-year-old man shows a 2.8-cm irregular, partly solid left upper lobe nodule with pleural tags. FNAB revealed bronchioloalveolar cell carcinoma.

carcinomas (42). This appearance is caused by a desmoplastic reaction to the tumor that distorts the airways (50,51).

Margin

Edge characteristics indicative of malignancy include irregularity, spiculation, and lobulation (10) (Fig 1b). Edge irregularity and spiculation are associated with the radial extension of malignant cells along interlobular septa, lymphatics, small airways, or blood vessels and have been likened to the spokes of a wheel (52).

In a study with thin-section CT, all nodules with a halo margin—97% with densely spiculated margins, 93% with ragged margins, and 82% with lobulated margins—were malignant (53). Nodule halos (peripheral nonsolid component) should not be confused with the corona radiata, which is a radiolucent halo associated with paracarcinomatous emphysema (52,54). The presence of spiculation has a predictive value for malignancy of approximately 90% and should prompt an aggressive work-up (3,4,10,42,55). While an irregular margin is indicative of

malignancy, it can occasionally be seen in granulomatous disease, lipid pneumonia, organizing pneumonia, and progressive massive fibrosis (4,56). A smooth margin does not indicate benignity, as up to one-third of malignant lesions have smooth margins and many of these tumors are metastatic (7,9,54) (Figs 7, 16).

A lobulated margin indicates that the nodule has uneven rates of growth (Fig 16). In a series by Siegelman et al (3), approximately 40% of smooth-edged lobulated nodules were malignant. However, close inspection of any nodule that appears to be lobulated is necessary. Adjacent tiny nodules, called satellite nodules, may mimic the appearance of a lobulated margin, and the presence of these nodules is strongly associated with benignity (Fig 17). Even so, the presence of satellite nodules does not allow confident diagnosis of benignity, as 10% of dominant nodules with satellite nodules will be malignant (4,52). When cancerous, satellite nodules are usually the result of peripheral foci of tumor or skip metastatic lesions (52).

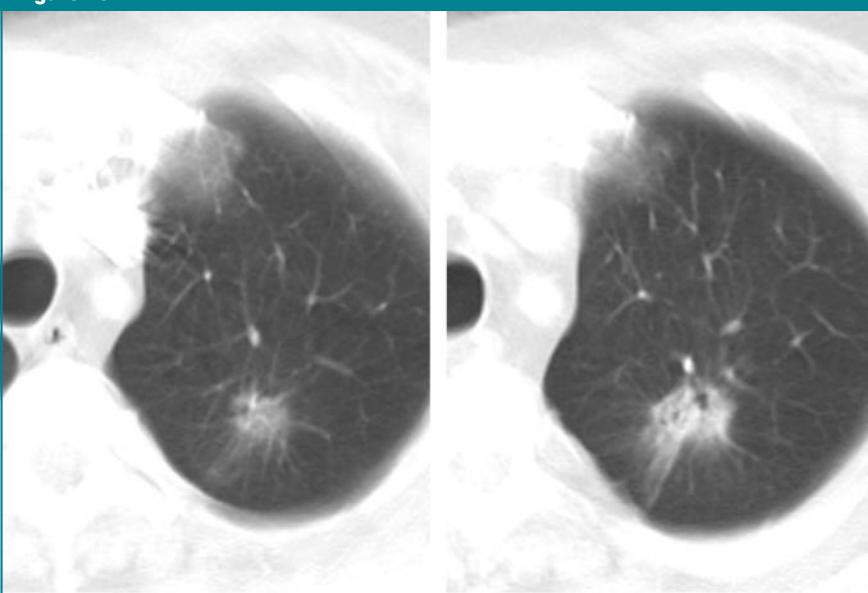
Cavitation

Both benign and malignant nodules can form a cavity. Up to 15% of lung cancers form a cavity, but most are larger than 3 cm in diameter (57). However, cavitation may be seen in SPNs as small as 7 mm in diameter. SPNs with irregular-walled cavities thicker than 16 mm tend to be malignant (84%–95% of SPNs), while benign cavitated lesions usually have thinner smoother walls; approximately 95% of lesions with cavity walls thinner than 4 mm are benign (58–60). However, because there is much overlap, cavity wall characteristics cannot be used to confidently differentiate benign and malignant SPNs (Figs 18, 19).

