



Diagnosis and management of peripheral lung nodule

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Abstract: A solitary pulmonary nodule (SPN) is a well-defined radiographic opacity up to 3 cm in diameter that is surrounded by unaltered aerated lung. Frequently, it is an incidental finding on chest radiographs and chest CT scans. Determining the probability of malignancy is the first step in the evaluation of SPN. This can be done by looking at specific risk factors and the rate of radiographic progression. Subsequent management is guided by the type of the nodule. Patients with solid nodules and low pretest probability can be followed radiographically; those with high probability, who are good surgical candidates, can be referred for surgical resection. When the pretest probability is in the intermediate range additional testing such as biopsy should be done. Various modalities are now available to obtain tissue diagnosis. These modalities differ in their yield and complication rate. Patients with SPN should be well informed of each approach's risks and benefits and should be able to make an informed decision regarding the different diagnostic and therapeutic modalities.

Keywords: Solitary pulmonary nodule (SPN); sub-solid nodule; ground glass nodule (GGN)

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Introduction

Solitary pulmonary nodule (SPN) is defined as a single well circumscribed radiographic opacity, up to 30 mm in diameter, surrounded by unaltered aerated lung with no associated atelectasis, hilar enlargement or pleural effusion (1,2). Lesions larger than 30 mm in diameter are called lung masses and are usually considered malignant (3).

In recent years, there has been an increase in the number of lung nodules found on imaging, both incidentally and as part of lung cancer screening programs. Incidental pulmonary nodules are found on 0.1–0.2% of routine chest radiographs (4,5) and on 13% of non-screening chest CT scans (6). In a high-risk smoker population such as the national lung cancer screening trial, the incidence increases to 9% on chest radiographs and 33% using low dose CT scan (7,8). Most of the identified SPN are benign. A final

diagnosis of malignancy is obtained in 1–12% (9-15).

Lung cancer is the leading cause of cancer death in the world (16). The 5-year survival rate of patients with lung cancer drops from 82% for stage IA to 6% for stage IV. Accordingly, timely diagnosis of lung cancer at an early stage is of essence since it results in the highest cure rate (17). It is important for the physician to evaluate the clinical and radiological risk factors to identify nodules at high risk for malignancy, thus warranting further evaluation, while avoiding unnecessary procedures for lower risk nodules.

Clinical evaluation

The focus of the clinical evaluation is to determine the presence of risk factors for malignancy and to evaluate the presence of non-malignant conditions that are associated with SPN.

Patients with SPN are usually asymptomatic. When symptoms are present, they usually reflect the underlying condition that resulted in the development of the lung nodule. In the setting of malignancy, the presence of symptoms may represent advanced metastatic disease. Risk factors such as smoking, advanced age, prior history of malignancy, interstitial lung disease, emphysema, and exposure to asbestos, uranium, and radon are associated with a higher chance of a malignant SPN (18-24).

A detailed travel history to areas with high prevalence of mycosis and tuberculosis should be obtained to rule out benign infectious etiology of SPN (25,26). In addition, autoimmune conditions such as rheumatoid arthritis and granulomatosis polyangiitis are frequently associated with pulmonary nodules and should be included in the differential diagnosis of SPN (27).

Radiographic imaging

Chest plain film

Many SPNs are now detected on CT scans but some are still seen first on chest X-ray. It is important to review prior imaging when available to determine any change in the SPN (28). A nodule that is highly calcified or has been stable in size for more than 2 years when compared to previous radiographs has a high likelihood of being benign (29). Technical innovations including bone-suppression software programs have been suggested to improve the sensitivity of chest X-ray for depicting nodules. Frequently, an SPN require further radiological evaluation (30).

CT scan

For accurate characterization of small nodules, reconstructed thin-section (≤ 1.5 mm) CT images should be obtained as it decreases the effect of volume averaging. Measurements should be expressed to the nearest whole millimeter. Routine acquisition of coronal and sagittal series is recommended as it facilitates the distinction between nodules and scars (28). Specific morphologic features such as size, attenuation, location, borders, characteristics, calcification, morphological pattern, and nodule enhancement may be helpful to differentiate benign from malignant disease (*Figure 1*).

Size

The likelihood of malignancy rises with the increase in the

diameter of a nodule. Nodules < 5 mm in diameter have a $< 1\%$ chance of malignancy. The risk increases to 6–28% for nodules between 5–10 mm and to 33–60% for lesions > 10 mm (29). In the NELSON screening study, nodules smaller than 5 mm had a 0.4% chance of being malignant which was not considered different from the risk of malignancy in a patient without nodules (30). Recent guidelines have modified the minimal size for determining the need for monitoring up to 5 mm for the BTS guidelines (6) and 6 mm for the Fleischner society guidelines (28).

Attenuation

Nodule attenuation allows the classification of the SPN into solid or sub-solid nodules. Sub-solid nodules are further divided into pure ground-glass nodules (GGN) with no solid component and partly-solid (PSN) with areas of soft-tissue attenuation interspersed with areas of ground-glass attenuation (31). Solid nodules are homogeneous and dense. Sub-solid nodules contain a portion of ground-glass attenuation that is higher than that of normal lung parenchyma and lower than that of soft tissue such that airways and vessels can be visualized through them. They may result from infection, inflammation, hemorrhage, or neoplasm. Those associated with infection may resolve quickly. Persistent sub-solid nodules are more likely to be malignant, specifically primary lung adenocarcinoma (32). To note that in a screened population, Henschke *et al.* found that sub-solid nodules were more likely to be malignant than a solid one, even when nodule size is taken into account (33).

Location

Upper lobes location of SPN is considered an independent risk factor for malignancy (34). This could be due to a higher concentration of inhaled carcinogens in the upper lobes resulting from cigarette smoking (35).

