THE SOLITARY PULMONARY NODULE

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The evaluation of a solitary pulmonary nodule (SPN) is a common diagnostic dilemma that has become more prevalent with the increasing use of helical CT. The ultimate goal of imaging in the evaluation of SPNs is to accurately distinguish benign from potentially malignant lesions. This has practical importance because the ultimate goal of imaging is to avoid referring a patient with a benign SPN for unnecessary surgical resection, while being certain not to characterize a small malignant SPN incorrectly that may represent resectable (i.e., curable) early stage lung cancer as benign.

Although most SPNs prove to be benign, the distinction of benign from malignant lesions can be difficult. One of the most important but understated aspects of SPN evaluation is to be certain that a focal opacity detected radiographically actually represents a solitary intrapulmonary lung nodule. Once this has been determined, demographic features including patient age, smoking history, history of prior malignancy, and environmental exposures are important in guiding evaluation because these factors influence the post-test probability of malignancy independent of imaging characteristics of the lesion in question. An important characteristic of the lesion that can often be discerned from a review of prior radiographs is an assessment of growth rate that helps determine the likelihood of malignancy. Following this preliminary assessment, assuming the risk of malignancy remains significant, most patients undergo thin-section CT for detailed analysis of size, internal density, and morphologic features of the SPN. Adhering to strict criteria for defining benign SPNs leaves most lesions indeterminate. These patients require more detailed nodule evaluation with contrast-enhanced CT or positron emission tomography (PET); some ultimately require biopsy or resection for definitive diagnosis.

DEFINITION

An SPN is defined as a single round intraparenchymal opacity, at least moderately well-marginated and no greater than 3 cm in maximum diameter. This size limitation is based on the fact that most solitary lung lesions larger than 3 cm in diameter (termed masses) are malignant, whereas most lesions less than 3 cm are benign. In addition, the detection of benign patterns of calcification in a solitary lung lesion allows the confident diagnosis of a benign lesion only when it is less than 3 cm.

It is important when considering a radiographically detected SPN to be certain that the density in question is truly solitary, lies within the lung, and represents a nodule. As
many as 50% of patients with suspected SPNs detected radiographically actually prove to have multiple nodules on CT evaluation. This is particularly important because the presence of multiple lung nodules is suggestive of metastatic or granulomatous disease and requires a different approach than the SPN. Even when an SPN is detected as an incidental finding on helical CT or in the course of screening for lung cancer, a detailed analysis of both lungs, particularly with thin-section collimation (i.e., < 5 mm) and overlapping reconstructions viewed on a workstation, can allow detection of multiple lesions that may alter the diagnostic evaluation.

The intrapulmonary localization of a nodular opacity seen on only a single radiographic projection can likewise be difficult. For a lesion to be considered intrapulmonary on conventional radiographs it must be a discrete opacity completely circumscribed by aerated lung on orthogonal projections. Pseudonodules caused by EKG pads or other devices on the patient’s skin surface can mimic intrapulmonary lesions on frontal radiographs. Cutaneous lesions including moles, nipple shadows, hemangiomas, neurofibromas, and lipomas that protrude from the patient’s skin and are surrounded by atmospheric air also may appear intrapulmonary on a single radiographic projection (Fig. 1). Careful examination of the skin surface usually readily identifies these lesions; if necessary these can be confirmed easily by repeat frontal and oblique radiographs or limited chest fluoroscopy following placement of localizing metallic markers. Other lesions that may mimic a SPN include sclerotic bone lesions, such as bone islands; healing rib fractures; and spinal osteophytes. Although these usually are easily recognized after review of prior radiographs, detailed views of the area in question, chest fluoroscopy, or CT may be necessary in selected cases. Likewise, mediastinal and pleural lesions that are pedunculated and project into the lung (i.e., pleural plaques) can appear as SPNs when viewed en face. A tangential view of the region of contact between the lesion and the mediastinum or pleura, however, usually shows an indistinct border that forms obtuse angles.

