CHAPTER

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Solitary Pulmonary Nodule: How and How Much to Investigate?

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Introduction

A solitary pulmonary nodule (SPN) is radiologically defined as an intraparenchymal lung lesion that is < 3 cm in diameter and is not associated with atelectasis or adenopathy.[1] Lung lesions > 3 cm in size are defined as lung masses. A solitary pulmonary nodule is noted on 0.09 to 0.20 per cent of all chest radiographs.[2] An estimated 150,000 such nodules are identified each year. Ninety per cent of these are incidental radiologic findings, found unexpectedly in radiographs obtained for unrelated diagnostic workups. Although the causes may include many benign conditions, bronchogenic carcinoma as a cause of solitary nodules has been increasing, especially in the elderly.[3,4] However, in developing countries, tuberculosis and fungal infections are important clinical entities in the differential diagnosis of an SPN, especially in young age, non-smokers, and immunocompromised individuals. Table 1 lists the various causes of a solitary pulmonary nodule. In patients with resected malignant nodules, survival may be as high as 80 per cent at five years; in contrast, survival rates at five years among those with advanced malignant disease remain below 5 per cent. Ideally, diagnostic approaches to pulmonary nodules would permit definitive resection when possible and avoid resection in patients with benign disease. Recent developments in the approach to pulmonary nodules include improvements in radiographic imaging, techniques to distinguish benign from malignant nodules without surgery, lung-cancer screening, and minimally invasive surgical approaches.[5] Early detection of small nodules may potentially reduce lung cancer–specific mortality.

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 2). The likelihood of lung cancer increases in direct proportion to the number of pack-years as a smoker. 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.[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. 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.[7]

Table 1 : Causes of a Solitary Pulmonary Nodule

Types of Cause	Disease Entity
Neoplastic	
Malignant	Primary pulmonary carcinoma
	Adenocarcinoma, squamous cell carcinoma, bronchioloalveolar cell
	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
	mycobacterium tuberculosis
	Fungal (*Histoplasmosis, Coccidiodomycosis, Blastomycosis, Cryptococcosis, Aspergillosis)*
	Dirofilaria immitus
	Bacterial *(Nocardia, Actinomycosis, 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

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Table 2 : Hierarchy of Likelihood Ratios for Malignancy

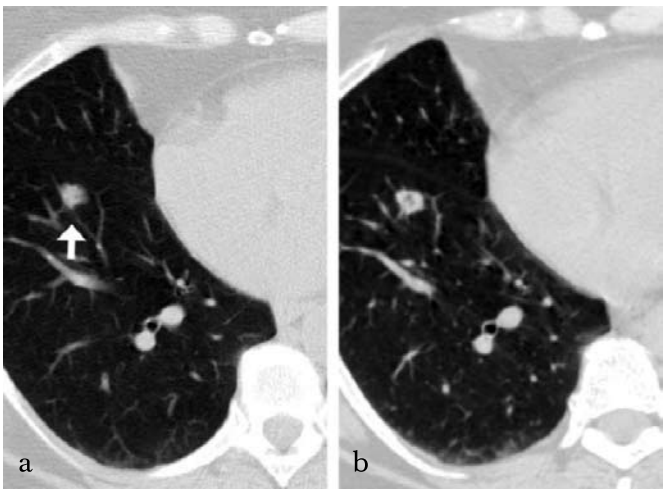
Characteristic	Likelihood Ratio
Cavity wall thickness (mm)	
> 16	37.97
> 4–16	0.72
≤ 4	0.07
Size (cm)	
> 3.0	5.23
2.1–3.0	3.67
1.1–2.0	0.74
≤ 1.0	0.52
PET standardized uptake value	
> 2.5	4.30
≤ 2.5	0.04
Age (y)	
> 70	4.16
50–70	1.90
30–39	0.24
20–29	0.05
Growth rate (d)	
> 465	0.01
7–465	3.40
< 7	0
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: Reference 11

Radiographic Evaluation of an SPN

The chest X-ray is an excellent initial tool for evaluating patients with symptoms or known pulmonary disease. However, X-rays may miss

Figure 1 : Chest CT scans (5-mm section width) in a female 48-year-old former smoker (a) scan shows a10-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.