Border characteristics

A spiculated margin, often described as sunburst or corona radiata sign is associated with the highest risk of malignancy (36). It has a positive predictive value of up to 90%. Some benign conditions such as lipoid pneumonia, focal atelectasis, tuberculoma, and progressive massive fibrosis, may also have a spiculated margin (35,37).

Well-defined smooth or polygonal margins are typically seen in benign nodules but up to one-third may be malignant (2). A lobulated margin has an intermediate risk

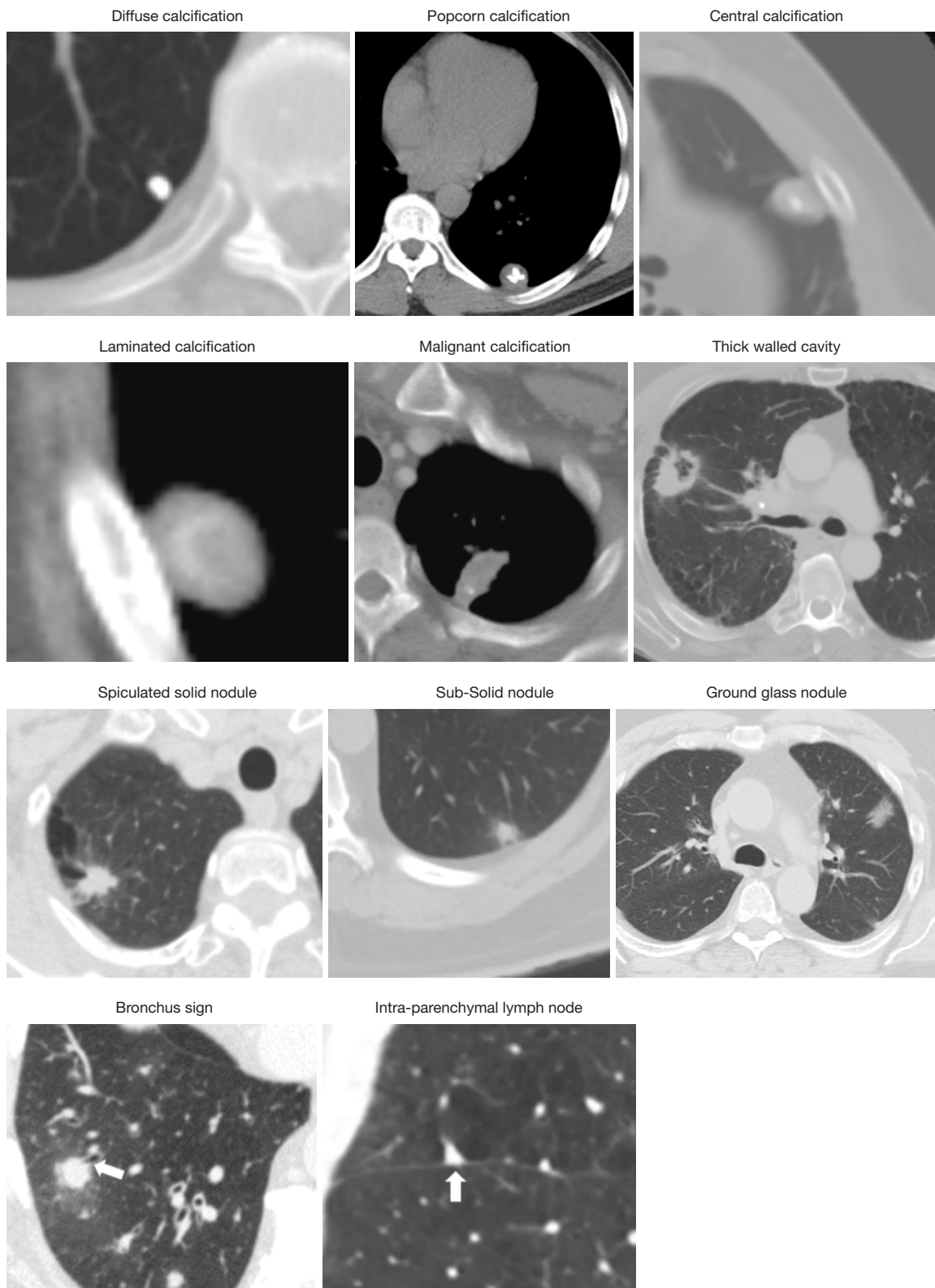


Figure 1 Radiographic findings in solitary pulmonary nodule.

for malignancy (36).

Calcifications

Common benign patterns of calcification include diffuse solid calcifications, central, lamellar, and popcorn. Diffuse, central, and lamellar patterns are typically seen in granulomatous infections whereas popcorn calcifications are seen in hamartomas. Calcifications pattern such as stippled or eccentric have been associated with malignancy (36).

Morphologic patterns

Fat attenuation between -40 to -120 Hounsfield unit (HU) is suggestive of a hamartoma. It may be seen in metastases, liposarcoma, renal cell cancer and lipoid pneumonia (38).

Cavitation occurs in both infectious and inflammatory conditions as well as malignant SPNs such as squamous cell carcinoma. Wall thickness is a helpful marker. Smooth, thin walls are typically seen in benign lesions, whereas thick, irregular walls are seen in malignant lesions. It has been reported that 95% of cavitory nodules with a wall thickness greater than 15 mm are malignant, and 92% of cavitory nodules with a wall thickness less than 5 mm are benign. A cavity wall thickness of 5–15 mm is not reliable to differentiate benign versus malignant nodules (39,40).

