

Solitary Pulmonary Nodules - What Every Clinician Should Know

Renata D'Alpino Peixoto^{1,2}, Elie Fiss¹, Tercia Tarciane de Sousa¹, Bruna do Nascimento Santos Crouzillard^{3*}, Francisco de Assis Maia Junior³, João Carlos das Neves Pereira¹, Fernando Conrado Abrão¹

¹Hospital Alemão Oswaldo Cruz, Brazil

²Universidade Nove de Julho, Brazil

³Faculdade de Ciências Médicas da Santa Casa de São Paulo, Brazil

*Corresponding author: Bruna do Nascimento Santos Crouzillard, Faculdade de Ciências Médicas da Santa Casa de São Paulo, Brazil. Tel: +551135491365; Email: bruna.crouzillard@gmail.com

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Abstract

Solitary Pulmonary Nodules (SPNs) are one of the most common thoracic radiological finding at computed tomography scans. However, dealing with SPN is challenging for both surgeons and clinicians. Differentiating a benign from a malignant nodule is usually the major question in the evaluation of SPNs as it defines the proper subsequent management. Here we describe the 3 most used recommendations from important medical societies to guide doctors in managing a SPN.

Keywords: Lung Nodule; Malignant Pulmonary Nodule; Solitary Pulmonary Nodule

Introduction

Solitary Pulmonary Nodules (SPNs) are one of the most common thoracic radiological finding at Computed Tomography (CT) scans [1] and thus, it is likely that even professionals who do not deal with pulmonary diseases will face this subject one day. SPNs are typically defined as single, small (≤ 30 mm), well-circumscribed, radiographic lesions that are completely surrounded by pulmonary parenchyma [2,3]. In addition, there must be no contact with the hilum or mediastinum, as well as no enlarged thoracic lymph nodes, atelectasis, or pleural effusion. Lesions larger than 3 cm are considered masses and are not classified as SPN. These lesions should be dealt as cancer until proven otherwise and will not be discussed in this manuscript.

According to a large American epidemiologic study including more than 200,000 patients who underwent 415,581 chest CT examinations, the frequency of nodule identification was 31%, with a rate of 6.6 per 1,000 person-years [4]. Moreover, when only the population of smokers who perform lung cancer screening is evaluated, SPNs may be incidentally encountered in more than 50% of the cases.

Dealing with SPN is challenging for both surgeons and clinicians. Although some professionals target the question only in the mere differentiation between benign and malignant lesions, it is

very important to mention that some benign lesions also require surgical resection due to bronchial obstruction or bleeding. Thus, more than the simple discussion whether a SPN is a benign or malignant lesion, there are two additional important issues that should be taken into consideration:

- Should the SPN be investigated or merely observed?
- Should it be surgically resected or not?

Differentiating a benign from a malignant nodule is usually the major question in the evaluation of SPNs as it defines the proper subsequent management. Potential harms to both health care system and individual patients may be a consequence of inappropriate SPNs evaluation. Both clinical and radiographic factors are essential in the determination of the malignancy risk. The discrimination between a benign and a malignant lesion detected at CT may be very difficult due to an overlap of radiographic characteristics such as shape, size, edge, and location within the lungs [5]. Therefore, integration of clinical and imaging information into the evaluation of the malignancy risk of a lesion is of utmost importance. When the patient is asymptomatic and there are no other radiographic abnormalities (such as hilar or mediastinal adenopathy and pleural effusion) suggestive of malignancy, management may include CT scan surveillance, nonsurgical biopsy, or surgical biopsy. In this manuscript, we aim at reviewing the risk of a SPN being malignant as well as its optimal management according to the most important guidelines in the literature.