upto 19% of SPNs and have been shown to cause substantial delay in diagnosis of lung cancer with upstaging of lesions from T1 to T2 during the delay period.[8] Spiral CT with IV contrast enhancement is the imaging modality of choice for the SPN and should be obtained on all newly diagnosed SPNs. (Figure 1)

At chest radiography, an SPN is seldom evident until it is at least 9 mm in diameter. Traditionally, absence of growth over a 2-year time period has been believed to be a reliable indicator of benign disease. Therefore, for patients with an SPN that is visible on the CXR, all previous CXRs should be reviewed. For all patients with previous CXRs, an SPN that is unchanged for > 2 years does not require further diagnostic evaluation. Benign lesions typically have a doubling time of either < 1 month or > 16 months.[9] Malignant nodules have a doubling time from anywhere from 40 to 360 days.[10] Although the optimal frequency of follow-up imaging is not known, the traditional standard of imaging at three-month intervals during the first year after a nodule is discovered and then at six-month intervals during the next year is logical, provided that high-resolution CT is used, rather than plain film radiography.

SPN Size

The size of the SPN is not a reliable predictor of benignity; 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.[11,12] 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.[13] In comparison, the Early Lung Cancer Action Project screening study showed that only 8% of lesions smaller than 1 cm in diameter were malignant.[14]

SPN Location

Lung cancer is 1.5 times more likely to occur in the right lung than in the left lung.[15] Studies have shown that 70% of lung cancers are located in the upper lobes and occur most frequently in the right lung.[16,17] Thus, one should carefully scrutinize the upper lobes when reviewing chest images, as most missed lung cancers are located in the right upper lobe. As benign nodules are equally distributed throughout the upper and lower lobes, location alone cannot be used as an independent predictor of malignancy. 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.[18]

Calcification

The most important imaging feature that can be used to distinguish benign 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%.[3,19] Popcorn calcifications are observed in one-third of hamartomas, and the other patterns are seen with histoplasmosis and tuberculosis.

Figure 2 : CT scan shows eccentric dense calcification in a right lower lobe carcinoid tumor.

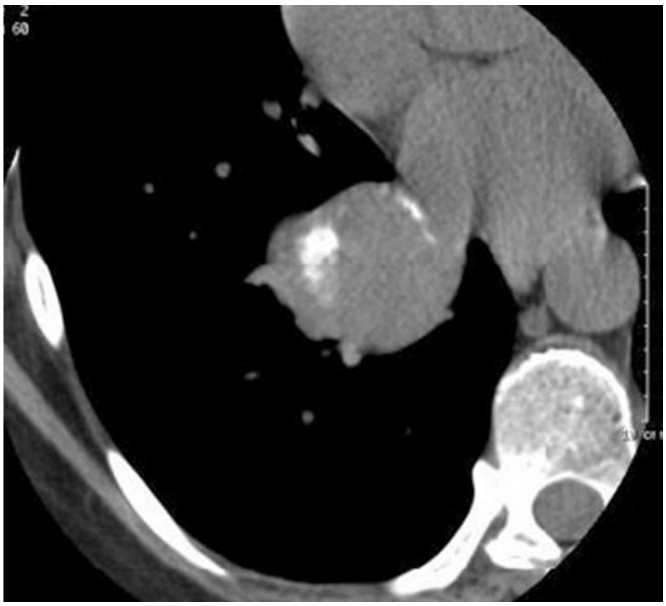
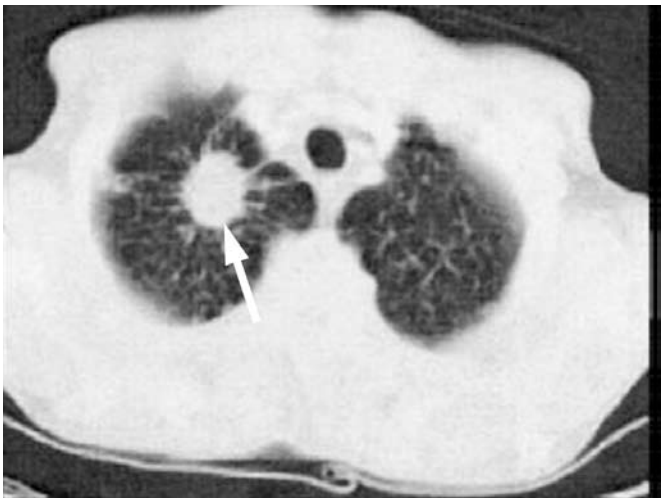


Figure 3 : CT scan showing a nodule with a corona radiata. Multiple fine striations extend perpendicularly to the surface of the nodule, which is surrounded by a radiolucent halo formed by emphysematous lung tissue.