Nodule enhancement

SPNs that enhance more than 20 HU after the injection of intravenous contrast material are usually malignant, whereas enhancement of less than 15 HU suggests benign etiology. This technique is not helpful for nodules smaller than 5 mm as they have a higher likelihood of benignity (35).

Growth rate

Growth is an important factor to differentiate benign and malignant lesions. Growth is assessed by the volume doubling time (VDT). Since nodules are spherical structures, the volume is calculated using the equation $4\pi r^3$. Therefore, a 26% increase in the diameter results in doubling of the volume (41,42). In the NELSON screening trial, the risk of malignancy was 0.8%, 4% and 9.9% for a VDT of >600 days, 400–600 days and <400 days respectively (43). Malignant, solid SPNs usually have a VDT of 20–400 days with the majority having VDT <100 days (42). A VDT <20 days is usually reflective of an infectious process (44). Revel *et al.* reported a negative predictive value for malignancy of 98% when the VDT exceeded 500 days (45). For pure GGO and PSN, a longer VDT of 813 ± 375 and 457 ± 260 has been suggested

to document stability (46). The BTS guidelines have incorporated the VDT as part of the management of lung nodules that are 6 mm or larger (6).

Intraparenchymal lymph node (IPN)

IPN, also known as perifissural nodules (PFN), are common causes of benign SPN. On CT imaging, they have sharp borders with oval, rounded, lentiform or triangular shape. They are located below the level of the carina, within 15 mm of the fissure or the pleura. The typical IPNs have contact with interlobar septum. Atypical IPNs are nodules that either meet all above features except being attached to a visible fissure or are attached to a fissure but are convex on one side only (47,48). IPN represent dilated lymphatic channels (49). Large studies looking at long term follow up of patient of more than 4 years suggested that IPN often show larger size and can have interval growth on follow up imaging but are not malignant (50,51). Fleischner society guidelines do not recommend follow-up CT IPN, even if the average dimension exceeds 6 mm (28).

Positron emission tomography (PET)

PET is a recognized imaging modality with a capability of differentiating malignant from normal tissue based on glucose metabolism. Metabolic activity can be measured using the standardized uptake value (SUV). A high SUV indicates increased FDG uptake due to high metabolic glycolytic activity and suggests malignancy or infection/inflammation (48).

Integrated PET/CT is superior to either modality alone (52,53). Therefore, PET scan nowadays is rarely performed without a concurrent CT. In a retrospective study including nodules 7–30 mm, the sensitivity for CT, PET, and PET/CT was 93%, 69%, and 97%, respectively (54). Specificity was 31%, 85% and 85% for the 3 modalities respectively. False negative findings on PET are mainly seen in tumors with low metabolic activity (adenocarcinoma *in situ* and carcinoid tumors), small tumors (<7 –10 mm), and hyperglycemia. False positive results are often secondary to an infectious or inflammatory process (3,55). In a high-risk SPN, a negative PET/CT does not reliably exclude malignancy, and a surgical or non-surgical biopsy may still be needed. Finally, Fleischner society 2017 guidelines recommend PET/CT (along 3-month CT follow-up or biopsy) for the evaluation of SPN >8 mm regardless of pretest risk evaluation (28).

Mayo Clinic Calculator		Brock University Calculator	
Variable	Assigned value (if present)	Variable	Assigned value (if present)
Age	Value in years	Age	Value in years
Upper lobe location	1	Upper lobe location	0.6581
Nodule diameter	Value in mm	Nodule diameter	Value in mm
Spiculation	1	Spiculation	0.7729
Smoking	1	Emphysema	0.2953
Extra-thoracic cancer >5 years	1	Nodule type:	
		• GGO	0.1276
		• Subsolid	0.377
		• Solid	0
		Sex	
		• Female	0.6011
		• Male	0
		Nodule count	Number of nodules
		Family history of lung cancer	0.2961
Malignancy Probability = $100 \times e^X / (1 + e^X)$ $X = (0.0391 \times \text{age}) + (0.7917 \times \text{smoker}) + (1.3388 \times \text{cancer}) + (0.1274 \times \text{diameter}) + (1.0407 \times \text{spiculation}) + (0.7838 \times \text{upper lobe}) - 6.8272$		Malignancy Probability = $100 \times e^Y / (1 + e^Y)$ $Y = (0.0287 \times (\text{age} - 62)) + \text{sex} + \text{family history lung cancer} + \text{emphysema} - (5.3854 \times ((\text{nodule size}/10)^{-0.5} - 1.58113883)) + \text{nodule type} + \text{nodule upper lung} - (0.0824 \times (\text{nodule count} - 4)) + \text{spiculation} - 6.7892$	

Figure 2 Common models used to estimate the probability of malignancy of a solitary pulmonary nodule.

Models to estimate pretest probability of malignancy

An individualized approach is essential when an SPN is found. The selection and interpretation of subsequent tests highly depend on the SPN pretest probability of malignancy. Several factors including patients' age, smoking status, SPN characteristics (size, location, attenuation, and spiculation), family history of lung cancer or personal history of extra-thoracic malignancy, play a role in determining the pretest probability of malignancy (3,6,19,34,56).

Multiple quantitative models have been developed to help with the calculation of the pretest probability of malignancy (Figure 2). The most familiar and validated ones include the Mayo Clinic (34), the Veterans Affairs (19), and the Brock University (56) models. There is no clear evidence that any model is superior to the others. Hence, the characteristics of the targeted population should preferably guide the selection of the predictive model (3). For example, Brock University model was developed and validated based on cohorts of high-risk patients enrolled in lung cancer screening programs (smokers, and former smokers) (56). Applying this model to non-smoker patients with SPNs may lead to overestimation of their

risk of malignancy. The Mayo Clinic model may better predict the risk of malignancy in the general population with incidentally found SPNs (34). The inclusion of PET imaging (Herder model) (57) or nodule volume (58) to the Mayo Clinic risk calculator improves its predictive value.

