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

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

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

*Momen M. Wahidi, MD, FCCP; Joseph A. Govert, MD; Ranjit K. Goudar; MD; Michael K. Gould, MD, FCCP; and Douglas C. McCrory, MD*

***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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**Table 1—*Prevalence of SPNs in Studies of Lung Cancer Screening**

| Study/Year | Subjects, No. | Smoking Status | Detection Modality | Geographic Location | Prevalence of Any Abnormality | Prevalence of SPNs (Nodule < 3 cm) | Prevalence of Cancer in Patients With Nodules, % (No./Total) | Prevalence of Cancer in All Patients, % (No./Total) |
|---|---|---|---|---|---|---|---|---|
| Veronesi et al[4]/2006 | 5,189 (66% men) | 80% current | LDCT | Italy | 10% recall rate | NR (10% recall rate) | Approximately 10 (54/520) | 1 (54/5,189) |
| Henschke et al[5]/2004 | 2,897 | | LDCT | New York, NY | NR | 21.3% (616 of 2,897) | 13 (81/616) | 2.8 (81/2,897) |
| Gohagan et al[6]/2004 | 1,660 (58% men) | 60% current; 42% former | LDCT | United States | 20.5% (n = 325) | 8% (26/1660) | 3.8 (1/26) | |
| Li et al[7]/2004; Li et al[8]/2002; Takashima et al[9]/2003; Hasegawa et al[10]/2000; Sone et al[11]/2001 | 7,847 (55% men) | NR | LDCT | Nagano, Japan (1996–1999) | NR | NR (819 of 17,892 total scan results abnormal; 605 patients with 747 nodules received follow-up scans) | 10.1 (76/747) | 1% of nodules receiving follow-up scans (76/7,847) |
| Swensen et al[12]/2003; Swensen et al[13]/2002 | 1,520 (52% men) | All current or former (≥ 20 pack-yr) | LDCT | Minnesota | NR | 51% (782 of 1,520) | 1.1% of 2,244 nodules measured in serial CT; 3.5 (36/1,038) of participants with nodules ≤20 mm; 3.8 (40/1,049) of participants with nodules of any size; 1.4 (40/2,832) of nodules of any size | |
| Nawa et al[14]/2002 | 7,956 (79% men) | 62% are current or former smokers | LDCT | Fukuoda, Japan | NR | 26.3% (2,099 of 7,956) | 1.7 (20/2,099) | 0.44 (35/7,956) |
| Henschke et al[15]/2001 (republication of the original data by Henschke et al[16]) | 1,000 (54% men) | NS (all patients had at least a 10–pack-yr cigarette smoking history) | Single-slice helical CT | New York, NY | NR | 23% (233 of 1,000; only noncalcified nodules reported; no size reported; solitary and multiple nodules included[17]) | 12 (27/233) | 2.7 (27/1,000) |
| Diederich et al[18]/2000 | > 700 | All patients are heavy smokers (> 20 pack-yr) | LDCT | Munster, Germany | NS | 20% for SPNs; 40% for SPNs and multiple nodules (precise numbers not reported) | | 1.1 (8/700) |

*LDCT = low-density CT; NS = not specified; NR = not reported.

