

Association
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The Solitary Pulmonary Nodule

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Literature review current through June 2023

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Educational Objectives:

1. Review the definition and subtypes of pulmonary nodules
2. Understand useful imaging characteristics that can be applied to medical decision making
3. Review the Fleischner Society Guidelines and their application to nodule follow up

Scenario:

Mr. Davis, a 65-year-old male with a history of COPD (FEV1 40% predicted), coronary artery disease, and diabetes, presents to your office for evaluation of a 1.5 cm ground glass right upper lobe lesion (surrounded by lung parenchyma) noted incidentally on chest x-ray. It was confirmed by a CT scan obtained during a recent admission for pneumonia. There are no calcifications noted. His recent admission was prompted by a left lower lobe consolidation and symptoms consistent with bacterial pneumonia. In addition to the RUL lesion and the LLL consolidation, his CT scan showed mild emphysema. He was treated with 7 days of levofloxacin for community-acquired pneumonia, recovered without complication, and is now back to his baseline respiratory status. He was told to follow up with a pulmonologist for this CT abnormality to discuss the next steps in management. His last imaging CXR, obtained about 13 years ago during an ER visit for chest pain, was unremarkable. He is a former smoker with a 30-pack-year history, quit smoking 6 years ago, and has no family history of lung cancer.

Question 1: How would you characterize this abnormality noted on CT scan? What are the criteria for a "solitary pulmonary nodule" (SPN) vs. a lung mass? What are the relevant sub-types of SPNs?

A SPN must be 3 cm or less and surrounded by lung parenchyma. In addition, there is typically no associated adenopathy, pleural effusions, etc. Any lesion >3 cm is considered a "mass" rather than nodule. Nodules are typically described as appearing solid or subsolid (non-solid or ground glass, allowing for visualization of pulmonary parenchyma through it or partially invisible when viewed on thin sections with mediastinal/soft tissue window). A part-solid nodule is a type of subsolid nodule with both solid and subsolid components. From the description provided, this patient would have a solitary subsolid pulmonary nodule.

Computerized Tomography Representation of Types of Nodules

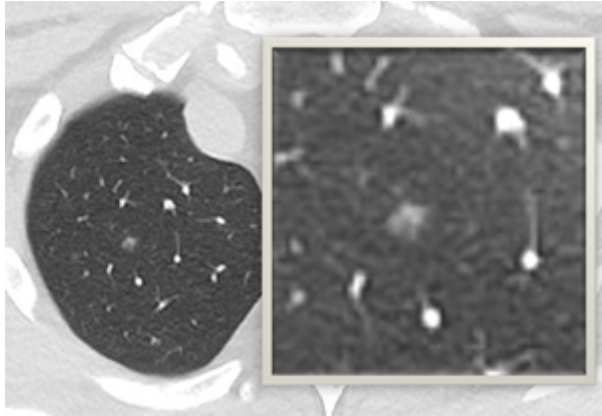


Fig 1: Right Upper Lobe Ground Glass Nodule. Magnified view provided.

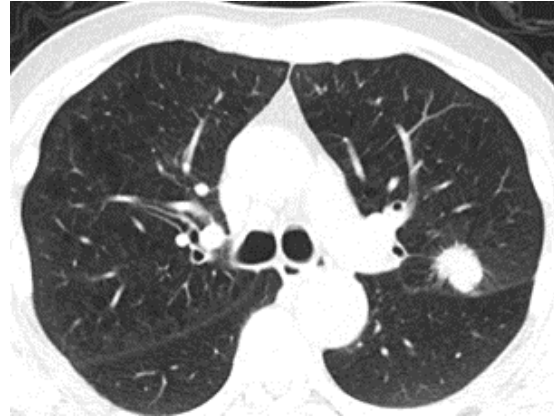


Fig 2: Left Upper Lobe Solid Nodule. Note the spiculated appearance and fissural tethering.



Fig 3: Right Lower Lobe Semi-Solid Nodule. Combination of solid and ground glass components.

Question 2: Mr. Davis asks you what this lung nodule might be. What is the differential diagnosis for an SPN?

