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Solitary Pulmonary Nodule

12

Rachel K. McDonald and Thomas M. Ciesielski

GENERAL PRINCIPLES

- The solitary pulmonary nodule (SPN) is defined as a ≤3-cm isolated, spherical, well-circumscribed radiographic opacity completely surrounded by aerated lung without associated atelectasis, hilar enlargement, or pleural effusion.[1,2]
- A lesion >3 cm is referred to as pulmonary mass and should be considered malignant until proven otherwise.[1,3]
- Some authorities also distinguish subcentimeter nodules (<8 mm), which are much less likely to be malignant and are more difficult to characterize on imaging, as well as more difficult to approach with nonsurgical biopsy.[1,4]
- The large majority of SPNs are discovered incidentally on plain CXRs or CT scan of the chest obtained for other reasons.[5]
- The prevalence of SPNs is dependent on the characteristics of the population studied (e.g., age, smoking status, etc.) and the technique used (i.e., CXR or CT). It has been reported to range from 0.2% up to 20%,[2,3] and even up to 40–60% in lung cancer screening trials.[1]
- Importantly, long-term survival is dramatically better after resection of a malignant SPN compared with that for advanced lung cancer (80% at 5 years vs. <5% at 5 years, respectively).[3]
- The goal of the physician is to diagnose surgically curable malignant nodules before the disease is no longer surgically curable while at the same time avoiding surgery in patients with benign disease.[5]

- The causes of SPN are broad and are listed in Table 12-1.
- The rate of malignancy in patients with SPNs varies greatly depending on study population and methods of detection. Certain imaging characteristics increase the risk of malignancy; these are discussed below.

TABLE 12-1 Partial Differential Diagnosis of Solitary Pulmonary Nodule

Neoplastic	**Infectious**
Malignant	*Granulomatous*
Primary Lung Cancer	Tuberculosis
Adenocarcinoma	Nontuberculous mycobacteria
Squamous cell	Histoplasmosis
Small cell	Coccidiomycosis
Large cell	Cryptococcosis
Carcinoid	Aspergillosis
Lymphoma	Blastomycosis
Metastatic (e.g., breast, colorectal, prostate, etc.)	*Nongranulomatous*
Benign	Parasitic (e.g., ascariasis, echinococcosis, etc.)
Hamartoma	Round pneumonia
Vascular	Lung abscess/septic embolus
Arteriovenous malformation	**Other**
Hemangioma	Healed or nonspecific granulomas
Focal hemorrhage	Nonspecific inflammation or fibrosis
Pulmonary infarct	Round atelectasis
Inflammatory	Bronchogenic cyst
Sarcoidosis	Intrapulmonary lymph node
Granulomatosis with polyangiitis	Pulmonary sequestration
Rheumatoid arthritis	Amyloid

DIAGNOSIS

Clinical Presentation

The vast majority of patients with an SPN will be asymptomatic with regard to the nodule itself due to the fact that most SPNs are discovered incidentally on chest imaging obtained for another reason.[5]

History

- Age, smoking status, history of extrathoracic cancer ≥5 years before detection of the nodule, and hemoptysis are perhaps the most important historical features that increase the likelihood of malignancy.[5,6]
- Patients should also be asked about constitutional symptoms that may be due to malignancy or infection, such as fever, chills, sweats, weight loss, anorexia, weakness, fatigue, and malaise.

Physical Examination

The physical examination is usually normal with regard to the SPN. Nonetheless, a careful pulmonary examination is indicated.