**Table 2—*Prevalence of Malignancy in Nodules With Varying Size**

| Study/Year | Participants, No. | Nodules, No. | Overall Prevalence of Malignancy, % | Reference Test | Nodule Size | Nodules With Characteristic, % (No./Total) | Prevalence of Malignancy, % |
|---|---|---|---|---|---|---|---|
| Henschke et al[5]/2004 | 2,897 | 616 | 2.8 | Histologic confirmation and radiographic stability | < 5 mm | 61 (378/616) | 0 |
| | | | | | 5–9 mm | 39 (238/616) | 6 |
| Takashima et al[9]/2003 | 13,786 | 80 | 39 | Cancers: tissue diagnosis; benign: 2-yr follow-up or tissue | < 10 mm | 56 (45/80) | 31 |
| | | | | | 10–15 mm | 28 (22/80) | 64 |
| | | | | | 16–20 mm | 12 (10/80) | 60 |
| | | | | | > 20 mm | 4 (3/80) | 67 |
| Henschke et al[19]/2002 | 233 | 233 | 12 | Not mentioned in this study, but this is report from the ELCAP study | 2–5 mm | 58 (136/233) | 0.7 |
| | | | | | 6–10 mm | 30 (70/233) | 20 |
| | | | | | 11–20 mm | 9 (22/233) | 45 |
| | | | | | 21–45 mm | 2 (5/233) | 80 |
| Henschke et al[16]/1999 | 1,000 | 233 | 12 | Cancers: tissue diagnosis; benign: 2-yr follow-up or tissue | 2–5 mm | 62 (99) | 1 |
| | | | | | 6–10 mm | 29 (46) | 24 |
| | | | | | 11–20 mm | 6 (9) | 33 |
| | | | | | 21–45 mm | 3 (5) | 80 |
| Suzuki et al[20]/1999 | 92 | 92 | 39 | Histologic confirmation | < 5 mm | 2 (2/92) | 100 |
| | | | | | 5–< 10 | 32 (29/92) | 21 |
| | | | | | 10–< 20 | 53 (49/92) | 41 |
| | | | | | ≥ 20 mm | 12 (11/92) | 64 |
| Zerhouni et al[21]/1986 | 369 | 384 | 60 | Cancers: tissue diagnosis; benign: 2-yr follow-up | 0–1 cm | 25 (73/295) | 55 |
| | | | | | 1–2 cm | 32 (94/295) | 51 |
| | | | | | 2–3 cm | 17 (49/295) | 82 |
| | | | | | 3–6 cm | 12 (36/295) | 97 |
| | | | | | NR | 3 (5) | 65 |
| Siegelman et al[22]/1986 | 720 | 720 | 56 | Cancers: tissue diagnosis; benign: 2 yr follow-up | 5–10 mm | 18 (113/634) | 28 |
| | | | | | 11–15 mm | 31 (197/634) | 44 |
| | | | | | 16–20 mm | 19 (121/634) | 51 |
| | | | | | 21–25 mm | 11 (72/634) | 82 |
| | | | | | 26–30 mm | 10 (61/634) | 82 |
| | | | | | > 30 mm | 11 (70/634) | 93 |

*ELCAP = Early Lung Cancer Action Program. See Table 1 for expansion of abbreviation.

*What Is the Prevalence of Malignancy in Nodules With Varying Characteristics?*

We identified three nodule characteristics for analysis: size, morphology, and type of opacity (Tables 2–4). Seven studies[5,9,16,19–22] that assessed nodule size found a proportional increase in the risk for malignancy as the diameter of the nodule increased (Table 2). With the exception of one small retrospective study[20] in which two of two nodules < 5 mm in diameter were malignant, the prevalence of malignancy in nodules that measured < 5 mm was exceedingly low (range, 0 to 1%). The risk for malignancy was higher in nodules that measured between 5 and 10 mm (range, 6 to 28%), and it was very high in nodules that measured > 2 cm in diameter (range, 64 to 82%). It is not clear how many of these lesions were > 3 cm and therefore would qualify as pulmonary masses instead of nodules.

Data from six studies[9,21–25] of patients with incidental or screening-detected nodules showed that the risk for malignancy was approximately 20 to 30% in nodules with smooth edges, although one study[25] reported a prevalence of malignancy of 58% in nodules with smooth borders. In nodules with irregular, lobulated, or spiculated borders, the risk for malignancy was higher but varied across studies from 33 to 100% (Table 3).

SPN morphology may be classified as solid, partially solid, or ground glass. Some investigators use the term *nonsolid* to describe the traditional ground-glass morphology. Whereas two studies[7,9] found pure ground-glass opacities to be predominantly malignant (59 to 73%), another study[18] using different terminology found that partially solid nodules had a higher likelihood of malignancy (63%) as compared with nonsolid nodules (18%; Table 4). When partially solid and nonsolid nodules were pooled,[26] the aggregate prevalence of malignancy in such nodules was 32%. The prevalence of malignancy in solid nodules was generally lower (7 to 9%).