Factors That Should be Taken into Consideration When Evaluating a SPN

Clinical aspects

Some clinical characteristics may be associated with an increased risk of a malignant SPN, such as advanced age, past or current history of smoking, asbestos exposure, prior malignancy and family history [6,7]. A retrospective study from 1974 was the first to report the association between age and the risk of malignancy. It stratified the percentage of nodules that were cancer according to age group. The risk increased from 3% among individuals aged 35-39 to more than 50% among patients older than 60 [6]. Another study including 955 resected lung nodules reported a higher proportion of malignancy in patients >50 years of age compared with younger patients (65 versus 33 percent)⁷. In fact, 65% of the lesions among individuals older than 60 years of age were malignant, most of them bronchogenic carcinoma [7]. The probability of cancer is also higher among smokers, especially current smokers. In a large trial, 3,318 heavy or long-term smokers were randomized to receive either a screening low-dose CT scan or screening chest radiograph (CXR). The cancer detection rate among screened subjects was 1.9% in the low-dose CT scan arm and 0.45% in the CXR arm, which is higher than among a non-smoker population [8].

Imaging aspects

In order to better evaluate a SPN, either a CT scan or positron emission tomography (PET-CT) may be requested. Some CT features that may be used to predict whether a nodule is malignant include size, pace of growth, border, presence of calcification, location and attenuation. The size of a nodule is typically measured as its maximum diameter. It is well known that the size is an independent predictor for malignancy as the risk of malignancy rises with increasing diameter of the nodule [9-12]. Based on a study with 1,000 pulmonary nodules, those <10 mm represented benign lesions in 67.5%. For those 10-20 mm, benign and malignant nodules shared equal probability; for >20 mm SPNs, malignant nodules represented 85% [3]. Nodule growth over time is also clearly related to the risk of harboring malignancy as SPNs that grow on serial imaging are very suspicious. Conversely, a stable SPN for two years is more likely to be benign. It is important to make every attempt to secure old imaging studies, including prior CTs (preferably) and chest radiographs, because size comparisons can be used to determine whether the nodule has been stable or growing over time.

Attenuation is another radiographic aspect of a SPN that requires attention. Solid nodules are typically homogeneous and dense while subsolid ones have less density and are further subdivided according to the presence (part-solid) or absence (ground glass) of a solid component. In fact, part-solid lesions have a higher likelihood of being malignant and are less amenable to functional imaging and biopsy [13,14]. The histology type in

part-solid or nonsolid nodules is predominantly bronchioloalveolar carcinoma or adenocarcinoma with bronchioloalveolar features, contrasting with other subtypes of adenocarcinoma found in the solid nodules [15]. Identification of a solid component increases the risk of malignancy [13].

The aspect of a SPN border, the pattern of its calcification and location in the lung also dictate the risk of malignancy. Irregular borders, especially corona radiata and speculated lesions are highly suspicious, while smooth borders carry less risk of harboring cancer [16]. Homogeneous calcification as well as central, concentric and popcorn patterns suggest a benign SPN [13]. Meanwhile, those with asymmetric calcification are more dangerous. In addition, SPNs located in the upper lobes have increased probability of being malignant [13].

Functional imaging, especially positron emission tomography (PET), may also be used in SPN to assess the risk of malignancy. Although higher Fluorodeoxyglucose (FDG)-avidity (> 2.5) increase the risk of a malignant nodule, the optimal cutoff point that accurately distinguishes benign from malignant lesions remains unknown [17]. A metabolically inactive nodule does not exclude entirely the risk of malignancy, especially when small (≤8 mm) and/or sub solid [18,19].

Differential Diagnosis of SPN

Typical causes of a malignant SPN are primary lung cancer (including lung carcinoid tumors) and lung metastases, which most commonly present as multiple pulmonary nodules. A prior history of any cancer should raise suspicion on the possibility of metastatic disease. The most common histologic subtype of primary lung cancer presenting as a SPN is adenocarcinoma, followed by squamous cell carcinoma [2]. Other causes of malignant SPN are extremely rare, including primary extra-nodal lymphoma.