The accuracy of most predictive models appears to be similar (59,60) if not inferior (61) to that of expert clinicians. Therefore, their additive value continues to be challenged. The British Thoracic Society (BTS) incorporated the use of predictive models (Brock and Herder) in its 2015 guidelines (6). On the other hand, the 2013 American College of Chest Physicians (ACCP) guidelines recommend estimating pretest probability for solid nodules >8 mm, but do not advise for or against using predictor tools (62). Based on these models, the probability of malignancy is usually classified into low (<5%), intermediate (5–65%) and high (>65%) (3).

Management

The Fleischner society and the BTS guidelines are the most updated and accepted guidelines for diagnosis and management of incidental pulmonary nodules management (6,28). It is to be noted that the Fleischner guidelines are not applicable for patients less than 35 year old,

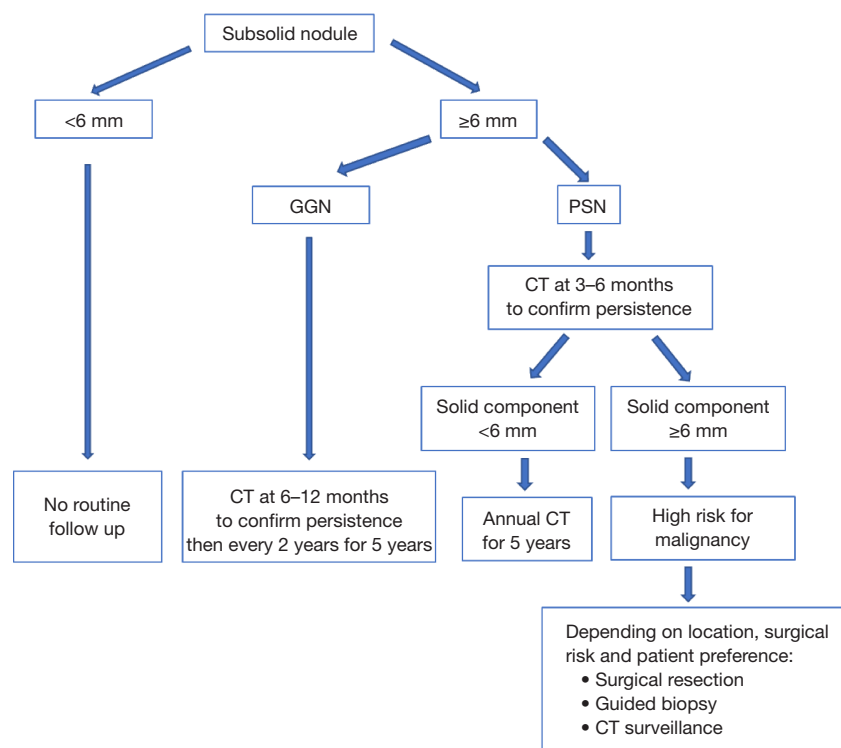


Figure 3 Suggested management of patients with a subsolid solitary pulmonary nodule. Modified from reference (28). GGN, ground glass nodule; PSN, partially solid nodule.

immunocompromised patients, or those who are already diagnosed with cancer (28). In contrast, BTS guidelines do not exclude nodules in patients with current or previously treated malignancy (6). Both guidelines recommend not to offer follow-up or further investigation for nodules with benign patterns of calcification (diffuse, central, laminated or popcorn), macroscopic fat or typical perifissural/intrapulmonary lymph node. Prior imaging studies should always be reviewed whenever available to determine possible growth or stability (6,28). These guidelines have separate recommendations for solid and sub-solid nodules and are based on nodule size and cancer risk of the patient (Figures 3,4).

Ground glass nodule (GGN)

GGN <6 mm

No routine follow-up is recommended. An optional 2–4 years follow up can be considered depending on suspicious morphology and risk factors. This recommendation comes from the Asian population data, which shows that up to 10% of such nodules can grow in size and nearly 1% may

progress to adenocarcinoma over many years (64).

GGN ≥6 mm

Follow up scanning is recommended initially at 6–12 months, then every 2 years for 5 years (after initial 6–12 months CT). An average of 3–4 years is usually required to establish growth (65,66).

Part solid nodule (PSN)

The amount of solid component is an indicator of aggressive behavior and invasive features. Nodules with solid components <6 mm represent either adenocarcinoma *in situ* or minimally invasive adenocarcinoma. Nodules with a solid component ≥6 mm have a substantial higher risk of invasiveness and metastasis and require closer follow-up (28,67).

PSN <6 mm

No routine follow up is recommended.