Many apparent focal nodular opacities seen radiographically actually represent vascular structures that are tortuous, seen en face, or are superimposed on other vascular structures that lie in the same sagittal plane. These usually can be identified by review of prior radiographs taken at slightly different obliquities or by performing chest fluoroscopy; CT should be reserved for equivocal cases. Occasionally, a mucocele within a dilated bronchus appears as a SPN. This diagnosis is usually readily apparent by detailed review of thin-section CT images that show a tubular or branching lesion of water attenuation; residual air between the mucocele and bron-
chial wall is seen sometimes. Other presumed SPNs are found to represent linear parenchymal scars seen en face. Unless this is easily recognized on current or prior radiographic studies, thin-section CT is often necessary to display the two-dimensional linear nature of the opacity and help distinguish this lesion from a spherical nodule.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a SPN is extensive and includes neoplastic, infectious, inflammatory, vascular, traumatic, and congenital conditions (Table 1). Most benign SPNs are granulomas, hamartomas, or intrapulmonary lymph nodes, whereas bronchogenic carcinomas represent most malignant SPNs.

CLINICAL DATA

Once a SPN has been definitively identified, a detailed investigation almost invariably ensues. Specific clinical features affect the likelihood of benignancy or malignancy, however, and in conjunction with the imaging characteristics of the lesion can impact both the diagnostic approach and choice of therapeutic options. Bayesian analysis allows for a more precise determination of the likelihood of malignancy by combining radiographic findings with clinical information (specifically age, smoking history, and symptoms) to calculate mathematically the probability of malignancy of a specific SPN. Bayes’ theorem uses an odds-ratio formula where the odds of malignancy are divided by the odds of malignancy plus one. The equation for determining the overall odds of malignancy is calculated by multiplying the patients’ prior odds of malignancy by the radiographic likelihood ratio of malignancy by the clinical likelihood ratio of malignancy. In this equation, the prior odds of malignancy are the prevalence of malignancy for a given population divided by the prevalence of benign disease of that population. The likelihood of malignancy ratios are intuitive measures of diagnostic information provided by radiographic test results or clinical findings. Clinical information or radiographic test results strongly suggestive of malignancy have a likelihood ratio much greater than one, whereas those findings suggestive of benignity have a likelihood ratio close to zero, and information or test results that are considered to contain no diagnostic information have a likelihood ratio of one.

The clinical factors to consider in evaluating the likelihood of malignancy include

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patient age; smoking history; symptoms; comorbid conditions (particularly severe emphysema); history and type of prior malignancy; and environmental exposures. For example, a 30-year-old nonsmoking patient without a history of malignancy found to have a smooth round SPN has a high likelihood of a benign lesion and radiologic followup to ensure stability is a reasonable and cost-effective approach. Conversely, one could argue that a spiculated SPN in a 50-year-old cigarette smoker should proceed to immediate resection because the likelihood of lung cancer is so high that the results of diagnostic studies are unlikely to impact the patient’s management. As in many areas of clinical practice, semiquantitative techniques, such as bayesian analysis of SPNs, have not gained widespread use because of the large number of variables to be estimated and differences in local practice, particularly the availability and expertise with advanced imaging techniques, such as PET.

CHARACTERISTICS OF SOLITARY PULMONARY NODULES

Size

There is no size criterion that reliably distinguishes benign from malignant SPNs. In general, smaller nodules are more likely to be benign and larger lesions, particularly those exceeding 3 cm in diameter, are more likely to be malignant. Although 80% of benign SPNs are less than 2 cm in diameter, small size is not necessarily reliable evidence of benignity because 15% of malignant nodules are less than 1 cm in diameter (Fig. 2) and approximately 42% are less than 2 cm in diameter. As shown in the prevalence data from the Early Lung Cancer Screening Project, a growing number of smaller malignant SPNs will likely be detected if lung cancer screening with low-dose helical CT gains widespread acceptance. For these reasons, SPN size is helpful information but does not allow definitive distinction of benign from malignant SPNs.