In terms of benign etiologies for a SPN, the most encountered causes are infectious granulomas (80%), such as histoplasmosis, coccidioidomycosis, tuberculous and nontuberculous mycobacteria [3], which are fully-calcified on imaging. Less frequent infectious SPN are abscess-forming bacteria, *Pneumocystis jirovecii*, and dirofilariasis. Benign tumors may also present as SPN. Hamartomas are responsible for approximately 10 percent of benign nodules found in the lung and typically demonstrate focal areas of fat, alternating with calcification [3]. Benign tumors presenting as SPN may also include hemangiomas, fibromas, pneumocytomas, leiomyomas, and amyloidomas [3]. Other rare benign causes of SPN are Pulmonary Arteriovenous Malformations (PAVMs), varices, infarcts, contusion, hematoma, inflammatory lesions, rounded atelectasis, bronchogenic cyst, mucoid impaction, and pulmonary lymph nodes [3].

Management of SPNs According to Expert Groups – Guidance Through Guidelines

Although many physicians estimate the probability of malignancy of a SPN using their own clinical judgement, several quantitative prediction models exist to assist professionals in more accurately evaluating the risk of a nodule harboring cancer [11,13,20-22]. Those tools usually combine clinical and radiographic features to estimate this probability. However, they are not always easily available for the attending physician who needs to make a decision in front of the patient. Therefore, understanding the issued recommendations from important medical societies may help doctors choosing the best management strategy for a SPN.

In this review article, the discussion will be based on three of the most well-known guidelines for SPN management:

1. The first is the National Comprehensive Cancer Network Guidelines (NCCN), currently in its Version 4.2017 [23].
2. The second is the American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines in its 3rd edition [2].
3. The third is from the Fleischner Society, which is an international, multidisciplinary medical society for thoracic radiology, dedicated to the diagnosis and treatment of diseases of the chest [24].

NCCN Version 4.2017

The NCCN Guidelines Version 4.2017 states that in the presence of a suspected pulmonary nodule, the first two actions that must be taken are: multidisciplinary evaluation (including thoracic surgeons, thoracic radiologists, and pulmonologists) and smoke cessation counseling (if the patient smokes). Risk assessment includes 13 variables which divide SPNs in low or high risk for malignancy.

Seven patient criteria are used to access risk:

1. Age
2. Smoking history
3. Previous cancer history
4. Family history in first-degree relative
5. Occupational exposures: asbestos, radon or uranium
6. Other lung diseases: chronic obstructive pulmonary disease (COPD), pulmonary fibrosis
7. Exposure to infectious agents or risk factors or history suggestive of infection

NCCN Guidelines Version 4.2017 considers as high risk patients those who have a history of smoking or other known risk factors, which include history of lung cancer in a first-degree relative

or exposure to asbestos, radon, or uranium. Regarding smoking history, current or past smokers are considered at risk for developing lung cancer, while exposure to second-hand smoker is not. Although a dose-response relationship exists between smoking tobacco and the risk of developing lung cancer, there is no risk-free level of tobacco exposure. Despite cessation of smoking decreases the risk for lung cancer, former smokers are still at increased risk for lung cancer compared with never-smokers. Low risk patients are the ones with minimal or absent history of smoking or other risks. Six radiologic factors are also considered in order to classify the patient into a low or high risk group.

1. Change or stability of the nodule when compared with a previous imaging study, if available.
2. Size
3. Shape
4. Density
5. Associated parenchymal abnormalities
6. FDG avidity on PET imaging

In addition, this guideline divides recommendations based on solid or subsolid radiologic features of the nodule. Solid nodules are classified into four categories of diameter considering the cutoffs of 4, 6, and 8 mm. For subsolid nodules, the cutoff is 5 mm.