Key Point

Several imaging features (nodule attenuation, presence of air bronchograms, edge characteristics, and cavity wall thickness) must be considered when assessing the likelihood of malignancy; however, there is considerable overlap in the appearance of benign and malignant lesions.

Figure 15



a.

b.

Figure 15: (a) Transverse CT scan in a 75-year-old man shows a 2.0-cm-diameter non-solid left upper lobe nodule. FNAB revealed no malignant cells; thus, no specific diagnosis was made. (b) The lesion was followed up with serial CT; 25 months later, the nodule was slightly increased in size and had converted to a partly solid attenuation lesion with air bronchograms. Volumetric measurement showed the doubling time of the opacity to be 1375 days. Repeat FNAB showed bronchioloalveolar cell carcinoma.

CT Examination

In any patient with a newly discovered SPN, a standard CT examination without contrast material enhancement may be performed in the chest. This examination will ensure there are no other findings, such as additional nodules, lymphadenopathy, pleural effusion, chest wall involvement, or adrenal mass. Because of concerns about radiation dose to the patient, subsequent follow-up CT may be limited to the nodule location. Thin-section CT scans obtained through the nodule provide information regarding nodule size (by using diameters from the largest cross-sectional area or volume measurement), attenuation, edge characteristics, and the presence of calcification, cavitation, or fat (42) (Fig 1b, 1c). Sequential thin-section CT (1–3-mm section width) performed through the entire nodule with a single breath hold and without contrast material enhancement should allow these features to be analyzed. Demonstration of certain findings, such as fat or a benign pattern of calcification, may be all

that is required to ascertain that the nodule is benign (42) (Figs 2b, 8).

The cause of many SPNs, however, will remain undetermined after the initial and thin-section CT examinations. If the nodule is at least 10 mm in diameter, a contrast material-enhanced examination may be performed. The use of contrast material may be especially helpful in regions where granulomatous disease is endemic. Contrast enhancement is directly related to the vascularity of the nodule, and blood flow is usually greater in malignant nodules than in benign nodules (61,62). To perform the study, the nodule is examined with 3-mm collimation before and after administration of a weight-related dose of intravenous contrast material. Contrast-enhanced examinations are performed at 1-minute intervals up to 4 minutes after injection of contrast material. Nodule enhancement is determined by subtracting baseline attenuation from peak mean attenuation during the contrast-enhanced examinations (31). The use of multi-detector row CT facilitates performance of this examination because the nodule is likely to be in the examined volume, despite varying breath holds.

Nodule enhancement of less than 15 HU after administration of contrast material is strongly indicative of benignity (positive predictive value, approximately 99%). Rare false-negative findings are associated with central noncavitating necrosis and adenocarcinomas (especially bronchioloalveolar cell carcinoma), which may be related to mucin production (31,63,64). Although enhancement of more than 15 HU is more likely to represent malignancy, only 58% of nodules are malignant; the remainder represent enhancing lesions due to active inflammatory disease that have increased blood flow, such as granulomas or organizing pneumonias (31,63,65). Enhancing nodules should still be considered indeterminate and require further work-up. In summary, nodule behavior after contrast material administration is sensitive but not specific for malignancy. Contrast-enhanced CT examinations should not be

Figure 16



Figure 16: CT scan in a 56-year-old man shows a 2.9-cm smooth lobulated central right middle lobe nodule (arrow). FNAB revealed squamous cell carcinoma.