*What Is the Histologic Type and Natural History (Growth Rate) of Small Pulmonary Nodules With Varying Characteristics?*

Nine studies[9,10,27–33] analyzed the histology of pulmonary nodules with purely or primarily ground-glass attenuation on HRCT (Table 5). Bronchioloalveolar carcinoma (BAC) was the most common histologic subtype in such nodules (range, 70 to 100%).

Hasegawa et al[10] reported the VDT for malignant SPNs on the basis of their morphologic characteristics: 813 ± 375 days for pure ground-glass opacities, 457 ± 260 days for mixed or partial ground-glass opacities, and 149 ± 125 days for solid opacities. The same study[10] found the VDT for nodules < 10 mm in diameter to be nearly double that of nodules > 2 cm (536 ± 283 days vs 299 ± 273 days). A second study[33] reported VDT by tumor type but not by radiographic appearance.

**Table 3—*Prevalence of Malignancy in Nodules With Varying Edge Characteristics***

| Study/Year | Participants, No. | Nodules, No. | Overall Prevalence of Malignancy, % | Reference Test | Nodule Characteristic | Nodules With Characteristic, % (No./Total) | Prevalence of Malignancy, % |
|---|---|---|---|---|---|---|---|
| Tozaki et al[23]/2005 | 45 | 45 | 64 | Histologic confirmation (2-yr follow-up for a few benign nodules) | Smooth | 20 (9/45) | 22 |
| | | | | | Lobulated | 27 (12/45) | 58 |
| | | | | | Irregular | 53 (24/45) | 83 |
| Takashima et al[9]/2003 | 13,786 | 80 | 39 | Cancers: tissue diagnosis; benign: 2-yr follow-up or tissue | Spiculation | 38 (23/61) | 35 |
| | | | | | Lobulation | 62 (38/61) | 50 |
| Swensen et al[24]/1997 | 629 | 629 | 23 malignant, 65 benign, 12 "indeterminate" | Cancers: tissue diagnosis; benign lesions: either path or 2-yr stability; indeterminate lesions did not meet above criteria | Smooth | 33 (114/344) | 17 |
| | | | | | Spiculated | 8 (29/344) | 83 |
| | | | | | Shaggy | 38 (131/344) | 33 |
| | | | | | Spiculated and shaggy | 7 (24/344) | 50 |
| | | | | | Lobulated | 13 (46/344) | 50 |
| Swensen et al[25]/1995 | 163 | 163 | 68 | Histologic confirmation (2-yr follow-up for a few benign nodules) | Infiltrating | 13 (21/163) | 76 |
| | | | | | Lobulated | 1 (2/163) | 100 |
| | | | | | Smooth | 45 (73/163) | 58 |
| | | | | | Infiltrating, lobulated | 11 (18/163) | 78 |
| | | | | | Lobulated, smooth | 24 (39/163) | 69 |
| Siegelman et al[22]/1986 | 720 | 720 | 56 | Cancers: tissue diagnosis; benign: 2-yr follow-up | Sharp and smooth | 11 (66/634) | 21 |
| | | | | | Moderately smooth | 55 (350/634) | 42 |
| | | | | | Slight spiculation | 26 (165/634) | 87 |
| | | | | | Grossly irregular with complete spiculation | 8 (53/634) | 94 |
| Zerhouni et al[21]/1986 | 369 | 384 | 60 | Cancers: tissue diagnosis; benign: 2-yr follow-up | Infiltrating | 31 (91/295) | 88 |
| | | | | | Lobulated | 16 (48/295) | 58 |
| | | | | | Smooth | 44 (130/295) | 38 |
| | | | | | Not recorded | 9 (26/295) | 73 |

*What Are the Performance Characteristics of Tests for SPN Diagnosis?*

An abundant body of evidence exists for the performance of positron emission tomography (PET) in the evaluation of SPN. Except for one study, the sensitivity of PET for identifying malignancy was consistently high (80 to 100%; Table 6).[34–50] In contrast, the specificity of PET was lower and highly variable (40 to 100%). The point on the summary receiver operating characteristic curve that corresponded to the median specificity reported in 17 studies of PET had a sensitivity of 87% and a specificity of 82.6%.