Broad Category	Examples
Malignant: primary or metastatic	<ul style="list-style-type: none"> • Adenocarcinoma most common type of primary lung cancer presenting as SPN • Metastatic: esp. breast, head and neck, melanoma, colon, kidney, sarcoma, germ cell tumor • Carcinoid tumor can present as SPN
Granulomatous infection	<ul style="list-style-type: none"> • Tuberculosis • Non-tuberculous mycobacteria • Fungal: histoplasmosis, coccidioidomycosis
Other infections	<ul style="list-style-type: none"> • Bacterial abscess • Parasites (Dirofilaria, Echinococcus, Ascaris) • Pneumocystis
Benign Neoplasm	<ul style="list-style-type: none"> • Hamartoma • Others: fibromas, leiomyomas
Vascular	<ul style="list-style-type: none"> • Arteriovenous malformation (AVM)
Developmental	<ul style="list-style-type: none"> • Bronchogenic cyst
Miscellaneous	<ul style="list-style-type: none"> • Rheumatoid nodule • Granulomatosis with polyangiitis (GPA) • Sarcoidosis • Amyloidoma
Pulmonary nodule mimics	<ul style="list-style-type: none"> • Rounded atelectasis • Pseudotumor (loculated pleural effusion) • Mucoïd impaction

Question 3: Once you mention the possibility of cancer, Mr. Davis is very concerned. He asks you if you can tell his probability of cancer based on the CT pictures. What are helpful imaging features from CT scanning?

Clinical and imaging features are combined to predict the probability of malignancy regarding an SPN. This is done either by clinician judgment or by quantitative predictive models that have already been validated. In clinical studies, predictive models tend to overestimate the actual probability of cancer.

Imaging features that can help with malignancy prediction are:

- Size: malignancy probability increases with size (<1% for SPNs <6 mm; >50% for SPNs >2 cm).
- Type of nodule: Partially solid nodules (a combination of subsolid/ground glass and a solid component) are more likely to be malignant than pure solid or pure ground-glass nodules.
- Location: Upper lobes and right lung locations are associated with increased malignancy compared to the lower lobes and left lung, respectively
- Growth: A typical volume-doubling time of malignancy is between 20 and 400 days. One volume doubling corresponds to a 26% increase in diameter.
 - i. Solid lesion stable for 2 years: likely to be benign
 - ii. Purely subsolid lesion stable for 3 years: likely to be benign, but current recommendation (see below) suggests following for 5 years
- Shape: Smooth vs. irregular borders/spiculation
- Calcification (see next question)

Clinical features that can help with malignancy prediction are:

- Age: the risk of cancer increases significantly with age
- Smoking history: the probability of lung cancer is higher
- Other factors: family history, female sex, emphysema, prior malignancy, asbestos exposure, radon exposure

Question 4: Because Mr. Davis' nodule has some worrisome features you decide to go review his scan personally with one of the radiologists. She mentions to you that there are no calcifications seen. What does the presence or absence of calcifications indicate?

Calcifications can often but not always indicate the presence of a benign lesion. For example, calcifications described as homogenous, central, laminated or "popcorn" typically indicate a benign nodule whereas eccentric calcifications may indicate malignancy.

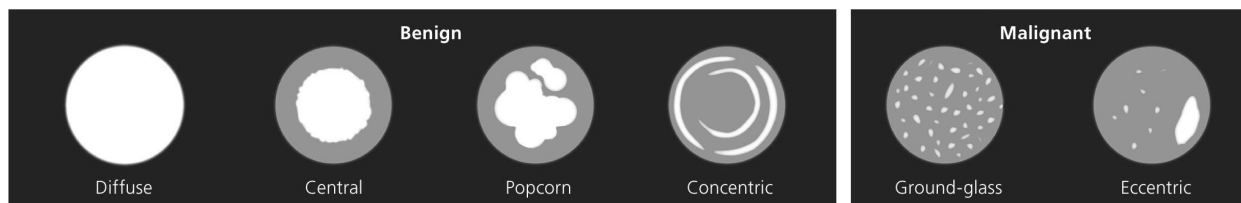


Figure from Kikano, et al. *Evaluation of the Solitary Pulmonary Nodule (calcification patterns)*

Question 5: You are now considering the next steps in the diagnostic workup for Mr. Davis. What are the current recommendations?

Based on the guidelines below, he would warrant a repeat CT scan in 6-12 months (although, given his risk factors, you may opt for the 6-month range).