Figure 17

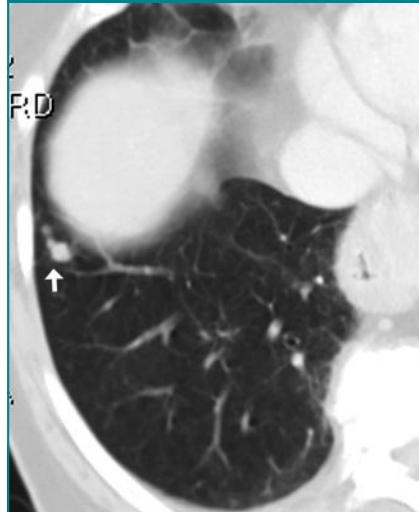


Figure 17: CT scan shows a right lower lobe subcentimeter nodule with adjacent tiny satellite nodules (arrow). The larger nodule was calcified (not shown). The appearance is that of benign granulomatous disease.

Figure 18

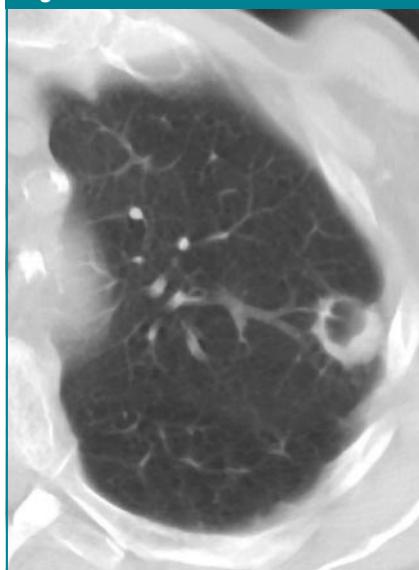


Figure 18: CT scan in an 83-year-old man shows a 2.3-cm left upper lobe cavitary nodule. The wall is variable and the cavity wall is as thick as 8 mm. FNAB revealed squamous cell carcinoma.

83%, respectively (11). Demonstration of a hypermetabolic state, especially in smaller lesions, is of concern for malignancy and necessitates either intervention or close scrutiny. The probability of malignancy in association with positive FDG PET findings is high (90% if the patient is older than 60 years); likewise, the probability of malignancy in association with negative FDG PET findings is low (<5%) (67,68) (Fig 20). Once lung cancer has been diagnosed in a solid nodule, particularly if FDG uptake is high, PET may be helpful in the detection of mediastinal lymph node metastases, even when the nodes are not enlarged on CT scans (69). Occult extrathoracic metastases and synchronous extrathoracic primary malignancies also may be detected with PET.

False-positive PET findings are associated with focal infections, inflammation, and nonneoplastic diseases (eg, tuberculosis, sarcoidosis, and rheumatoid disease) and are more frequent in regions with endemic fungal diseases such as *Histoplasma* and *Coccidioides* infections. The high negative predictive value of PET in low-risk populations supports

the strategy of observing nodules that are negative at PET. However, certain neoplasms, such as carcinoid and bronchioalveolar cell carcinoma, have a low metabolic rate that may result in false-negative examinations. Furthermore, sensitivity and specificity are not as high for nodules that are smaller than 1 cm in diameter (69).

Key Point

FDG PET examination of an SPN larger than 1 cm in diameter is the best test to determine if a lesion is malignant or benign.

Bayesian Analysis

Bayesian analysis can be useful in the evaluation of SPN. Bayesian analysis involves the use of likelihood ratios of numerous imaging findings and clinical features associated with SPNs to establish the probability of malignancy (10,70) (Table). In addition to imaging findings, age and smoking history are factors that are included in the Bayesian analysis. A general principle in Bayesian models is that each characteristic used

in the development of the model is conditionally independent of all others.

Investigators in one study analyzed many of the characteristics used in the model and found that three clinical (age, smoking history, and history of previous malignancy) and three radiographic (diameter, spiculation, and upper lobe location) features are independent predictors of malignancy (16). Investigators in another study compared the assessment made with the clinical prediction model with that made by the clinicians. Receiver operating characteristic analysis showed no difference between the assessments. However, physicians overestimated the probability of a malignant lesion in patients with low risk of malignant disease. The authors concluded that the logistic model could be used to improve the care of patients with SPNs that are likely to be benign (6).

