Evidence for the Treatment of Patients With Pulmonary Nodules: When Is It Lung Cancer?*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **The solitary pulmonary nodule (SPN) is a frequent incidental finding that may represent primary lung cancer or other malignant or benign lesions. The optimal management of the SPN remains unclear.**

Methods: **We conducted a systematic literature review to address the following questions: (1) the prevalence of SPN; (2) the prevalence of malignancy in nodules with varying characteristics (size, morphology, and type of opacity); (3) the relationships between growth rates, histology, and other nodule characteristics; and (4) the performance characteristics and complication rates of tests for SPN diagnosis. We searched MEDLINE and other databases and used previous systematic reviews and recent primary studies.**

Results: **Eight large trials of lung cancer screening showed that both the prevalence of at least one nodule (8 to 51%) and the prevalence of malignancy in patients with nodules (1.1 to 12%) varied considerably across studies. The prevalence of malignancy varied by size (0 to 1% for nodules < 5 mm, 6 to 28% for nodules 5 to 10 mm, and 64 to 82% for nodules > 20 mm). Data from six studies of patients with incidental or screening-detected nodules showed that the risk for malignancy was approximately 20 to 30% in nodules with smooth edges; in nodules with irregular, lobulated, or spiculated borders, the rate of malignancy was higher but varied across studies from 33 to 100%. Nodules that were pure ground-glass opacities were more likely to be malignant (59 to 73%) than solid nodules (7 to 9%). The sensitivity of positron emission tomography imaging for identifying a malignant SPN was consistently high (80 to 100%), whereas specificity was lower and more variable across studies (40 to 100%). Dynamic CT with nodule enhancement yielded the most promising sensitivity (sensitivity, 98 to 100%; specificity, 54 to 93%) among imaging tests. In studies of CT-guided needle biopsy, nondiagnostic results were seen approximately 20% of the time, but sensitivity and specificity were excellent when biopsy yielded a specific benign or malignant result.**

Conclusions: **The prevalence of an SPN and the prevalence of malignancy in patients with an SPN vary widely across studies. The interpretation of these variable prevalence rates should take into consideration not only the nodule characteristics but also the population at risk. Modern imaging tests and CT-guided needle biopsy are highly sensitive for identifying a malignant SPN, but the specificity of imaging tests is variable and often poor.** ***(CHEST 2007; 132:94S–107S)***

Key words: CT imaging; diagnosis; lung cancer; MRI; prevalence; solitary pulmonary nodule

Abbreviations: BAC = bronchioloalveolar carcinoma; HRCT = high-resolution CT; PET = positron-emission tomography; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SPN = solitary pulmonary nodule; VDT = volume doubling time

The solitary pulmonary nodule (SPN) is defined as a spherical radiographic opacity that measures up to 3 cm in diameter and is completely surrounded by lung tissue. Because of the widespread use of CT in the investigation of respiratory symptoms, the SPN is a frequent incidental finding. The cause of SPN ranges from lung cancer and metastases from an extrathoracic primary malignancy to infections, scar formation, and other benign lesions. As imaging techniques improve and more nodules are detected, the optimal management of SPN remains unclear. Current strategies include radiographic follow-up, tissue sampling, or surgical resection. Although surgical resection for early stage lung cancer offers potentially curative treatment and the best chance of survival, it is not free of complications and may not be necessary in a significant number of patients with benign SPNs. Evidence-based clinical decision making must incorporate data on the prevalence of SPNs and malignancy in a representative patient population, the radiographic characteristics of the nodule, and the demographic and clinical factors of the patient. We conducted a systematic review to address the following questions: (1) what is the prevalence of SPNs; (2) what is the prevalence of malignancy in nodules with varying characteristics (size, morphology, and type of opacity); (3) what are the relationships between growth rates, histology, and other nodule characteristics; and (4) what are the performance characteristics and complication rates of tests for SPN diagnosis?

Materials and Methods

The review methods were defined prospectively in a written protocol. The SPN Guideline Subcommittee, who authored the accompanying guideline, was consulted. Primary outcomes included prevalence of SPNs, stratified by smoking status, age, and other risk factors; prevalence of malignancy associated with specific nodule characteristics; histologic type and growth rates associated with specific nodule characteristics; diagnostic accuracy (sensitivity, specificity) of tests to determine whether a nodule is malignant; and complication rates of those diagnostic procedures. Secondary outcomes included changes in patient treatment or patient outcomes after diagnostic test or intervention.

Electronic database searches of MEDLINE (through August 19, 2005) and the Cochrane Library (through third quarter 2005) were conducted. The search was limited to English-language articles published since 1995. Additional and older citations were sought through consultations with experts and by identifying citations from included articles, review articles,[1,2] and practice guidelines.[3]

We sought observational studies as well as diagnostic test evaluation studies (question 4) and, when available, experimental studies, such as randomized, controlled trials, that compared the diagnostic interventions of interest. For studies of diagnostic accuracy, we sought single-arm trials that permitted computation of specificity and sensitivity in relation to a reference standard that included histopathologic verification of positive tests and at least clinical follow-up of negative lesions. These studies were required to have at least 10 patients, including at least 5 participants with malignant nodules. We included studies that enrolled patients with pulmonary nodules that measured up to 4 cm in diameter.

A single reviewer screened titles and abstracts for full-text retrieval, and a second reviewer reviewed citations marked as uncertain. Review of full-text articles was conducted in the same manner to determine inclusion in the systematic review. One reviewer performed primary data abstraction, and a second reviewer reviewed the evidence tables for accuracy. All disagreements were resolved by consensus. Findings were reviewed and approved by members of the lung cancer panel, Thoracic Oncology NetWork, Health and Science Policy Committee, and Board of Regents of the American College of Chest Physicians.

What Is the Prevalence of SPNs?

From the literature review, eight large studies[4–18] of lung cancer screening were identified (Table 1). It is important to note that nodules that are detected in screening studies differ in important ways from nodules that are detected in routine clinical practice. In screening studies, the nodules tend to be smaller, the prevalence of malignant nodules is much lower, and the tumor volume doubling times (VDTs) of malignant nodules are generally longer.

The included studies enrolled populations that are believed to be at high risk for lung neoplasm, usually as a result of tobacco use. Both the prevalence of SPNs (8 to 51%) and the prevalence of malignancy in participants with SPNs (1.1 to 12%) varied across studies. The results of these studies were reported in varying manners. Whereas some reported only the number of nodules detected, others provided the percentage of patients with SPNs. In addition, patients with multiple nodules were not clearly separated from those with SPNs, further complicating the attempt to pool data. Gohagan et al[6] reported a 20.5% "positivity rate" (*ie*, 20.5% of patients had a CT scan that was concerning for lung cancer), but the SPN prevalence rate was not reported. Li et al[7,8] reported that 7,847 patients underwent 17,892 screening low-dose and follow-up high-resolution CT (HRCT) scans; the number of patients with pulmonary nodules was not reported, but 819 of those CT scan findings were described as abnormal. In some cases, the same nodule could have appeared on several scans, but also a single patient could have had multiple nodules, making it difficult to estimate prevalence.

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The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Manuscript received May 30, 2007; revision accepted June 5, 2007.

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DOI: 10.1378/chest.07-1352