Growth

The absence of growth over at least a 2-year period is a reliable indicator of benignity. To establish firmly the absence of growth, sequential films obtained with comparable radiographic technique are necessary. Limited thin-section CT should be performed for more accurate lesion measurement if there is any question whether a SPN has increased in size. The use of doubling time, which for spherical lesions is defined as a 25% increase in diameter, is based on the observation that benign

![Figure 2. Small solitary pulmonary nodule (SPN) represents non–small cell lung carcinoma. A, Prone CT scan through lower lobes shows a 12-mm irregular nodule in the superior segment of the right lower lobe. B, Scan during needle placement for biopsy shows needle approaching edge of lesion with a small pneumothorax. Biopsy yielded adenocarcinoma.](image)
lesions have doubling times of less than 30 days or greater than 450 days. SPNs with doubling times between 30 and 450 days require further evaluation.

The use of helical CT for evaluating SPN growth rates, particularly for small lesions, has recently received greater attention given advances in scanner technology, the ability to obtain nodule volumes using helical acquisition techniques and computer-aided evaluation of data sets, and the increasing number of small lesions detected on CT performed for other indications or to screen for lung cancer presenting as a SPN. A recent paper describes the use of a software program that segments SPNs and calculates nodule volume to within a 3% accuracy. In a small series of patients with SPNs and a definitive diagnosis, the doubling time as determined by change in nodule volume on repeat CT scans was less than 177 days for all malignant nodules and greater than 396 days for all benign lesions (Fig. 3). It is likely that computer-aided analysis of nodule volume will become an important part of the evaluation of small SPNs by helping to determine growth rates that allow distinction of benign from malignant SPNs. The technique may prove useful for irregularly shaped small lesions and lesions that grow in a cephalocaudal fashion that is difficult to discern on review of axial images given differences in scan planes and patient positioning on follow-up CT examinations.

Figure 3. CT-derived volumetric analysis of SPN growth. A, Scan shows a small left upper lobe nodule. Boxes at right show detailed sequential axial reconstructions through nodule. B, Repeat thin-section CT scan with sequential reconstructions shows questionable interval change in nodule shape. Illustration continued on following page
Density and Internal Characteristics

Calcification

The presence of a specific pattern of macroscopic calcification within a SPN as seen on conventional radiographs or CT is indicative of a benign lesion. These patterns include central, laminated, diffuse, or popcorn calcification (Fig. 4).\textsuperscript{30} Central, solid (Fig. 5), and laminated forms of calcification (Fig. 6) are found in association with prior granulomatous infection, most commonly histoplasmosis or tuberculosis. Popcorn calcification usually represents the chondroid calcification in a pulmonary hamartoma. Eccentric or amorphous calcification can represent a calcified granuloma engulfed by a malignancy or dystrophic malignant calcification, respectively, and should not be taken as evidence of benignancy (Fig. 7).\textsuperscript{20} Although the presence and pattern of calcification can sometimes be determined on conventional radiographs, approximately one third of noncalcified SPNs have calcification on CT.\textsuperscript{35} For this reason, definitive identification of calcium usually requires thin-section CT using 1- to 3-mm collimated scans reconstructed with a high spatial frequency algorithm. In lesions where calcification is not visible on thin-section CT scans, quantitative CT densitometry can be performed to determine the attenuation value of the nodule. Quantitative CT densitometry can be performed by comparing the CT density of the SPN with that of a microscopically calcified prosthetic reference nodule placed
within a chest phantom model. Most thoracic radiologists no longer use a reference CT phantom for this purpose and instead calculate the average attenuation value through the central portion of the nodule. A value of 200 H or greater from at least 10% of the central pixels or throughout the nodule is reliable evidence of microscopic calcification and indicates benignity.

The absence of calcium is of little value in distinguishing benign from malignant SPNs because 38% to 63% of benign nodules, two thirds (67%) of carcinoid tumors, and as many as 94% of all lung cancers do not contain appreciable calcium.