Not all Bayesian models are effective: Comparison of a Bayesian approach with FDG PET alone revealed that FDG PET outperformed the model (68). A standard uptake value of more than 2.5 with PET yields a likelihood ratio of 4.30 for malignancy, whereas a negative PET examination has a likelihood ratio of 0.04. Bayesian analysis is equivalent or slightly superior to evaluation by an experienced radiologist in the stratification of benign and malignant pulmonary nodules (69). An explanation of the mathematics of Bayesian modeling is beyond the scope of this article; however, for a particular patient, one can easily determine the probability that an SPN is cancerous at the following Web site: <http://www.chestx-ray.com>.

Key Point

A Bayesian analysis that includes PET findings is an effective method that can be used to calculate the probability of malignancy.

Growth Rate Measured from Serial Studies

The notion that an SPN exhibiting no growth for at least 2 years is benign is widely accepted and is the standard of

Figure 19



Figure 19: CT scan in an 80-year-old man shows a right upper lobe 2.9-cm cavitary nodule with a smooth, uniform 2.5-mm-thick cavity wall. FNAB revealed non–small cell lung cancer.

Figure 20

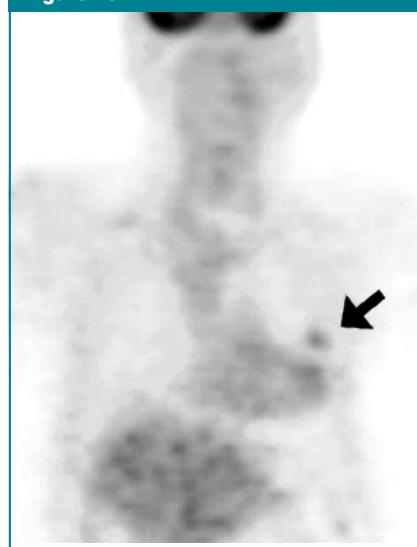


Figure 20: FDG PET scan shows a lingular nodule (arrow) with a standardized uptake value of more than 2.5. FNAB revealed carcinoid tumor. (Image courtesy of Dr E. Long, Goshen General Hospital, Goshen, Ind.)

care (71,72). Yankelevitz and Henschke (73) have challenged the basis of 2-year stability as a reliable indicator that SPNs are benign. They used no growth as the predictor of benignity and calculated the predictive value as 65%, the sensitivity as 40%, and the specificity as 72%. The 2-year rule is still being used; however, one should exercise caution and attempt to obtain radiographs and CT scans older than 2 years because even a substantial increase in volume may be missed in small nodules (73).

The time for a nodule to double in volume is referred to as the doubling time. For radiographic measurement, the nodule diameter is measured in at least two dimensions and averaged on two serial images. Doubling time (T_d) is calculated with the following equation: $T_d = T_i \cdot \log 2/3 \cdot \log(D_f/D_i)$, where T_i = interval time, D_i = initial diameter, and D_f = final diameter. For example, a diameter increase of 26% corresponds to a volume increase of 100%. Diameters measured with electronic calipers are preferable to diameters measured manually; however, it is difficult to reliably show changes in size that are smaller than 2 mm (74). As new software becomes more widely available, automated volume measurement algorithms will likely become more important in the evaluation of indeterminate nodules (75) (Fig 1d). Automated measurement with multi-detector row CT (which speeds up image acquisition, thus decreasing motion and partial volume effects) may enable growth to be detected with serial CT examinations performed as little as 4 weeks apart (48).

A limitation of nodule measurement is that adjacent inflammatory change, atelectasis, or scars may inadvertently be included in the measurement, thus making the lesion appear larger than it is. Tumors may undergo necrosis, hemorrhage, or cavitation, any of which would alter their size. The partial volume effect may lead to substantial overestimation of lesion size, particularly if thin CT sections are not used. Even with thin CT sections, volume measurements in very small nodules may show substantial variability and be inaccurate, especially if the diameter of the nodule

is close to the CT section width (32,74,76). Another limitation of the automated volumetric assessment is the potential to not include in the measurement the ground-glass component of a partly solid nodule, which has a high frequency of malignancy.