While CT studies have shown that up to 13% of lung cancers have some calcification,[20,21] this is true of only 2% of lung cancers smaller than 3 cm in diameter.[20] 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 benign calcified lesion. (Figure 2) Furthermore, central calcification in a speculated 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. A stippled appearance or psammomatous calcification can be seen in SPNs that are metastases from mucin-secreting tumors, such as colon or ovarian cancers. With the exception of SPNs in patients with a history of bone malignancy, SPNs with a benign pattern of calcification are indeed benign.

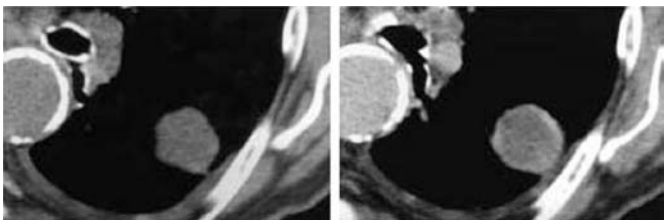
Nodule Attenuation

The advent of CT has led to improved recognition of the frequency with which nodules are nonsolid, partly solid, or solid. Approximately 34% of nonsolid nodules are due to malignancy. Malignancies such as bronchioloalveolar carcinomas or invasive adenocarcinomas with bronchioloalveolar cell features may appear to be nonsolid nodules. 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. 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. While solid nodules are usually noncancerous (granulomas), most lung cancers are found in solid nodules. Histologic types of cancerous solid nodules include adenocarcinomas and squamous cell, large-cell anaplastic, neuroendocrine, carcinoid, and (rarely) small-cell carcinomas.[22]

Margin

Two patterns of the margins of a nodule are relatively specific for cancer. One is the corona radiata sign, consisting of very fine linear strands extending 4 to 5 mm outward from the nodule,

Figure 4 : CT scan showing a solitary pulmonary nodule with regular margins before (left frame) and after (right frame) contrast administration showing enhancement of the walls indicating benignity

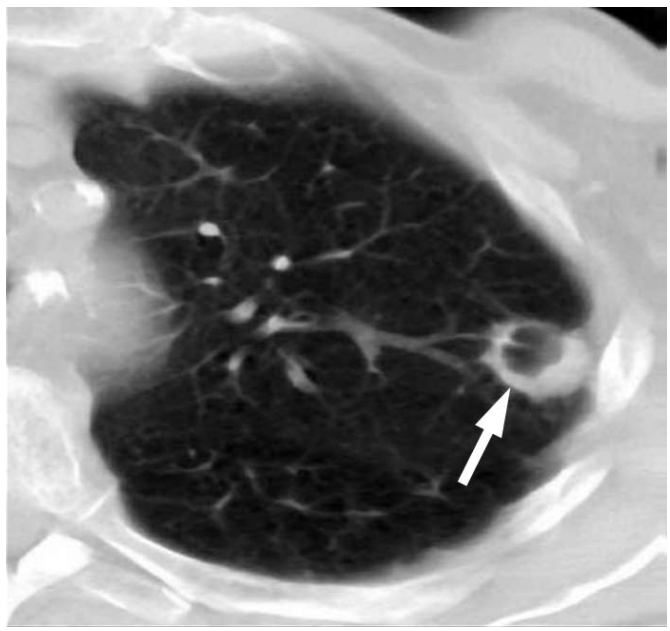


originally described on plain tomographs; they have a spiculated appearance on plain radiographs (Fig. 3). A scalloped border is associated with an intermediate probability of cancer, whereas a smooth border is more suggestive of a benign diagnosis. Edge characteristics indicative of malignancy include irregularity, spiculation, and lobulation. Nodule halos (peripheral nonsolid component) should not be confused with the corona radiata, which is a radiolucent halo associated with paracicatricial emphysema. The presence of spiculation has a predictive value for malignancy of approximately 90% and should prompt an aggressive work-up.[3,11,19] While an irregular margin is indicative of malignancy, it can occasionally be seen in granulomatous disease, lipoid pneumonia, organizing pneumonia, and progressive massive fibrosis. 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.[23] 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. Another indicator of benignity is the presence of enhancement of the wall of the nodule after contrast administration (Figure 4).[24]