**Fat**

The identification of fat within a SPN with smooth or lobulated margins is indicative of benignity. A pulmonary hamartoma, the third most common cause of a SPN, is a benign neoplasm composed of disorganized epithelial and mesenchymal elements normally found in the bronchus or lung. Up to 50% of hamartomas have fat that can be detected on thin-section CT (Fig. 8), with 30% showing calcification or ossification that is often pop-corn in appearance. These lesions typically develop in middle-aged adults and demonstrate slow growth. In patients with characteristic findings on thin-section CT, pathologic confirmation is usually unnecessary and radiographic follow-up to confirm stability over a 2-year period is recommended, although transthoracic needle biopsy can be performed if a definitive diagnosis is deemed necessary.

**Cavitation**

Although cavitation can occur in necrotic malignant SPNs, particularly squamous cell
Figure 5. Calcified SPN from tuberculosis. A, Frontal chest radiograph shows a peripheral right upper lobe nodule. B, Thin-section CT scan shows a completely calcified nodule representing prior tuberculosis.
**Figure 6.** Laminated calcification in histoplasmosis.  

_A_, Scout view from CT scan shows a sharply marginated peripheral right upper lobe nodule.  

_B_, Thin-section CT scan shows laminated calcification. The patient had a history of prior histoplasma infection.
Figure 7. Dystrophic calcification in lung cancer. A, Frontal chest radiograph shows a large left lower lobe mass. B, Unenhanced thin-section CT scan shows eccentric punctate calcifications. Biopsy revealed adenocarcinoma.
carcinoma, inflammatory lesions, such as abscesses, infectious granulomatous lesions, Wegener’s granulomatosis, and pulmonary infarcts, can also cavitate. The thickness of the cavity wall can be helpful in distinguishing benign from malignant lesions. Cavities with a greatest wall thickness less than 5 mm are almost always benign, whereas most of those with a maximal wall thickness greater than 15 mm are malignant (Fig. 9).  

**Air Bronchograms or Bubbly (Cystic) Lucencies**

The assessment of the internal density of a noncalcified SPN as evaluated with thin-section CT can provide useful information. Homogeneous nodule attenuation is observed more frequently in benign (55%) than malignant lesions (20%). Internal inhomogeneity, particularly the presence of air bronchograms...
or cystic or “bubbly” lucencies within a SPN, is highly suggestive of an adenocarcinoma, particularly the localized form of bronchioloalveolar cell carcinoma (Fig. 10). Other malignancies, however, such as lymphoma and benign lesions including organizing pneumonia, pulmonary infarcts, and mass-like sarcoidosis, can produce a similar appearance.

Margins

A detailed assessment of the margins of a SPN as depicted on thin-section CT can provide useful information. Although smooth, well-defined margins most often indicate a benign nodule (Figs. 8 and 11), 21% of malignant nodules have a smooth well-defined margin. Alternatively, a lobulated margin may reflect uneven growth of a SPN and can indicate malignancy (Fig. 12), although 25% of benign nodules, particularly hamartomas, are lobulated. A nodule that has an ill-defined margin and demonstrates an irregular or spiculated contour most often represents a malignancy. Spiculated margins result from cicatrization (scarring) of the lung interstitium surrounding a lesion (Fig. 13). It is important to recognize, however, that whereas a spiculated margin is highly suspicious for lung cancer, cicatrization producing a spiculated nodule can also be seen in benign inflammatory processes, such as lipoid pneumonia, organizing pneumonia, tuberculosis, and the mass-like lesions of progressive massive fibrosis seen in complicated silicosis.

There are several other features of the margins of SPNs as depicted on thin-section CT that are of diagnostic value. The presence of small satellite nodules surrounding the periphery of a smooth dominant nodule is strongly suggestive of a granulomatous infection (Fig. 14). The pleural tail is a linear opacity seen extending from the edge of a peripherally situated SPN to indent the pleura. Although this finding can be associated with lung cancer (see Fig. 13), in particular bronchioloalveolar cell carcinoma, it is also seen with peripheral granulomas and its presence is of limited diagnostic value. The halo sign refers to the presence of ground-glass opacity surrounding a nodule or mass. When seen in a neutropenic patient, this finding is highly suggestive of an angioinvasive opportunistic infection, particularly aspergillosis. The detection of feeding and draining vessels entering the hilar aspect of a round or lobulated SPN is diagnostic of a pulmonary arteriovenous malformation, which is seen more commonly in patients with hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome).