An early study showed that all nodules doubling in size in less than 7 days and almost all nodules doubling in size in more than 465 days were benign (77). Some benign lesions, such as granulomas and hamartomas, grow slowly; therefore, growth in and of itself cannot be used to predict malignancy (78). Many investigators have estimated the growth rates of various types of lung cancer with chest radiography (79–84). The volume-doubling time for most lung cancers was reported to be between 1 and 18 months. Few CT studies have been reported, but they have shown that lung cancer doubling times have a wider range than anticipated on the basis of the previously reported chest radiography literature. CT-derived doubling times have been reported to range from 32 days to virtually no detectable growth (32,85,86) (Figs 15, 21). It has been speculated that the wider range of growth rates may be related to the use of a more sensitive modality in nodule detection and measurement. The majority of lung cancers have rapid or moderately rapid growth rates; however, CT may preferentially depict slow-growing adenocarcinomas that are not depicted with radiography (86). Tumors with doubling times of more than 730 days will appear stable during a 2-year observation period (87) (Fig 15). Growth rate is an independent and important prognostic factor in patients with lung cancer, so one can expect longer survival in patients with slow-growing tumors (88).

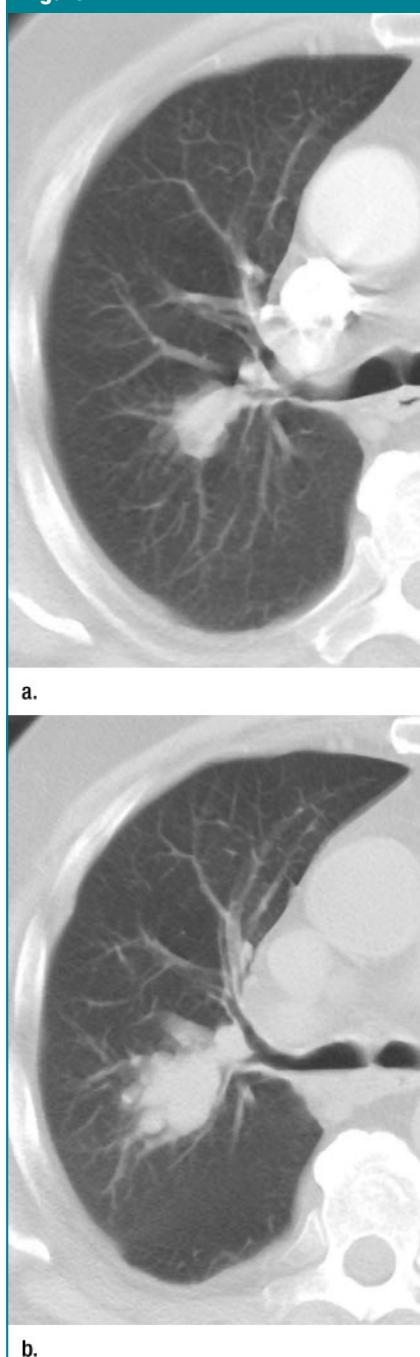
Key Point

Cancerous tumors with doubling times of more than 730 days may appear stable during the 2-year observation period.

SPN Biopsy

For nodules that have clinical and imaging features of malignancy, a tissue sam-

Figure 21



b.

Figure 21: (a) CT scan in an 80-year-old man shows a 2.5-cm right upper lobe nodule at the posterior segment. (b) Repeat CT scan obtained prior to treatment performed 2 months later shows rapid interval enlargement. The volumetric doubling time was 26 days. FNAB revealed mixed small cell and non-small cell carcinoma.

ple is required. There are many methods of obtaining tissue from an SPN, such as video-assisted thoracoscopic or open surgical biopsy; however, the method radiologists are frequently asked to perform is fine-needle aspiration biopsy (FNAB). CT-guided FNAB has been a great advancement in the diagnosis of small pulmonary nodules larger than 5 mm in diameter. In patients who are not candidates for surgery because of comorbidities, FNAB can be used to diagnose malignancy and determine the histologic type of malignancy. In patients who are candidates for surgery, FNAB may be used to diagnose benign disease, thus obviating surgery (89–91) (Fig 1). Contraindications to FNAB include inability of the patient to cooperate (eg, inability to reproduce breath holds, lie immobile on the CT table for more than 30 minutes, or withhold coughing). Other relative contraindications include bleeding diathesis, previous pneumonectomy, severe emphysema, severe hypoxemia, pulmonary artery hypertension, or nodules in which successful biopsy cannot be per-

formed because of their small size or location.