PSN ≥6 mm

For solitary PSN ≥6 mm, initial CT is recommended at

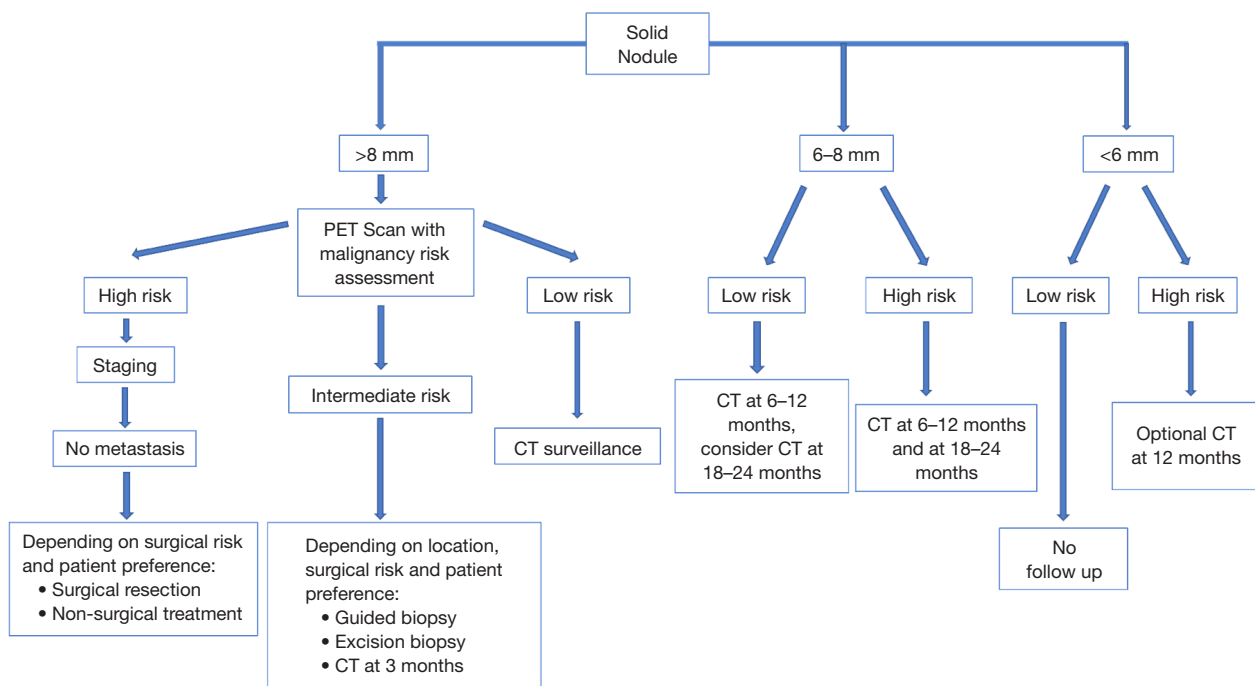


Figure 4 Suggested management of patients with a solid solitary pulmonary nodule. Modified from reference (28,63).

3–6 months to confirm persistence. When the solid component is <6 mm and the PSN is unchanged, a yearly follow up for a minimum of 5 years is recommended. PSNs with a solid component ≥ 6 mm after an initial follow-up are highly suspicious of invasive malignancy (68). For nodules with suspicious morphology, growing solid component or a solid component >8 mm, further testing with PET/CT, biopsy or surgical resection are recommended (28).

Multiple sub-solid nodules

In case of multiple sub-solid nodules, if the largest nodule is less than 6 mm, infectious causes are most likely and a CT at 3–6 months should be considered. If lesions remain persistent after an initial follow-up scan at 3–6 months, consider follow-up at 2 and 4 years. When at least one of the multiple sub-solid nodules is >6 mm, a CT at 3–6 months should be considered and subsequent management should be based on the most suspicious nodule(s).

Solid nodule

Solid nodule <6 mm

According to Fleischner guidelines, single solid nodules smaller than 6 mm (5 mm or smaller) do not require routine

follow-up in low-risk patients. In case of a solid nodule <6 mm but with high-risk factors, there is an option to follow up with a CT in 12 months. An early follow up before 12 months is not recommended in high-risk nodules <6 mm as they rarely advance in stage.

Solid nodule 6–8 mm

Solitary non-calcified solid nodules measuring 6–8 mm in patients with low clinical risk are recommended to undergo initial follow-up at 6–12 months depending on size, morphology, and patient preference. One follow up study is sufficient in most of the cases, but if the stability of the node is uncertain or morphology is suspicious, a second follow up at 18–24 months can be obtained. High-risk 6–8 mm nodules should be followed with two follow-up studies at 6–12 months and again at 18–24 months.

Solid nodule >8 mm

There is a strong recommendation about early follow up with CT scan at 3 months, PET/CT, tissue biopsy or a combination of these modalities. The use of a validated model to estimate the pretest probability of malignancy can help in guiding the management of these patients. Depending on patient preference, that management could be a follow-up in low-risk patients ($<5\%$ annual

risk), surgical resection in high risk (>65% annual risk) operable patients, or to perform additional test such as PET/CT and/or tissue sampling in patients who are considered to have an intermediate risk (6–65%) of malignancy (69).

Non-surgical biopsy

CT-guided transthoracic biopsy

CT guided transthoracic needle biopsy (TTNB) is one of the non-surgical modalities available to establish the etiology of a suspicious lung nodule. Done under CT guidance, its accuracy depends on several factors, including the size of the nodule, the number of passes and the presence of on-site pathologist. Another factor is the size of the needle used, which could be important if one suspects a lymphoma or a benign etiology. Studies looking into the value of TTNB or aspiration in establishing the diagnosis of peripheral bronchogenic carcinoma found a sensitivity of 90% (CI: 88–91%) and a specificity of 97% (CI: 96–98%) (62). While the rate of false positive is rare (average of 1%), there is a substantial false negative rate (average of 22%). Therefore, in the absence of a malignant result, a benign diagnosis is reassuring; however, a non-diagnostic result should not be used to rule out malignancy. In such cases, other diagnostic modalities, such as surgery, may be needed.

The main complications associated with TTNB include the risk of pneumothorax, pulmonary hemorrhage, infection, and rarely death. Wiener *et al.* found a low risk of hemorrhage (1%), but a risk of pneumothorax of 15% (70). However, most pneumothoraces were not substantial, with 6.6% of the patients developing a pneumothorax that necessitated a chest tube insertion. Risk factors for pneumothorax post TTNB include age, smoking, COPD, deeper location, small nodule size, number of needle passes and the need to traverse a fissure (3,70).