CT NODULE ENHANCEMENT

The technique of contrast enhancement of SPNs on CT has developed as an extension

Figure 10. Cystic lucencies in bronchioloalveolar cell carcinoma. Thin-section CT scan through left upper lobe shows an irregularly marginated nodule containing small cystic lucencies. Biopsy revealed bronchioloalveolar cell carcinoma.
Figure 11. Smoothly marginated benign SPN. A. Coned-down view of right lung shows a nodule at the right base. B. Thin-section CT scan shows a smoothly marginated middle lobe nodule. Biopsy revealed a granuloma caused by *Coccidioides immitis* infection.

Figure 12. Lobulated margin in malignant SPN. Coned-down view of right upper lobe shows a 20-mm nodule with a lobulated margin. Biopsy revealed adenocarcinoma.
Figure 13. Spiculated margin in malignant SPN. CT scan at the level of the aortic arch shows a spiculated right upper lobe nodule with a pleural tail extending posteriorly to distort the major fissure. Biopsy showed adenocarcinoma.

Figure 14. Satellite nodules in granulomatous SPN. Prone CT scan before transthoracic biopsy of a radiographically detected SPN shows a cluster of small nodules in the posterior segment of the right upper lobe with a larger central nodule (arrow). Biopsy revealed granulomatous inflammation with a specific organism identified.

of the observation that malignant lung tumors are relatively hypervascular compared with benign lesions. CT nodule enhancement after intravenous contrast administration is now accomplished easily with the use of power injectors and rapid-scan acquisition with helical CT. The technique involves thin-collimated (3 mm) spiral acquisitions through a SPN between 6 and 30 mm in diameter before and after intravenous contrast injection. Scans obtained each minute for 4 minutes after contrast injection are compared with baseline unenhanced scans. An enhancement value is then determined by calculating the mean attenuation value through the center of the nodule at peak contrast enhancement and subtracting the baseline value. A recent prospective multicenter study has shown that an enhancement value of less than 15 H is virtually diagnostic of a benign lesion (i.e., the test has a high sensitivity for malignancy) (Fig. 15). The rare false-negative study is usually caused by central necrosis or a mucin-producing malignant neoplasm, such as a bronchioloalveolar cell carcinoma (Fig. 16). An enhancement value exceeding 15 H is
Figure 15. Benign nodule by contrast-enhanced SPN on CT scan. Frontal (A) and lateral (B) chest radiographs in a 54-year-old man show a subtle right lower lobe nodule seen best on the lateral film. C, Sequential contrast-enhanced scans obtained at baseline (upper left) and every minute after contrast injection (upper left, lower left, lower right, respectively) show enhancement of 5 H from baseline. Biopsy revealed a granuloma.
nonspecific because both inflammatory lesions and malignancies can enhance (Fig. 17); this limits the positive predictive value of the test to 68%.

Because of the rapid image acquisition with spiral CT, CT nodule enhancement can be performed following routine scanning of the chest without need for additional contrast administration and little additional scan time and radiation dose. The technique requires meticulous attention to detail, however, and may be less accurate in larger SPNs (i.e., those > 2 cm) because these lesions are more often necrotic and may produce false-negative examinations. The technique may prove to be most useful for the evaluation of probably benign SPNs when transthoracic needle biopsy is unavailable, cannot be performed, or is nondiagnostic and the patient is a poor surgical candidate.