Solid nodules in low risk patients and suggested management

Solid SPNs in low risk patients are divided into 4 categories, according to the nodule diameter:

- <4 mm: no follow up needed
- 4 to ≤ 6 mm: CT at 12 months. If stable, no further follow-up needed
- 6 to ≤ 8 mm: CT at 6 and 12 months. If stable, repeat CT at 18 and 24 months
- ≥ 8 mm: CT at 3, 9 and 24 months. Consider PET CT or biopsy.

Solid nodules in high risk patients and suggested management

Solid SPNs in high risk patients are also divided into the same 4 categories as for low risk patients. However, recommendations suggest a closer follow-up:

- <4 mm: follow-up is needed; CT at 12 months. If stable, no further follow-up
- 4 to ≤ 6 mm: CT at 6 and 12 months. If stable, repeat CT at 18 and 24 months
- 6 to ≤ 8 mm: CT at 3 and 6 months. If stable, repeat CT at 9, 12 and 24 months

- ≥ 8 mm: the same recommendations as for low risk patients. CT at 3, 9 and 24 months. Consider PET CT or biopsy.

Additional attention must be taken when dealing with sub-solid nodules, as they may represent the indolent histologic spectrum of peripheral adenocarcinomas, including premalignant atypical adenomatous hyperplasia, bronchioloalveolar carcinoma and mixed subtype adenocarcinoma. For this reason, they must be followed-up for at least 3 years, biopsied or resected.

NCCN divides subsolid nodules into 3 imaging categories based on its size (≥ 5 mm or < 5 mm), presence of pure ground-glass or part-solid feature, and number of subsolid nodules, as follows:

- Solitary pure ground-glass nodules
 - < 5 mm: no further follow-up needed
 - ≥ 5 mm: CT at 3 months and annual CT for at least 3 years
- Solitary part-solid nodules
 - Persistent and solid component < 5 mm: CT at 3 months and annual CT for at least 3 years
 - Persistent and solid component ≥ 5 mm: biopsy or surgical resection
- Multiple subsolid nodules
 - Pure ground glass ≤ 5 mm: CT at 2 and 4 years
 - Pure ground glass > 5 mm, without a dominant lesion: CT at 3 months and annual CT for at least 3 years
 - Dominant nodule (s) with part-solid or solid component: CT at 3 months. If persistent, biopsy or surgical resection (especially if ≥ 5 mm and with solid component).

Despite all those recommendations, patients with a strong clinical suspicion of early stage NSCLC must be promptly operat-

ed without delay. Preoperative biopsy may be considered in cases with a strong clinical suspicion of early stage NSCLC. It should also be indicated when an intraoperative frozen-section histological diagnosis is difficult to obtain or if a non-lung cancer diagnosis is strongly suspected. In this case, the etiology of the nodule must be confirmed by percutaneous or transbronchial biopsy. When a preoperative histological diagnosis is not available, an intraoperative frozen-section analysis must be performed after a wedge resection, nodulectomy with free borders or needle biopsy before deciding to complete an oncologic lobar, bilobar or pulmonary resection with lymph node dissection.

Bronchoscopy is not usually required for treatment decisions. It may, however, be indicated in the preoperative evaluation of an airway obstruction or to verify the position of an intra-luminal lesion before choosing the level of bronchial resection.

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in Its 3rd Edition

The ACCP is one of the most known guidelines regarding the evaluation of individuals with pulmonary nodules. As the NCCN Guidelines, ACCP also consider the difference between solid, non-solid pure ground glass nodules and part-solid nodules, the stability of the lesion for at least 2 years, and its diameter. ACCP considers 8 mm as the cutoff for solid nodules (with further division into 3 categories: 4, 6 and 8 mm) and 5 mm for pure ground glass nonsolid nodules. However, for part-solid nodules, ACCP guidelines consider the cutoff of 8 mm, differently from NCCN, where 5 mm was chosen.

The ACCP guideline suggests 3 categories for the assessment of the probability of malignancy: low ($<5\%$), intermediate ($5\%-65\%$) and high ($>65\%$), based in 4 assessment criteria: clinical factors, FDG-PET scan, nonsurgical biopsy and CT scan surveillance (Table 1).