Conventional bronchoscopy

In the AQUIRE Registry study, bronchoscopy was diagnostic in 312/581 (53%) of peripheral lesions. The diagnostic yield for the transbronchial biopsy (TBB), needle aspiration, brushing and bronchoalveolar lavage was 43%, 47%, 38%, and 19% respectively (71). The yield of bronchoscopy is affected by the size and location of the lung nodule. A low sensitivity of 34% has been reported for peripheral lung lesions <2 cm in size, compared to 63% for lesions >2 cm (62).

Role of fluoroscopic guidance

Baaklini *et al.* described a retrospective analysis of 177 patients undergoing bronchoscopy with fluoroscopy, the diagnostic yield was found to be dependent on the location and size of the nodule (82% for central, 61% for intermediate and 53% for peripheral nodules), with particularly low yield for lesions <2 cm in the outer third of the lung (14%) (72). Aoshima *et al.* reported a diagnostic yield of 62% for malignant lesions and 12% for benign lesions, in a cohort of 208 bronchoscopy procedures carried out with fluoroscopy (73).

Oki *et al.* described a case series of 98 patients with peripheral pulmonary lesions undergoing fluoroscopic guided bronchoscopy with a 3.5 mm thin bronchoscope. The median lesion was 30.5 mm, and the overall diagnostic yield was 69% (74).

Guided bronchoscopic biopsy

Several guided bronchoscopy technologies have been developed to improve the yield of conventional bronchoscopy with TBB. These include navigational bronchoscopy such as electromagnetic navigational bronchoscopy (ENB), virtual bronchoscopy (VB), radial endobronchial ultrasound (rEBUS) with ultrathin bronchoscopy.

VB

This technology uses images from a chest CT scan to reconstruct a 3-dimensional map of the airways and the surrounding lung tissue. It is then used to create a bronchoscopic view and pathway from the trachea to the target lesion. A meta-analysis by Asano *et al.*, showed a pooled diagnostic yield of 73%. The yield was lower (67%) for smaller lesions with a diameter <2 cm (75).

ENB

The addition of electromagnetic tracking to VB allows the bronchoscopists to use these virtual roadmaps to guide instruments to the SPN. A meta-analysis of the diagnostic yield of ENB showed a pooled diagnostic yield of 65% (76). A higher yield for ENB has been associated with the presence of bronchus sign leading to the SPN (77) (*Figure 1*), a lesion >3 cm (78), an upper lobe location (79), and the use of general anesthesia compared to conscious sedation (80).

In addition, some ENB system offers the additional flexibility of performing electromagnetic navigation with transthoracic needle aspiration (ETTNA) of the target lesion when the ENB bronchoscopic results are negative.

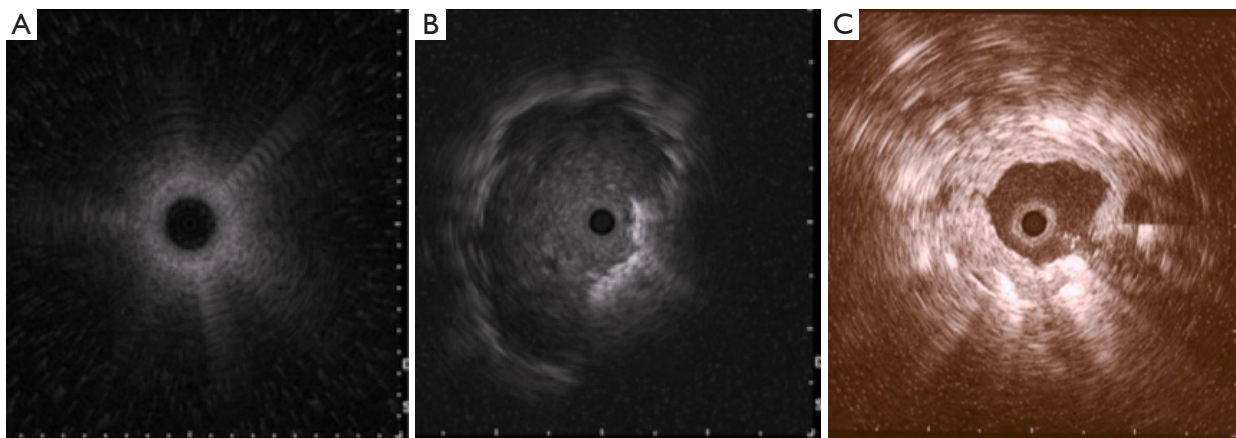


Figure 5 Radial ultrasonographic view when the probe is located in a normal lung parenchyma with a “snow- storm” appearance (A), adjacent to the nodule with an eccentric view (B), or inside the nodule with a concentric view (C).

In a study of 50 patients with varying SPN sizes, the overall diagnostic yield for such system was 83.3%. The yield was 77% for lesions without bronchus sign (81).

rEBUS

rEBUS offer real-time confirmation of the location of the SPN. The rEBUS image of normal lung parenchyma has a “snow- storm” appearance, whereas a solid lesion had a dark and “solid” appearance (*Figure 5*). The rEBUS can be used in combination with ENB or with an ultrathin bronchoscope. A recent systematic review of 57 studies and 7,872 lesions showed an overall diagnostic yield of 70.6%. The diagnostic yield was higher for lesions >2 cm in size, those associated with a bronchus sign and when the probe is located within the lesion as opposed to being adjacent to it (82,83) (*Figure 5*). A randomized study by Eberhardt *et al.* showed that ENB-assisted bronchoscopy combined with rEBUS is more sensitive than either modality alone (diagnostic yield of 88% *vs.* 69% and 59%, respectively) (79).