**POSITRON EMISSION TOMOGRAPHY**

There is a growing experience in the use of PET using the radiopharmaceutical fluoro-2-deoxy-d-glucose (FDG) in the evaluation of focal lung lesions including SPNs. FDG uptake in focal lesions is measured semiquantitatively by calculating a standardized uptake ratio. When assessing lesions greater than 10 mm in diameter, FDG-PET has a sensitivity of 94% to 96% and a specificity of 87% to 88% for the evaluation of SPNs (Fig. 18). The low false-negative rate of PET makes this a useful adjunct to thin-section CT in excluding malignancy and allows clinical follow-up of probably benign lesions. As with CT nodule enhancement, false-positive cases are usually seen in granulomas with active inflammation. The limited availability and high expense of FDG-PET are the main obstacles to widespread use in the evaluation of SPNs. Given the increasing availability of mobile PET scanners and the reimbursement for solitary nodule evaluation and lung cancer staging currently supported by Medicare, it is likely that the use of thoracic and whole-body PET will expand well beyond academic research centers and become a mainstay of solitary nodule evaluation and lung cancer staging.

**TECHNETIUM 99m DEPOTIDE SCINTIGRAPHY**

The affinity of malignant neoplasms including both small cell and non-small cell lung
Figure 17. Positive contrast-enhanced CT nodule study. A, Coned-down view of CT scan through right upper lobe shows an SPN with a lobulated and spiculated margin. B, Sequential contrast-enhanced scans obtained at baseline (upper left) and every minute after contrast injection (upper left, lower left, lower right, respectively) shows enhancement of 41 H from baseline. Biopsy revealed adenocarcinoma.
cancer for peptide analogues of somatostatin has led to at least two studies investigating the use of this agent in the noninvasive evaluation of SPNs. In a recent multicenter study using this agent commercially available as Neotect (Diatide, Londonderry, NH), 96.6% of malignant SPNs and masses were correctly identified (Fig. 19), although the specificity of the agent for distinguishing benign from malignant lesions was only 73%.2 Because the availability of single photon emission CT is currently greater than that of FDG-PET, this agent may have some clinical use in selected patients, most typically nonsurgical candidates with irregularly shaped lesions that are not amenable to CT nodule enhancement or percutaneous biopsy.

**PATHOLOGIC DIAGNOSIS OF SOLITARY PULMONARY NODULES**

**Transthoracic Needle Biopsy**

Image-guided transthoracic needle biopsy has become the semi-invasive procedure of choice for definitive characterization of peripheral SPNs. The procedure is most often performed under CT guidance and has been shown to have a sensitivity of over 90% for malignancy in most series, particularly when expert cytopathology is used (see Fig. 2).16, 18 The ability of transthoracic needle biopsy to obtain a specific benign diagnosis for focal lung lesions is limited by difficulty in aspirating diagnostic material from sclerotic granu-
Bronchial lomas. Recently, the use of small-gauge (< 20-gauge) cutting biopsy needles has provided histologic material from SPNs and can significantly improve the yield for benign lesions to 80% or greater.11

Bronchoscopy

In a patient with a SPN and findings suggesting central airway involvement (i.e., hemoptysis or bronchus entering hilar aspect of nodule on thin-section CT), bronchoscopy with brushings, washings, and endobronchial or transbronchial biopsy or transbronchial needle aspiration is the initial diagnostic procedure of choice, and in such situations can obtain a diagnosis in up to 80% of lesions.5 The diagnostic yield from bronchoscopy differs significantly with the size and location of the lesion and the experience of the bronchoscopist, however, with yields as low as 28% in one series.24 A cooperative bronchoscopic and transthoracic approach has been shown to be effective for peripheral nodules,13 and conventional or CT fluoroscopy helps guide accurate placement of transbronchoscopic brushes and needles to improve diagnostic yield.

Video-Assisted Thoracoscopic Surgery

This technique, usually performed by surgeons in the operating room under general anesthesia with single lung ventilation, can be used as both a diagnostic and therapeutic
procedure for SPNs. The indications for video-assisted thoracoscopic surgery resection of SPNs differ considerably between institutions, but it has been shown to have higher diagnostic accuracy with less morbidity than thoracotomy.19

Thoracotomy

Thoracotomy for resection of SPNs is usually limited to lesions with a high likelihood of malignancy when lobectomy and nodal resection are necessary for definitive lung cancer staging and treatment. Additional indications include a deeply situated nodule or other lesion not amenable to thoracoscopic localization and resection or when limited pulmonary reserve necessitates limited lung resection to preserve pulmonary function.

References


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