Assessment Criteria	Probability of Malignancy		
	Low ($<5\%$)	Intermediate ($5-65\%$)	High ($>65\%$)
Clinical factors alone (determined by clinical judgment and/or use of validated model)	Young, less smoking, no prior cancer, smaller nodule size, regular margins, and / or non-upper-lobe location	Mixture of low and high probability features	Older, heavy smoking, prior cancer, larger size, irregular / speculated margins, and / or upper-lobe location
FDG-PET scan results	Low-moderate clinical probability and low FDG-PET activity	Weak or moderate FDG-PET scan activity	Intensely hypermetabolic nodule
Nonsurgical biopsy results (bronchoscopy or transthoracic biopsy)	Specific benign diagnosis	Non-diagnostic	Suspicious for malignancy
CT scan surveillance	Resolution or near-complete resolution, progressive or persistent decrease in size, or no growth over ≥ 2 y (solid nodule) or $\geq 3-5$ y (subsolid nodule)	---	Clear evidence of growth

Table 1: ACCP Assessment of the probability of malignancy.

ACCP Recommendations for Solid Nodules

ACCP proposes 2 management algorithms for individuals with solid nodules: one for nodules measuring less than 8 mm in diameter and another for those with solid nodules measuring from 8 to 30 mm.

Solid nodules measuring less than 8 mm in diameter (Figure 1)

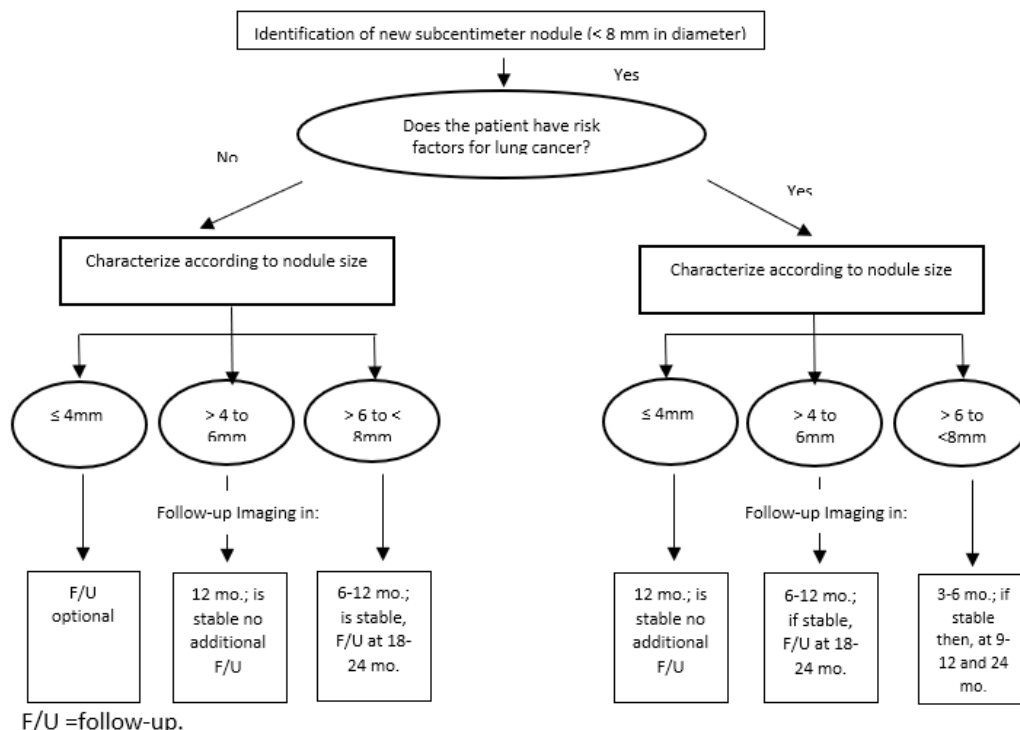


Figure 1: Management algorithm for individuals with solid nodules measuring < 8 mm in diameter.