FNAB has a sensitivity of 86.0% and a specificity of 98.8% in the diagnosis of malignancy (92); however, in nodules 5–7 mm in diameter, sensitivity is only 50% (93). Sensitivity of FNAB is also substantially lower (12%) in patients with lymphoma, and core biopsy (sensitivity, 62%) is recommended when patients are suspected of having lymphoma (94). The skills and experience of the cytopathologist are critical in the interpretation of biopsy specimens. Immediate cytologic interpretation increases the yield and accuracy of FNAB (95).

FNAB may be performed with fluoroscopic, CT, or ultrasonographic (US) guidance. With fluoroscopy, FNAB can be performed quickly and with the patient in a seated position, if necessary. CT allows localization of smaller nodules and enables planning of the needle path to avoid blebs and fissures. US may be useful when the lesion abuts the pleura. Most malignant lesions can be diagnosed with FNAB and with use of a

coaxial technique. FNAB is optimally used in peripheral nodules, although biopsies can be performed in more central lesions. Nodules that are in the lower lobes or adjacent to the heart may be difficult to access because of varying breath holds and diaphragmatic and cardiac motion. Core-needle biopsy can be reserved for cases where FNAB fails to provide a specific diagnosis, especially for cases of benign disease.

Interpretation of the FNAB specimens falls into one of three categories: malignant, specific benign, or nonspecific benign. When the FNAB sample is interpreted as malignant or if a specific benign condition is diagnosed, further decisions regarding care are dictated by the diagnosis. On the other hand, when a nonspecific benign condition is diagnosed, further evaluation is required. The lesion may be malignant, but the sample was obtained outside the nodule or from a necrotic area, thus precluding the pathologist from establishing a diagnosis. Core-needle biopsy is more likely than FNAB to provide a specific benign result. In a group of patients with benign nodules, a specific benign diagnosis was made in 69% of patients with core needle biopsy and in 31% of patients with FNAB (96).

A nonspecific benign diagnosis requires careful clinical and radiographic follow-up. Diagnoses such as atypical bronchioloalveolar hyperplasia or inflammation without organisms on a smear or a culture are considered nonspecific. If further growth occurs after a nonspecific benign diagnosis is obtained with FNAB, repeat biopsy or resection is indicated.

The most common complications of FNAB are pneumothorax and hemorrhage (87,89). Pneumothorax occurs in approximately 25% of patients, but it is often not clinically important. Only about 7% of patients with a pneumothorax will eventually require a chest tube (92). The use of an autologous blood patch (injecting the patient's own blood along the needle track while withdrawing the needle) has shown mixed results in reducing the rate of pneumothorax after FNAB (97). Presence of emphysema, deep lesion location, a lengthy