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.[25] However, cavitation may be seen in SPNs as small as 7 mm in diameter (Figure 5). SPNs with irregular-walled

Figure 5 : CT scan showing a 2.5-cm left upper lobe cavitary nodule. The wall is irregular and the cavity wall is thick.

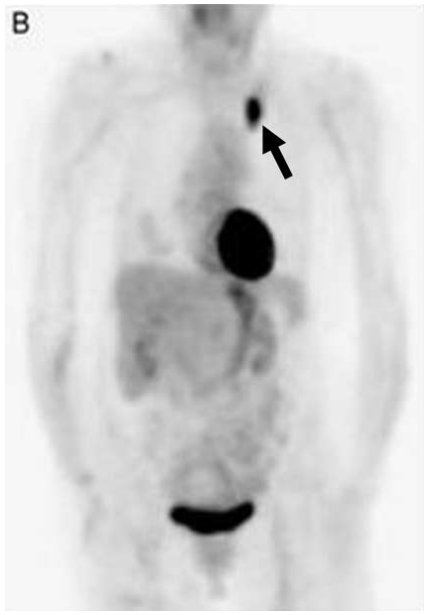


cavities thicker than 16 mm tend to be malignant (84%–95% of SPNs), while benign cavitated lesions usually have thinner smoother walls; approximately 95% of lesions with cavity walls thinner than 4 mm are benign.[26]

Positron Emission Tomography

Positron emission tomography (PET) is rapidly becoming a front-line modality in the evaluation of SPNs. Its diagnostic ability is based on increased glucose consumption of malignant cells. The radiopharmaceutical fluorine 18 fluorodeoxyglucose (FDG) is a glucose analog that is injected intravenously, transported through the cell membrane, and phosphorylated through normal glycolytic pathways, remaining unmetabolized in the cell. For solid pulmonary nodules 1–3 cm in diameter, sensitivity and specificity are approximately 94% and 83%, respectively.[27] (Figure 6) 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 ($< 5\%$).[28,29] False-positive

Figure 6 : PET scan image showing increased uptake in a nodule in the upper lobe of left lung



PET findings are associated with focal infections, inflammation, and nonneoplastic diseases (e.g., tuberculosis, sarcoidosis, and rheumatoid disease) and are more frequent in regions with endemic fungal diseases such as *Histoplasma* and *Coccidioides* infections. However, certain neoplasms, such as carcinoid and bronchioloalveolar 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.[29]