Diagnostic Testing

Imaging

CXR and Chest CT findings suggestive of malignancy are as follows:

- **The likelihood of malignancy increases rapidly with size.** SPNs <1 cm are not usually malignant, but those >3 cm often are.[2,6]
- Irregular, lobulated, or spiculated margins increase the likelihood of malignancy. Smooth margins are more likely to be benign, and scalloped margins have an intermediate likelihood.[2,6,7]
- Stippled and/or eccentric calcifications are associated with malignancy.[6,7]
- Laminated, central, and diffuse calcifications suggest a granuloma (e.g., histoplasmosis or tuberculosis), while the popcorn pattern suggests hamartoma.[2]
    - Patients with obviously benign calcifications do not need to be evaluated further as benign patterns of calcification in malignant nodules are exceedingly rare.[2,6]
    - The exception to this is that benign calcification patterns can sometimes be seen in pulmonary nodules in patients with a history of

bone malignancies (e.g., osteosarcoma or chondrosarcoma).[2]

- The volume doubling time for malignant SPNs is usually between 20 and 300 days, often <100 days.[1] One doubling time equates to an approximately 30% increase in diameter.
- Based on these assumptions, most authorities agree that SPNs that are stable in size for 2 years are very unlikely to be malignant.[1,2] However, slowly growing bronchoalveolar cancers are known to exist, and they may subsequently become more aggressive. This seems to be particularly true of lesions with a ground-glass appearance; lengthier follow-up may be indicated in these cases (see below).[1,4]
- Because of the importance of growth rate, it is critical to compare current with previous CXRs or CTs.
- Upper lobe lesions, particularly on the right, are more likely to be malignant, whereas benign nodules have no predilection for a particular location in the lungs.[2]
- High-resolution chest CT is clearly more sensitive and specific for the detection and characterization of SPNs. The American College of Chest Physicians (ACCP) recommends that all patients with an indeterminate SPN on CXR have high-resolution CT of the chest performed.[4] Any prior chest CTs should be reviewed.
- In addition to the radiographic features discussed above, CT characteristics suggestive of malignancy include the following[2,4,6,8]:
    - A nodule that appears as either (1) pure ground glass or (2) mixed ground glass and solid is more often malignant than purely solid nodule.
    - Vascular convergence
    - Dilated bronchus leading into the nodule
    - Pseudocavitation
    - Thick (>15 mm), irregular-walled cavitation
    - Dynamic contrast enhancement >15 Hounsfield units (HU) on chest CT
    - Fat attenuation (−40 to −120 HU) is strongly suggestive of hamartoma or lipoma. Some metastatic malignancies (e.g., liposarcoma or renal cell carcinoma) may occasionally contain fat.
- Fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) may also be used to further characterize SPNs.
    - Reviews have estimated the sensitivity to be 87–96.8% and specificity 77.8–83%.[3,4,9]

    - Sensitivity is less for subcentimeter SPNs (<8–10 mm), and therefore it is not recommended to obtain PET imaging for evaluation of subcentimeter nodules.[4]
    - It is important to recognize that false negatives can occur; if clinical suspicion still exists, a biopsy should be strongly considered.
    - The ACCP recommends ^{18}F-FDG PET for patients with low to moderate pretest probability and an SPN >8–10 mm in size with indeterminate CT characteristics. Indeterminate nodules are defined as lacking benign calcification, lacking fat pathognomonic of hamartomas, and lacking a feeding artery or vein typical of an arteriovenous malformation.[4]
    - In some centers, PET and CT can be combined in a single scan. This may provide additional diagnostic information as PET imaging is more accurate for detecting regional lymph node metastases, which may be present in up to 21% of T1 stage lung cancers.[10]
- The ACCP recommends that clinicians estimate the pretest probability of malignancy before ordering further imaging studies or biopsy. This may be done qualitatively using all of the factors discussed above, as appropriate. Furthermore, the pretest probability of malignancy may be predicted quantitatively using one of several prediction models that have been developed. The Bayesian prediction model has been shown in some studies to be more accurate than expert opinion in determining whether a nodule is benign or malignant. This model uses the radiographic characteristics of nodule size, edge, growth rate, location, and presence or absence of benign calcifications.[11] An alternative prediction model was developed by Swensen et al. In this model, the independent predictors are age, smoking (current or past), history of cancer diagnosed ≥5 years ago, nodule diameter, spiculation, and location in upper lobe.[12] Further studies using this model have found that the addition of nodule volume has enhanced the model's predictive ability.[13]