Fleischner Society 2017 Guidelines for Management of Incidentally Detected Pulmonary Nodules in Adults				
A: Solid Nodules*				
Nodule Type	Size			Comments
	<6 mm (<100 mm ³)	6–8 mm (100–250 mm ³)	>8 mm (>250 mm ³)	
Single				
Low risk†	No routine follow-up	CT at 6–12 months, then consider CT at 18–24 months	Consider CT at 3 months, PET/CT, or tissue sampling	Nodules <6 mm do not require routine follow-up, but certain patients at high risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-month follow-up (recommendation 1A).
High risk†	Optional CT at 12 months	CT at 6–12 months, then CT at 18–24 months	Consider CT at 3 months, PET/CT, or tissue sampling	Nodules <6 mm do not require routine follow-up, but certain patients at high risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-month follow-up (recommendation 1A).
Multiple				
Low risk†	No routine follow-up	CT at 3–6 months, then consider CT at 18–24 months	CT at 3–6 months, then consider CT at 18–24 months	Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A).
High risk†	Optional CT at 12 months	CT at 3–6 months, then at 18–24 months	CT at 3–6 months, then at 18–24 months	Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A).
B: Subsolid Nodules*				
Nodule Type	Size		Comments	
	<6 mm (<100 mm ³)	≥6 mm (>100 mm ³)		
Single				
Ground glass	No routine follow-up	CT at 6–12 months to confirm persistence, then CT every 2 years until 5 years		In certain suspicious nodules < 6 mm, consider follow-up at 2 and 4 years. If solid component(s) or growth develops, consider resection. (Recommendations 3A and 4A).
Part solid	No routine follow-up	CT at 3–6 months to confirm persistence. If unchanged and solid component remains <6 mm, annual CT should be performed for 5 years.		In practice, part-solid nodules cannot be defined as such until ≥6 mm, and nodules <6 mm do not usually require follow-up. Persistent part-solid nodules with solid components ≥6 mm should be considered highly suspicious (recommendations 4A–4C).
Multiple	CT at 3–6 months. If stable, consider CT at 2 and 4 years.	CT at 3–6 months. Subsequent management based on the most suspicious nodule(s).		Multiple <6 mm pure ground-glass nodules are usually benign, but consider follow-up in selected patients at high risk at 2 and 4 years (recommendation 5A).

Note.—These recommendations do not apply to lung cancer screening, patients with immunosuppression, or patients with known primary cancer.
 * Dimensions are average of long and short axes, rounded to the nearest millimeter.
 † Consider all relevant risk factors (see Risk Factors).

Figure from MacMahon H, et al. Fleischner Society Guidelines 2017

Question 6: How would you proceed if Mr. Davis had a solid 1.5 cm nodule rather than a subsolid ground glass nodule?

The next steps in management are determined by surgical risk, risk of malignancy, size of the lesion, and risk for nonsurgical biopsy. Discuss these factors for Mr. Davis using the figure below.