Ultrathin bronchoscope

This scope is much thinner than a standard flexible bronchoscope and has the ability to navigate beyond 5th or 6th order airways while retaining visualization. Ultrathin bronchoscopy is often combined with other techniques, such as VB or rEBUS for tissue sampling. Combination of rEBUS and ultrathin bronchoscopy has a reported overall diagnostic yield of 69% (84). The diagnostic yield for a lesion less than 2 cm was 36% compared with 77% for lesions larger than 2 cm.

Newer modalities

ENB biopsy is limited by the lack of real time confirmation of the location of the nodule. Intraprocedural cone-beam computed tomography (CBCT) imaging has been used to confirm the location of the lung nodule and overlay that location on live fluoroscopy imaging (augmented fluoroscopy). In a retrospective analysis of 75 patients who underwent ENB guided biopsy using intraoperative CBCT data with augmented fluoroscopy, a diagnostic yield of 83% was obtained. This yield was independent of the lesion size, location, fluoroscopic visibility or the presence of bronchus sign (85).

A robotic endoscopy system has been recently developed. It offers the potential of continuous direct visualization and precise control of the tools. In a small pilot feasibility study of 15 patients who have a suspected lesion with a bronchus sign, tissue acquisition under direct visualization was done in 14/15 (93%) patients. Cancer was confirmed in 9/15 (60%) patients, specific benign features were found in 5/15 (33%) patients and included necrotizing pneumonia, Loeffler syndrome, actinomycosis, surgical scar, and atypical mycobacteria. One patient had a non-diagnostic bronchoscopy and required surgical biopsy to confirm a malignant diagnosis. There were no reported adverse events (86).

Surgical resection

Surgical resection remains the gold standard diagnostic and therapeutic modality for suspicious pulmonary nodules. It

is indicated in cases where the suspicion for malignancy remains high despite a negative/undetermined non-surgical work-up, or if the risk of malignancy is high enough to merit proceeding directly to resection. The decision for resection has to balance the benefits of a definite diagnosis/therapy with the surgical risk.

Surgical techniques include video-assisted thoracic surgery (VATS), open thoracotomy and robotic assisted thoracoscopic surgery (RATS). Despite the lack of studies directly comparing VATS with open approach, the former is preferred, due to its less invasive and morbid nature (3,6). In a propensity matched analysis using a Medicare database, 1,195 patients who underwent VATS were compared to 1,195 patients who underwent open lobectomy. The VATS group had a significantly lower rate of morbidities including atelectasis, postoperative pneumonia and sepsis. The hospital mortality was lower for VATS compared to open thoracotomy (2.1% vs. 3.6%; $P=0.029$) but the overall 3-year survival and disease-free survival were similar (87). In a retrospective study comparing RATS, VATS and open surgery for early stage lung cancer, median length of stay was shorter in the RATS compared to VATS and open surgery (4.5 and 6 days respectively; $P<0.001$) (63). Other propensity matched analysis showed that RATS and VATS had a similar postoperative morbidity and length of stay, which were significantly lower than open thoracotomy (88,89). No significant difference in long-term survival has been found among the three groups (89).

The initial approach is to perform a wedge resection whenever possible (which may be difficult for central nodules) with intraoperative frozen section pathology. If malignancy is seen on the frozen section, more extensive resection should be attempted. The extent of the final resection (wedge resection, segmentectomy, and lobectomy) depends on the location of the nodule and the presence of comorbidities. In patients who can tolerate a lobectomy, the procedure is recommended over a sublobar resection (segmentectomy/wedge). This recommendation is primarily derived from data in early-stage lung cancer, where lobectomy was associated with a trend toward survival benefit and a decrease in the rate of recurrence, primarily locoregional recurrence (90,91).

Stereotactic body radiotherapy (SBRT)

SBRT is currently the recommended therapy for stage I non-small cell lung cancer (NSCLC) who are not surgical candidate because of their comorbidities or for those who

refuse surgery (2). In inoperable patients with early stage NSCLC, the 5-year local control rate of SBRT is reported to be above 90% (3,4). However, the efficacy of SBRT in operable patients remains unknown. Multiple randomized control trials in stage I NSCLC were closed prematurely due to low recruitment rate (5,6). A pooled analysis of 58 patients from these trials resulted in an estimated three year overall survival of 95% in the SBRT group compared to 79% in the surgery group ($P=0.037$) but the study has significant limitations (7).

Propensity score matching of retrospective data in patients with stage I–II NSCLC treated with VATS or SBRT shows mixed results. While some of these studies does not show any significant difference in the 3-year overall survival, disease free survival and freedom from local recurrence (8,9), other showed a significant advantage of VATS lobectomy compared to SBRT, with an overall five year survival of 68% vs. 37%, and recurrence free survival of 60% and 19% respectively (10).

SBRT target a small lung volume and has a low toxicity profile (3). Reported complications include grade 1 or 2 pneumonitis in 33–52% of the patients and grade 3 pneumonitis in 1% to 6%. Other minor complications such as rib pain, rib fracture, pleural effusion, hemoptysis and bacterial pneumonia have also been reported (8,9).

Functional preoperative evaluation

It is important to discuss the risks and benefits of the different therapeutic options, including surgical and non-surgical ones. Patients with low perioperative risk and high pretest probability for lung cancer may elect to proceed directly to surgery without tissue biopsy. On the other hand, patients with high perioperative risk need to be thoroughly evaluated to minimize perioperative morbidities, mortality and long-term disability.

The parameters to consider include age, the extent of planned resection, cardiac function, spirometry, diffusion capacity for carbon monoxide (DLCO), and the exercise capacity.