No risk factors for lung cancer

ACCP recommendations are exactly the same as the NCCN. For an individual with a solid nodule that measures less than 8 mm in diameter and without risk factors for lung cancer, ACCP also suggests that the frequency and duration of CT surveillance must be chosen according to the size of the nodule:

- ≤ 4 mm: No follow-up needed. The patient should be informed about the potential benefits and harms of this approach.
- > 4 mm to 6 mm: Re-evaluation at 12 months without the need for additional follow-up if unchanged.
- > 6 mm to 8 mm: Re-evaluation sometime between 6 and 12 months and then again between 18 and 24 months, if unchanged.

One or more risk factors for lung cancer

As recommended by NCCN, ACCP also suggests that the frequency and duration of CT surveillance should be chosen according to the size of the nodule for patients with one or more risk factors for lung cancer:

- ≤ 4 mm: Re-evaluation at 12 months without the need for additional follow-up if unchanged.
- > 4 mm to 6 mm: Re-evaluation sometime between 6 and 12 months and then again between 18 and 24 months, if unchanged.
- > 6 mm to 8 mm: Re-evaluation sometime between 3 and 6 months, then between 9 and 12 months, and again at 24 months, if unchanged.

Solid Nodules Measuring More Than 8 Mm in Diameter (Figure 2)