Figure 22

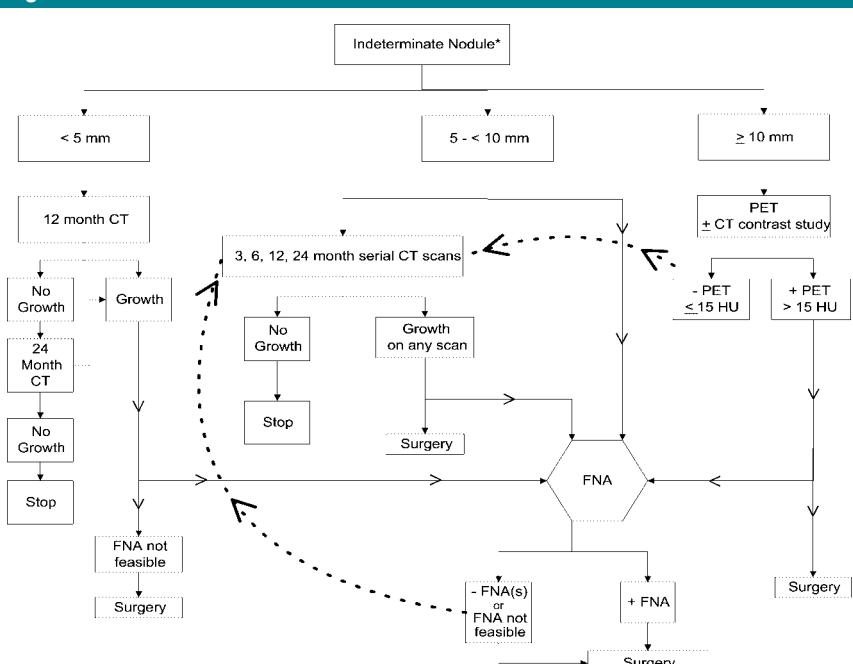


Figure 22: Flowchart for evaluation of the solitary indeterminate nodule for patients with intermediate and intermediate risk for malignancy. *FNA* = FNAB.

procedure, many pleural punctures, and traverse of the fissure all increase the risk for pneumothorax (98,99). As urgent intervention may be required, radiologists who perform lung biopsy procedures must be competent at aspiration of pleural air and insertion of a chest tube. Hemorrhage is almost always self-limiting, although it can occasionally be life-threatening (100). Bleeding complications are more likely to occur in patients with bleeding diatheses or pulmonary artery hypertension.

Air embolism is a rare complication; patients can present with symptoms resembling those of stroke, transient ischemic attack, seizure, or cardiopulmonary collapse. Treatment includes placing the patient in the left lateral decubitus position or Trendelenburg position and administering 100% oxygen. Hyperbaric oxygen therapy is recommended. A diagnosis may be established by performing immediate brain or cardiac CT to search for intravascular air bubbles (101).

Key Point

FNAB results other than a specific malignant or benign diagnosis should be viewed with caution.

Imaging Management of Indeterminate Nodules

There is no uniform approach for the management of an indeterminate nodule. In patients with a high or intermediate likelihood for malignancy, early intervention with FNAB or surgery is a good approach. In patients with a low likelihood for malignancy, close observation with serial CT might be preferred. In patients with a very low likelihood for malignancy (eg, a healthy nonsmoker younger than 30 years with a well-defined noncalcified nodule), one might consider observation with radiography if the nodule is visible on the chest radiograph.

The flowchart presented in Figure 22 is a guide proposed by the author for the care of patients with an SPN of intermediate or high likelihood for malignancy. Note that nodules smaller than 5 mm in diameter are often benign, and

their growth is difficult to detect. Thus, thin-section CT examinations performed to show stability at 12 and 24 months are acceptable (102,103). Nodules shown to be stable at 2-year follow-up are considered benign and are no longer followed with CT. It is possible that as volumetric measurements become routine, the current follow-up CT protocol (3-, 6-, 12-, and 24-month follow-up) will become compressed (73).

Nodules with low likelihood for malignancy that are at least 5 mm in diameter but smaller than 10 mm in diameter can be observed with CT for a 2-year period, while nodules with intermediate or high likelihood for malignancy may be sampled with FNAB or resected (104). Demonstration of nodule growth should prompt intervention with either FNAB or surgery. A new persistent nodule that develops during observation is worrisome for malignancy and warrants intervention (104).

For a nodule at least 10 mm in diameter, PET and contrast-enhanced CT may be helpful in deciding between observation or intervention. Patients with negative PET findings and enhancement of less than 15 HU on contrast-enhanced CT scans may be observed, while intervention and tissue diagnosis are indicated in patients with positive PET findings.

Summary

In general, SPNs can be considered benign if they exhibit a pattern of benign calcification and/or show no growth for 2 years. When the imaging features indicate that the probability of malignancy is high, tissue samples should be obtained for diagnosis.

In using the various imaging and diagnostic modalities described in this review, one should strive to not only identify small malignant tumors—where resection results in high survival rates—but also spare patients with benign disease from undergoing unnecessary surgery.

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