Obtaining Tissue Diagnosis

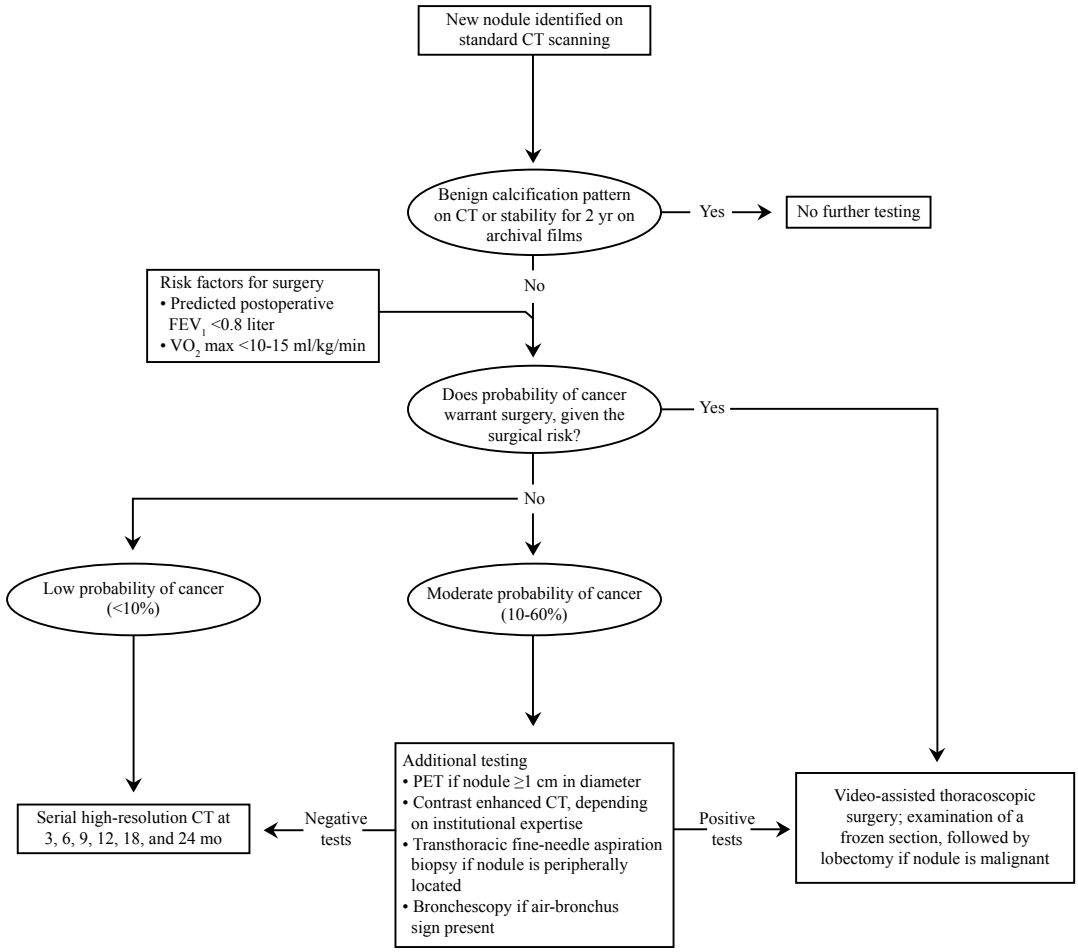
A. Transthoracic Fine-Needle Aspiration Biopsy

Transthoracic fine-needle aspiration biopsy identifies peripheral pulmonary lesions as malignant or benign in up to 95 per cent of cases. For malignant lesions, the sensitivity is 80 to 95 per cent and the specificity is 50 to 88 per cent. The positive predictive value in one study involving more than 200 patients was 98.6 per cent; the negative predictive value was 96.6 per cent.[30] Even for lesions that are less than 2 cm in diameter, transthoracic fine-needle aspiration biopsy has a sensitivity of more than 60 per cent for detecting a malignant process. However, the false negative rate is 3 to 29 per cent. Complication rates are higher than those for bronchoscopy, with an incidence of pneumothorax of up to 30 per cent, although in most cases, treatment is not required.[31,32] Unfortunately, the sensitivity of TTNA for a specific benign diagnosis is 12 to 68% but only 12% in a number of studies.[32] Adding automated cutting (core needle biopsy) to TTNA may increase the yield of a specific diagnosis of benign disease from 12 to 75%.[33] Relative contraindications to this procedure are the patient with pulmonary hypertension, coagulopathy or a bleeding diathesis, severe COPD, or vascular malformations. The most frequent complication of TTNA is pneumothorax in 25 to 30% of patients, with 5 to 10% of these patients requiring a chest tube. Pneumothorax is decreased by avoiding crossing pulmonary fissures and multiple punctures of the lung parenchyma. There can be up to a 10% incidence of hemoptysis and hemorrhage, which is increased by the use of cutting needles. Air embolus and tumor seeding are rare, 0.1% and 0.05% respectively.[34]

Bronchoscopy

The sensitivity of bronchoscopy for detecting a malignant process in a solitary pulmonary nodule ranges from 20 to 80 per cent, depending on the size of the nodule, its proximity to the bronchial tree, and the prevalence of cancer in the study population.[35,36] For nodules that are less than 1.5 cm in diameter, the sensitivity is 10 per cent, and for those that are 2.0 to 3.0 cm in diameter, it is 40 to 60 per cent. When CT reveals a bronchus leading to the lesion, bronchoscopy has 70 per cent sensitivity. Ultrathin bronchoscopy, which involves the use of fiberoptic technology in thin bronchoscopes that can reach beyond eighth-generation bronchi, has been used experimentally to allow direct visualization of peripheral lesions.