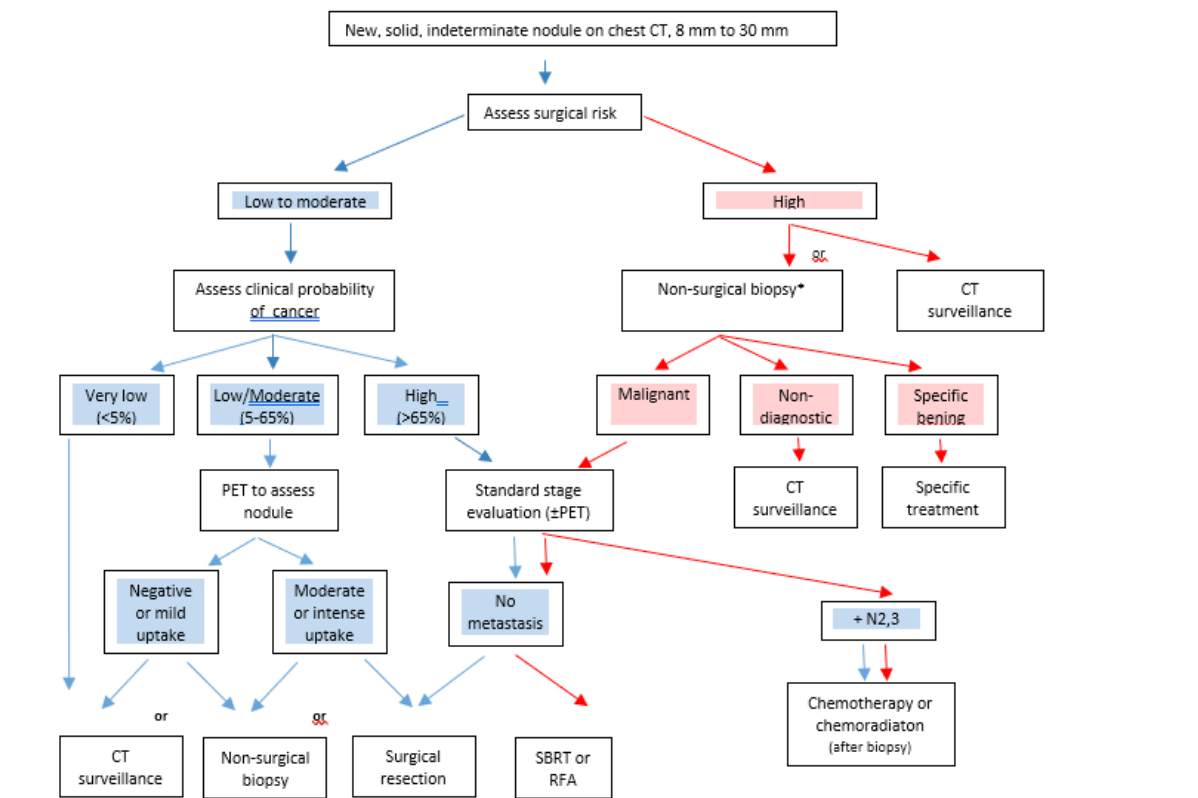


Figure 2: Management algorithm for individuals with solid nodules measuring 8 to 30 mm in diameter. Branches indicate steps in the algorithm following nonsurgical biopsy.

For patients with solid nodules measuring more than 8 mm in diameter, ACCP suggests a management algorithm based on 4 criteria:

1. Clinical probability of malignancy (very low, low-moderate or high),
2. The results of a functional imaging test (PET hypermetabolism or enhancement > 15 HUs in dynamic contrast CT)
3. Nonsurgical biopsy results
4. Fully informed patient preference

According to these 4 criteria, ACCP suggests three options to be discussed with the patient:

1. Surveillance with serial CT scans
2. Nonsurgical biopsy
3. Surgical diagnosis

Surveillance with Serial CT Scans

For individuals with a solid, indeterminate nodule that mea-

sures > 8 mm in diameter, ACCP suggests surveillance with serial CT scans in the following circumstances:

- When the clinical probability of malignancy is very low (< 5%).
- When the clinical probability is low (< 30% to 40%) and the results of a functional imaging test are negative (i.e., the lesion is not hypermetabolic by PET or does not enhance > 15 HUs on dynamic contrast CT), resulting in a very-low posttest probability of malignancy.
- When needle biopsy is non-diagnostic and the lesion is not hypermetabolic by PET.
- When a fully informed patient prefers this nonaggressive management approach.

For individuals with a solid, indeterminate nodule that measures > 8 mm in diameter who undergo surveillance, it is recommended that serial CT scans should be performed at 3 to 6, 9 to 12, and 18 to 24 months, using thin sections and non-contrast, low-dose tech-

niques. For those individuals with a solid, indeterminate nodule that shows clear evidence of malignant growth on serial imaging, nonsurgical biopsy and/or surgical resection is recommended, unless specifically contraindicated.

Nonsurgical Biopsy

For individuals with a solid, indeterminate nodule measuring > 8 mm in diameter, ACCP suggests nonsurgical biopsy in the following circumstances:

- When clinical pretest probability and findings on imaging tests are discordant.
- When the probability of malignancy is low to moderate (10% to 60%).
- When a benign diagnosis requiring specific medical treatment is suspected.
- When a fully informed patient desires proof of a malignant diagnosis prior to surgery, especially when the risk of surgical complications is high.

Surgical Diagnosis

For individuals with a solid, indeterminate nodule measuring > 8 mm in diameter, ACCP suggests surgical diagnosis in the following circumstances:

1. When the clinical probability of malignancy is high ($> 65\%$).
2. When the nodule is intensely hypermetabolic by PET or markedly positive by another functional imaging test.
3. When nonsurgical biopsy is suspicious for malignancy.
4. When a fully informed patient prefers undergoing a definitive diagnostic procedure.

For individuals with a solid, indeterminate nodule measuring ≥ 8 mm in diameter who choose surgical diagnosis, thoracoscopy to obtain a diagnostic wedge resection is recommended.

ACCP Recommendations for Nonsolid Nodules

Nonsolid nodules can be divided in two types: pure ground glass or part-solid nodule. For pure ground glass nonsolid nodule, the cutoff between categories of diameter is 5 mm as used by the NCCN guidelines. However, for part-solid nodules, the cutoff of 8 mm is used, which is different than NCCN recommendations.