TREATMENT

Once the clinical and imaging characteristics are known, the choice of subsequent management can be a close call between risk and benefit. Alternatives include observation with serial radiographs, additional diagnostic

workup (further imaging, nonsurgical biopsy, or a combination of the two), and surgery. Each of these has advantages and disadvantages that depend greatly on the likelihood of malignancy. **Most importantly, growth on subsequent imaging is presumptive of malignancy and requires further diagnostic evaluation rather than continued observation.**

- **Follow-up of subcentimeter pulmonary nodules:** In general, subcentimeter nodules have a low likelihood of malignancy and are therefore followed with serial imaging at time intervals determined by their initial size at discovery. The recommendations for continued evaluation of subcentimeter nodules are further determined according to their CT appearance (pure ground glass, pure solid, or mixed). The follow-up schedule recommended by the ACCP is outlined in Table 12-2.[4] Of note, the Fleischner Society, a thoracic imaging society, has guidelines that differ slightly from the ACCP.[14]
- **Follow-up Evaluation of SPNs >8 mm:** After estimating the pretest probability that an SPN is malignant, the decision must be made whether to further evaluate the nodule with additional imaging, nonsurgical biopsy, or surgical resection. Again, the Fleischner Society guidelines will differ slightly.[14]
    - **Observational follow-up consists of serial high-resolution CT scans at 3, 6, 12, and 24 months**. If the lesion is stable after 2 years, the risk of malignancy is very low. However, any evidence of growth is presumptive evidence of malignancy. Observation is appropriate for nodules in the following scenarios[2]:
        - Nodules with a very low likelihood of malignancy (<5%)
        - Nodules with low likelihood (<30–40%) of malignancy and a negative ^{18}F-FDG PET scan or dynamic contrast enhancement of <15 HU on chest CT
        - Nondiagnostic needle biopsy and a negative ^{18}F-FDG PET scan
        - Patients who decline aggressive evaluation
    - Biopsy is recommended for SPNs >8–10 mm in patients who would be appropriate candidates for surgical cure when[2]:
        - There is low to moderate probability of malignancy (6–28%).
        - The clinical likelihood of malignancy and results of imaging studies are not in agreement (e.g., high clinical suspicion but a negative ^{18}F-FDG PET scan).
        - A specific treatment is available for a benign diagnosis (e.g.,

fungal infection)
    - The patient wants biopsy confirmation prior to committing to surgery.
- **Usually the preferred biopsy technique is CT-guided transthoracic needle aspiration (TTNA)**, especially for more peripheral lesions. The most common complication of TTNA is development of a pneumothorax. However, the reported rate of pneumothorax development is variable, ranging from 15 to 40%.[2,3] Fortunately, chest tubes are only required in 4–18% of pneumothoraces caused by TTNA.[1–3] One limitation of TTNA is that the patient must be able to lie still for >30 minutes, perform a breath hold, and withhold from coughing during the duration of the procedure.[2]
- Bronchoscopic biopsy may be a viable alternative in specific situations (e.g., central lesions, lesions adjacent to a bronchus, an air bronchogram in the lesion) and when there is available expertise.[3] Electromagnetic navigation bronchoscopic biopsy is an emerging technique for peripheral lesions.

TABLE 12-2 Recommendations for Follow-up CT Imaging of Subcentimeter Pulmonary Nodules

Nonsolid Nodules (pure ground glass)	**Timing of Follow-Up**	
≤5 mm	No follow-up	
>5 mm	Annual CT for 3 years	
Partly Solid Nodules (>50% ground glass)	**Timing of Follow-Up**	
≤8 mm	Repeat CT at 3, 12, and 24 mo followed by annual CT for additional 1–3 years	
>8 mm	Repeat CT at 3 mo, then PET or nonsurgical biopsy or surgical resection for nodules that persist	
Solid Nodules	**Timing of Follow-Up**	
	No Lung Cancer Risk Factors[a]	**Risk Factors for Lung Cancer Present**
≤4 mm	Optional follow-up	12 mo, none further if stable
4–6 mm	12 mo, none further if stable	6–12 mo, if stable 18–24 mo
>6–8 mm	6–12 mo, if stable 18–24 mo	3–6 mo, 9–12 mo, and 24 mo if stable