Post-operative mortality increases with age and with the extent of resection (92). Studies have shown a higher rate of lobectomy and sub-lobar resections in the elderly compared to younger patients with similar long term outcome (92,93). Age by itself in the absence of comorbidities does not constitute a contraindication to resection (94). The ACCP recommend to fully evaluate the functional status of all patients who are potential candidates for surgical resection

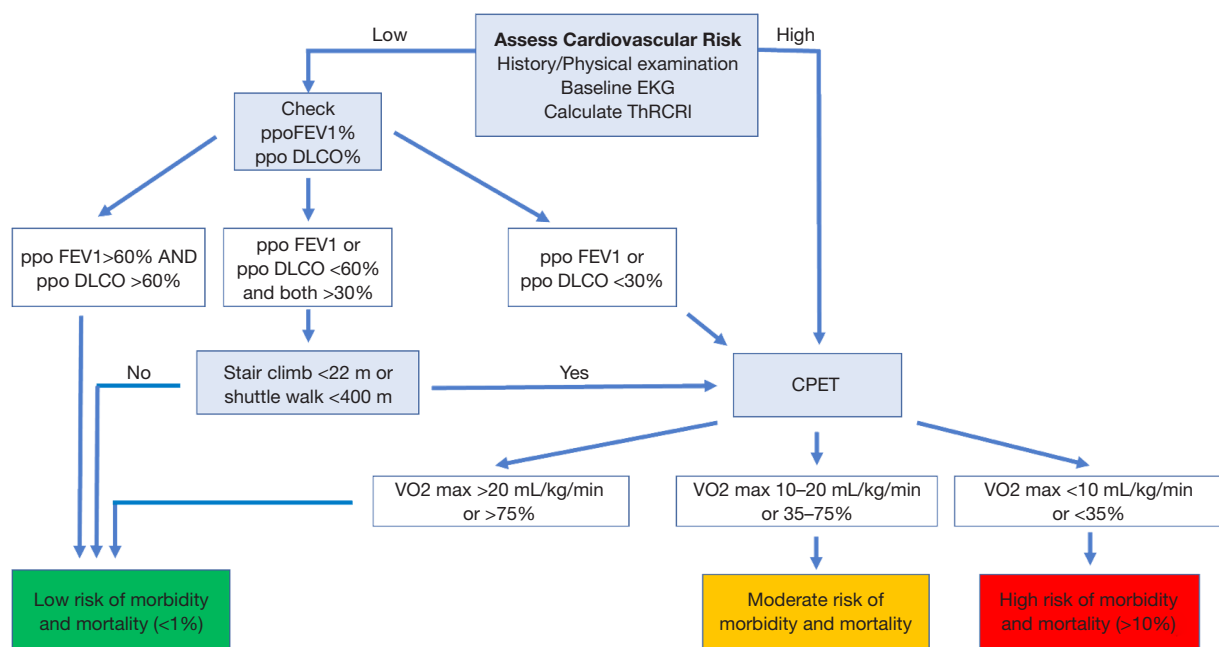


Figure 6 Pre-operative evaluation of patient with lung nodule being considered for surgical resection. Modified with permission from reference (95). ppo, predicted post-operative; CPET, cardiopulmonary exercise test; VO₂, maximal oxygen uptake.

regardless of their age (95).

The prevalence of coronary artery disease is high (11–17%) in patients with lung cancer. Cardiac consultation is recommended for patients with history of cardiac disease requiring medications, newly suspected cardiac disease, inability to climb 2 flights of stairs or a thoracic revised cardiac index (ThRCRI) ≥ 2 (96).

A lower absolute and percent predicted FEV1 has been associated with higher mortality. The BTS compiled data from more than 200 patients undergoing pulmonary resection. Using an absolute cut off value for FEV1 of >2 L for pneumonectomy and >1.5 L for lobectomy, the mortality rate was less than 5% (94). However, relying on absolute FEV1 creates a bias for older patients, women, and patients with shorter status and does not consider the functional contribution of the removed tissue.

The predicted post-operative FEV1 was shown to be a strong predictor of mortality and special attention to post-operative management is needed in patients with predicted post-operative FEV1 (ppoFEV1) of less than 30% (97). For a pneumonectomy, ppoFEV1 can be estimated using a perfusion scan by the following formula: $\text{ppoFEV1} = \text{preoperative FEV1} \times (1 - \text{fraction of total perfusion for the resected lung})$. For lobectomies, ppoFEV1 can be estimated using the following formula: $\text{ppoFEV1} = \text{pre-operative}$

$\text{FEV1} \times (1 - a/b)$ with a being the number of unobstructed segments to be resected and b the total number of unobstructed segments (98).

DLCO has been found to correlate better with post-operative death than FEV1. A DLCO $<60\%$ of predicted was found to be associated with increased mortality (99,100).

The ACCP recommends that further testing need to be done if the ppoFEV1 or ppoDLCO are expected to be less than 60% (95). If the patient is able to climb 5 flights of stairs (22 meters) or walk more than 400 meters on a shuttle walk test, the estimated operative mortality is low (1%) and he/she should be able to proceed to surgery (101). When the patient is unable to meet the above criteria, a symptom limited cardiopulmonary exercise test is recommended as it can assist in estimating the operative risk (95) (Figure 6).

Conclusions

SPN is a common finding in clinical practice. Determining the pretest probability of cancer should be the first step in the evaluation. This can be done by looking at specific risk factors such as age, smoking, location, size, type of the nodule (such as subsolid nodules), as well as the rate of progression when previous imaging are available. Validated models for risk stratification are available but clinical

estimation may be as good. Further management will depend on the size and the type of the pulmonary nodule. Patient should be well informed of each approach's risks and benefits and should be able to make an informed decision about potential diagnostic and therapeutic modalities.

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Footnote

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