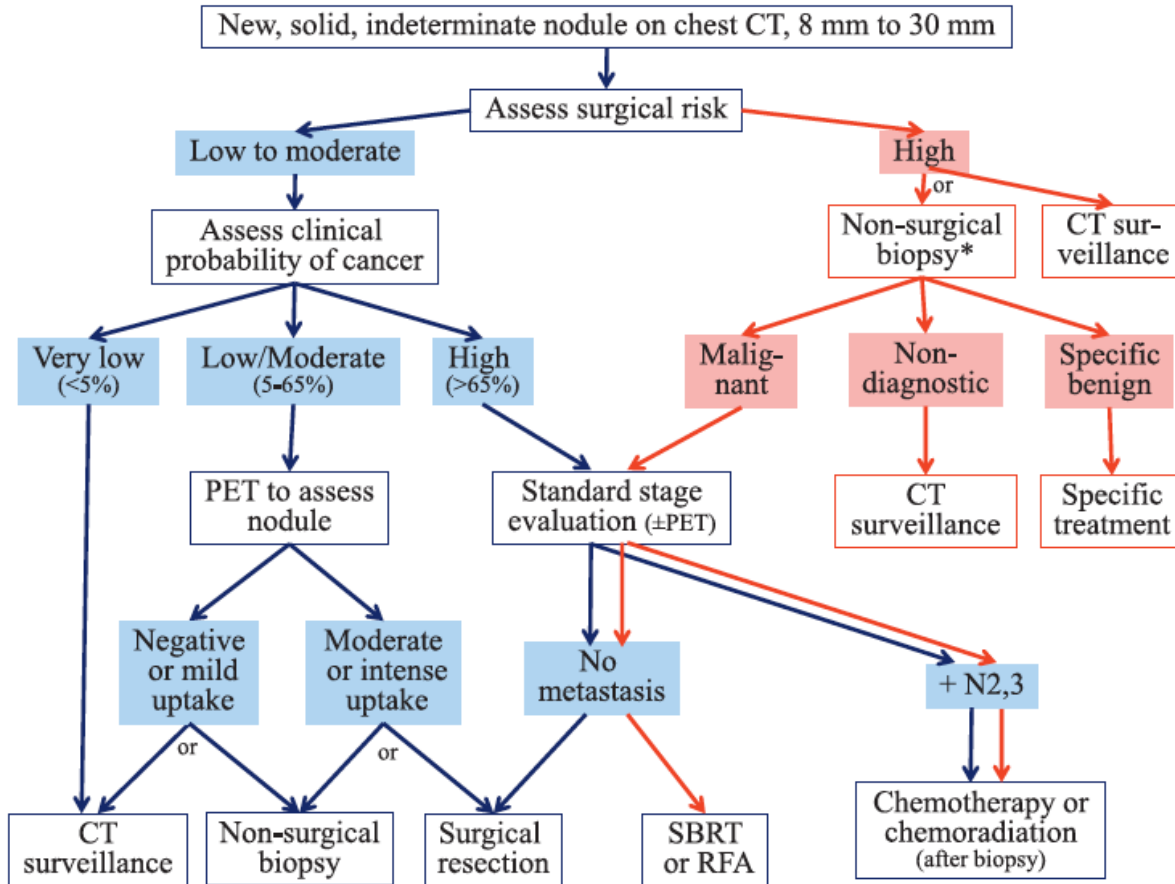


Figure borrowed from Gould MK, et al. Evaluation of Individuals with Pulmonary Nodules: When is it lung cancer? CHEST 2013.

Evaluation by a Multi-Disciplinary Conference is recommended in the management of

- 1) Appropriate diagnostic workup of indeterminate nodules
- 2) Guiding treatment in malignant nodules post-biopsy

Question 7: Given his smoking history and imaging characteristics, you estimate his risk of malignancy in the moderate to high range. However, many clinicians would still obtain a PET CT scan before surgical intervention in this case, particularly given his comorbidities. When is PET scanning potentially helpful? What are the important limitations of this testing?

- Typically, useful with solid or part-solid lesions >8-10 mm diameter
- False positive with infectious and inflammatory lesions
- False negatives with slowly growing tumors (adenocarcinoma in situ, minimally invasive adenocarcinoma, carcinoid tumors)

Question 8: If his nodule was only part-solid (>50% ground glass), what would be the recommended next steps in management?

- ≤ 6 mm diameter: no CT surveillance is required
- > 6 mm diameter: repeat chest CT at 3-6 months. If the nodule persists, then:
 - i. Solid component > 8 mm: PET
 - ii. Solid component ≤ 8 mm: repeat CT annually for 5 years

Question 9: What if Mr. Davis had multiple nodules?

- For multiple solid non-calcified nodules < 6 mm in diameter in a low-risk patient, no routine follow-up is indicated unless the patient is a high risk, then may repeat CT Chest in 12 months.
- For multiple solid non-calcified nodules, with one ≥ 6 mm in diameter in a low-risk patient, follow-up is recommended in 3-6 months, followed by an optional second scan in 18 – 24 months.
- If a larger or more suspicious nodule appears (often called a “dominant nodule”), let it guide your management plan.

Question 10: Can quantitative models be applied to determine the likelihood of malignancy?

- Yes, there are a variety of models available that have been validated; some of them have web calculators.
- Models use information like age, gender, smoking history, family history of lung cancer, presence of emphysema, as well as imaging characteristics (nodule size, type, location, number, and presence/absence of spiculation and even avidity on PET scan) to calculate the cancer probability. They are most useful in nodules between 8mm and 30mm.
- Examples of models include the Mayo Clinic model, the Veterans Association (VA) model, the Brock University model, the Herder model, and the PanCan model.
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There are not enough data to prove that one model is better. Data suggest that the prediction of malignancy by experienced physicians could be as good as these models. Considering the patient population before these predictive models are applied is important.