Nonsolid (Pure Ground Glass) Nodules

- ≤ 5 mm: No further evaluation.

- > 5 mm: Annual surveillance with chest CT for at least 3 years.

Part-solid nodules

- ≤ 8 mm: CT surveillance at approximately 3, 12, and 24 months, followed by annual CT surveillance for an additional one to 3 years.
- > 8 mm: repeat chest CT at 3 months, followed by further evaluation with PET, nonsurgical biopsy, and/or surgical resection for nodules that persist.

Fleischner Society Guideline for Managing Solid and Subsolid SPNs

Similar to the NCCN and the ACCP, the Fleischner Society guideline for managing solid and subsolid SPNs also considers patient and radiologic factors. It includes 3 patient variables and 5 radiologic factors. The Fleischner Society guideline considers as predictive patient variables for malignancy the following three factors:

1. Older age.
2. Current or past smoking history.
3. History of extra-thoracic malignancy more than 5 years before nodule detection.

Low risk patients are those who have little or no history of smoking and no other risk factors while high risk patients are those with a history of smoking or risk factors, such as first degree relative with lung cancer, or exposure to asbestos, radon, or uranium.

In addition, the Fleischner Society guideline considers as predictive imaging variables for malignancy the following 5 factors:

1. Size
2. Spiculation
3. Upper lobe location \geq
4. PET results
5. Stability for more than two years or a benign pattern of calcification

Follow-up recommendations for patients with a solid SPN are based on two types of risk factors: low or high risk patient factor and nodule diameter (Table 2). For subsolid SPNs, only size is used for follow-up recommendations (Table 3).

Nodule Size	Low Risk *	High Risk †
≤4 mm	No follow up	Follow-up at 12 months
5-6 mm	Follow-up at 12 months	Follow-up at 6-12 months and 18-24 months
7-8 mm	Follow-up at 6-12 months and 18-24 months	Follow at 3-6 months, 9-12 months, and 24 months
>8 mm	Follow-up at 3, 9, and 24 months; consider performing contrast-enhanced CT, PET-CT, or biopsy	Follow-up at 3, 9, and 24 months; consider performing contrast-enhanced CT, PET/CT, or biopsy
*Patients who have little or no history of smoking and no other risk factors are considered low risk. †Patients with a history of smoking or other exposure or risk factor are considered high risk.		

Table 2: Fleischner Society Recommendations for Follow-up of Patients with a Solid SPN.

Nodule size	Management Recommendations	Additional Remarks
GGNA ≤5 mm	No CT follow-up	Obtain contiguous 1-mm-thick sections to confirm that nodule is truly a pure GGAN
>5 mm	Follow-up CT at 3 months to confirm persistence, then annual surveillance CT for at least 3 years	FDG PET is of limited value, is potent
PSN	Follow-up CT at 3 months to confirm persistence; if persistent and the solid component is <5 mm, yearly surveillance CT should be performed for at least 3 years; if persistent and the solid component is ≥ 5 mm, biopsy or surgical resection should be performed	Consider PET/CT for partly solid nodules >10 mm
GGAN = ground-glass appearing nodule; PSN = pure solid nodule		

Table 3: Fleischner Society Recommendations for Management of Subsolid Pulmonary Nodules.

Conclusion

Indeterminate SPNs are commonly encountered in clinical practice and often result in costly and invasive procedures that may be unnecessary. Management options for SPNs include CT surveillance, nodule sampling or resection. Despite variation among institutions and guidelines regarding optimal management strategy for nodules, there is consensus that the management be individualized to each patient after consideration of the probability of malignancy by clinical and radiographic factors, local expertise, as well as patient preference. In order to improve SPN evaluation, we recommend that physicians choose one of the aforementioned guidelines and always consider multidisciplinary discussion.

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