[a]Major risk factors: smoking (current or past), history of radiation therapy, environmental toxin exposure

Adapted from Gould MK, Donington J, Lynch WR, et al. Evaluation of patients with pulmonary nodules: when is it lung cancer? Diagnosis and Management of Lung Cancer, 3rd edition: ACCP evidence-based clinical practice guidelines. *Chest* 2013;143(Suppl):e93S–e120S.

Surgical Management

Surgical management is recommended for indeterminate SPNs of >8–10 mm in appropriate surgical candidates when the clinical likelihood of malignancy is moderate to high, the ^{18}F-FDG PET is positive, a nonsurgical biopsy is suspicious for malignancy, or the patient prefers to undergo a definitive procedure.[1,4,15]

- Thoracotomy is the most definitive approach, particularly for more centrally located SPNs that are not accessible by other techniques. Operative mortality for the removal of malignant nodules is ~3–7%,

although it is <1% for resection of benign nodules.[3]

- Video-assisted thorascopic surgery (VATS) is a minimally invasive technique with a lower mortality rate, about 1%. It is usually the preferred method for SPNs in the peripheral third of the lung. In about 12% of cases, the procedure must be converted to a traditional thoracotomy.

REFERENCES

1. Ost DE, Gould MK. Decision making in patients with pulmonary nodules. *Am J Respir Crit Care Med* 2012;185:363–72.
2. Winer-Muram HT. The solitary pulmonary nodule. *Radiology* 2006;239:34–49.
3. Ost D, Fein AM, Feinsilver SH. Clinical practice. The solitary pulmonary nodule. *N Engl J Med* 2003;348:2535–42.
4. Gould MK, Donington J, Lynch WR, et al. Evaluation of patients with pulmonary nodules: when is it lung cancer? Diagnosis and Management of Lung Cancer, 3rd edition: ACCP evidence-based clinical practice guidelines. *Chest* 2013;143(Suppl):e93S–120.
5. Swensen SJ, Silverstein MD, Edell ES, et al. Solitary pulmonary nodules: clinical prediction model versus physicians. *Mayo Clin Proc* 1999;74:319–29.
6. Gurney JW. Determining the likelihood of malignancy in solitary pulmonary nodules with Bayesian analysis. Part I. Theory. *Radiology* 1993;186:405–13.
7. Jeong YJ, Yi CA, Lee KS. Solitary pulmonary nodules: detection, characterization, and guidance for further diagnostic workup and treatment. *Am J Roentgenol* 2007;188:57–68.
8. Swensen SJ, Viggiano RW, Midthun DE, et al. Lung nodule enhancement at CT: multicenter study. *Radiology* 2000;214:73–80.
9. Wahidi MM, Govert JA, Goudar RK, et al. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer? ACCP evidence-based clinical practice guidelines, 2nd ed. *Chest* 2007;132:94S–107.
10. Gould MK, Maclean CC, Kuschner WG, et al. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. *JAMA* 2001;285:914–24.
11. Gurney JW, Lyddon DM, McKay JA. Determining the likelihood of malignancy in solitary pulmonary nodules with Bayesian analysis. Part II. Application. *Radiology* 1993;186:415–22.
12. Swensen SJ, Silverstein MD, Ilstrup DM, et al. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. *Arch Intern Med* 1997;157:849–55.
13. Mehta HJ, Ravenel JG, Shaftman SR, et al. The utility of nodule volume in the context of malignancy prediction for small pulmonary nodules. *Chest* 2014;145:464–72.
14. MacMahon H, Austin JHM, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005;237:395–400.
15. Patel VK, Naik SK, Naidich DP, et al. A Practical Algorithmic Approach to the Diagnosis and Management of Solitary Pulmonary Nodules. *Chest* 2013;143:840–6.