Figure 7 : Diagnostic algorithm for evaluating a solitary pulmonary nodule[40]



Surgery

The patient with an SPN that is new and does not have benign appearing calcifications should be considered to have a malignancy until proven otherwise. Surgical resection is the ideal approach, as it is both diagnostic and therapeutic. The specimen should be sent for frozen section, so that conversion to a thoracotomy and lobectomy can be performed in the same setting should the nodule prove to be NSCLC. For the surgical candidate with an SPN proven to be NSCLC, lobectomy and systematic mediastinal lymph node dissection is the standard of care for complete oncologic resection and staging.[37] Five-year survival following complete resection of stage 1A or 1B NSCLC is 65 to 80% and 50 to 60%, respectively.[38] Video-assisted thoracoscopic surgery offers the potential for lower morbidity and a shorter hospital stay than conventional thoracotomy.[39] Video-assisted thoracoscopic surgery may be most successful for the treatment of peripheral lesions and some central lesions in the lower lobe. An initial, frozen section can be examined to assist in the decision about whether to proceed with a full lobectomy. As surgical morbidity and mortality decline, the strategy of proceeding directly to video-assisted thoracoscopic surgery becomes more effective than other diagnostic approaches.

Follow-up

The patient with an SPN who does not have a tissue diagnosis and who is deemed acceptable for observation should be followed up closely for a

minimum of 2 years. This should include an initial CXR, and CT scanning at 3, 6, 12, and 24 months for best monitoring for nodule growth. There is very little objective evidence for frequency of surveillance monitoring. Figure 5 shows the general recommended scheme for workup of a patient with SPN.

Conclusions and recommendations[41]

1. For patients with an SPN that is visible on CXR, all previous CXRs should be reviewed.
2. For all patients with previous CXRs, an SPN that is unchanged for > 2 years does not require further diagnostic evaluation.
3. For patients with an SPN visible on CXR in which benign central calcification is present, no further diagnostic evaluation is necessary.
4. For patients with an SPN, a spiral CT of the chest with contrast is indicated to better characterize the nodule, parenchyma, and mediastinum. CT can be useful in identifying nodules more likely to be benign and obviate the need for further diagnostic evaluation. Additionally, chest CT plays an important role in staging (as delineated in the chapter on noninvasive staging elsewhere in these guidelines).
5. For patients with an SPN, MRI is not indicated except in these special instances.
6. For patient with an SPN _ 1 cm in size, PET scanning is not currently recommended.
7. For patients with an SPN who are surgical candidates and have a negative mediastinal evaluation on CT, PET scanning with FDG as an investigational tool, where available, may be warranted.
8. For patients with an SPN who are marginal surgical candidates, if PET scanning with FDG results are negative, a repeat CT scan is required at least once in 3 months.
9. For patients with an SPN who are marginal surgical candidates, if there are unchanged results from prior CXR and negative PET scan findings, serial follow-up is recommended, consisting of an initial CXR, and CT scanning at 3, 6, 12, and 24 months.
10. For the patients with an SPN who are operable candidates, TTNA is not indicated. Level of evidence, good; benefit, none; grade of recommendation, D. For operable patients with an SPN who decline surgical intervention, TTNA or Transbronchial needle biopsy is the preferred procedure for establishing a diagnosis.
11. For patients with an SPN who are not operable candidates, or are at high risk, TTNA may be helpful to establish tissue diagnosis.
12. For patients with an SPN, bronchoscopy is usually not indicated.
13. For operable patients with an SPN, if the lesion is amenable to a wedge resection, then a wedge resection is the procedure of choice followed by a lobectomy if the pathologic finding is positive for cancer.
14. For operable patients with an SPN, if the lesion is not amenable to a wedge resection, a diagnostic lobectomy is acceptable.
15. All pulmonary resections, anatomic or nonanatomic, must include a systematic lymph node dissection.
16. For patients with an SPN who are marginal surgical candidates, a wedge resection or segmentectomy is acceptable.
17. For patients with an SPN without a definitive tissue diagnosis, a minimum follow-up of 2 years is recommended. This should include an initial CXR, and CT scanning at 3, 6, 12, and 24 months.

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