References:

1. Gould MK, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2013; 143(5)(Suppl):e93S-e120S.
2. Weinberger SE. Diagnostic evaluation and management of the solitary pulmonary nodule. UpToDate. Accessed at http://www.uptodate.com/contents/diagnostic-evaluation-and-management-of-the-solitary-pulmonary-nodule?source=search_result&search=solitary+pulmonary+nodule&selectedTitle=1~43 on Sept 15, 2022.
3. McWilliams A, Tammemagi MC, Mayo JR, et. al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med.* 2013; 369(10):910-9.
4. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. *Radiology* 2017; 284(1): 228-243.
5. Heuvelmans MA, Walter JE, Peters RB, Bock GH, Yousaf-Khan U, Aalst CMV, Groen HJM, Nackaerts K, Ooijen PMV, Koning HJ, Oudkerk M, Vliegenthart R. Relationship between nodule count and lung cancer probability in baseline CT lung cancer screening: The NELSON study. *Lung Cancer* 2017;113:45-50.
6. Al-Ameri A, Malhotra P, Thygesen H, Plant PK, Vaidyanathan S, Karthik S, Scarsbrook A, Callister ME. Risk of malignancy in pulmonary nodules: A validation study of four prediction models. *Lung Cancer* 2015;89(1):27-30.
7. Swensen SJ, Silverstein MD, Edell ES, TrastekVF, Aughenbaugh GL, Ilstrup DM, Schleck CD. Solitary pulmonary nodules: clinical prediction model versus physicians. *Mayo Clin Proc* 1999;74(4):319-329
8. Obayashi K, Shimizu K, Nakazawa S, Nagashima T, Yajima T, Kosaka T, Atsumi J, Kawatani N, Yazawa T, Kaira K, Mogi A, Kuwano H. The impact of histology and ground-glass opacity component on volume doubling time in primary lung cancer. *J Thorac Dis.* 2018 Sep;10(9):5428-5434. doi: 10.21037/jtd.2018.08.118. PMID: 30416791; PMCID: PMC6196174.

Pre/Post-Test Questions

1. You see a 65-year-old male who has never smoked with a history of BPH, hypertension, and chronic cough. As part of his evaluation for cough, he had a CT chest which showed multiple 3-4 mm nodules (total of 4 nodules) scattered bilaterally without any specific area of predominance. He is a never smoker and has no other known risk factors for malignancy. What do you recommend to him in terms of nodule follow-up?
 - a. Repeat CT at 3 months
 - b. Repeat CT at 6 months
 - c. PET CT scan
 - d. Surgical resection
 - e. No further follow-up is necessary
2. Which of the following is FALSE regarding the characteristics of lung nodules?
 - a. Part-solid lesions (a combination of subsolid or ground glass with a solid component) are unlikely to be malignant
 - b. The likelihood of malignancy rises significantly once a nodule is >8mm in size.
 - c. Popcorn calcifications are often but not always indicative of a benign nodule.
 - d. Irregular nodule borders increase the likelihood of malignancy.
3. An 85-year-old woman with end-stage renal failure (on dialysis), ischemic cardiomyopathy (EF 25%), severe COPD (FEV1 28%, on 4L NC home oxygen) and diabetes presents to your clinic for evaluation of a 2.5 cm smooth-bordered lung nodule. Her functional status is poor, and she can only walk across the room before becoming short of breath. She comes to see you regarding the next steps in evaluating her nodule. Which of the following would you recommend as a next step?
 - a. Limited surgical (wedge resection)
 - b. Lobectomy
 - c. Non-surgical tissue sampling via flexible bronchoscopy with EBUS
 - d. CT-guided percutaneous needle biopsy
 - e. PET scan
4. Which of these patients should you follow the Fleischner Guidelines for incidental pulmonary nodules?
 - a. A 36-year-old male with a 10mm right lower lobe lung nodule was found on a CT scan of the abdomen to evaluate abdominal pain.
 - b. A 65-year-old female with a history of lung cancer treated with LUL lobectomy 2 years ago was found to have an 8mm right upper lobe nodule on CT as part of surveillance.
 - c. A 50-year-old male with HIV-AIDS was found to have a 12mm left upper lobe lung nodule on a CT done as part of an evaluation of cough.
 - d. A 66-year-old female was found to have an 8mm right upper lobe spiculated nodule on CT as part of lung cancer screening.