Other studies used a variety of radiographic techniques to differentiate benign from malignant SPNs, including HRCT and dynamic CT with nodule enhancement. The latter technology yielded the most promising results (sensitivity, 98 to 100%;

**Table 4—*Prevalence of Malignancy in Nodules With Varying Morphology****

| Study/Year | Participants, No. | Nodules, No. | Overall Prevalence of Malignancy, % | Reference Test | Nodule Characteristic | Nodules With Characteristic, % (No./Total) | Prevalence of Malignancy, % |
|---|---|---|---|---|---|---|---|
| Li et al[7]/2004 | 222 | 222 | 27 | Histologic confirmation of malignant lesions, no histologic confirmation for benign nodules | Solid | 25 (15/59) | 9 |
| | | | | | Mixed GGO | 46 (27/59) | 49 |
| | | | | | Pure GGO | 29 (17/59) | 59 |
| Takashima et al[9]/2003 | 13,786 | 80 | 39 | Cancers: tissue diagnosis Benign: 2-yr follow-up or tissue | Predominant GGO | 41 (33/80) | 73 |
| | | | | | Predominantly solid | 59 (47/80) | 26 |
| Henschke et al[19]/2002 | 233 | 233 | 12 | Subset of ELCAP study | Solid | 81 (189/233) | 7 |
| | | | | | Partially solid | 7 (16/233) | 63 |
| | | | | | Nonsolid | 12 (28/233) | 18 |

*GGO = ground-glass opacity. See Table 2 for expansion of abbreviation.

**Table 5—*Histologic Type and Natural History (Growth Rate) of Small Pulmonary Nodules With Varying Characteristics**

| Study/Year | Participants, No. | Nodules, No. | Nodule Characteristic | Nodules With Characteristic, No. | Mean Size, mm | Histology, % (No./Total) | Growth Rate |
|---|---|---|---|---|---|---|---|
| Kishi et al[27]/2004 | 38 | 44 | Ground-glass attenuation | 36 | | 22 (8/36) AAH; 78 (24/36) AD | NR |
| | | | Bubble-like attenuation | 20 | | 15 (3/20) Sq; 85 (17/20) AD | |
| | | | Lobulation | 17 | | 12 (2/17) Sq; 88 (15/17 AD | |
| | | | Convergence of peripheral vessels | 21 | | 5 (1/21) AAH; 14 (3/21) Sq; 81 (18/21) AD | |
| | | | Spiculation | 17 | | 18 (3/17) Sq; 82 (14/17) AD | |
| Nakamura et al[28]/2004 | 100 | 100 | Pure GGO | 27 | 9.3 | 100 (27/27) BAC | NR |
| | | | Nonpure GGO | 73 | 21.2 | 29 (21/73) Sq; 32 (23/73) WD Ad; 21 (15/73) MD Ad; 15 (11/73)PD Ad | |
| Takashima et al[9]/2003 | 13,786 | 36 | GGO | 24 | 12.5 ± 4.5 | 21 (5/24) AAH; 71 (17/24) BAC; 8 (2/24) Ad | NR |
| | | | Air bronchogram | 16 | | 6 (1/16) AAH; 56 (9/16) BAC; 38 (6/16) Ad | |
| | | | Concave margin | 9 | | 33 (3/9) AAH; 44 (4/9) BAC; 23 (2/9) Ad | |
| Nakata et al[29]/2003 | | | Pure GGO | 33 | | 70 (23/33) BAC; 27 (9/33) AAH; 3 (1/33) Ad | NR |
| | | | Mixed GGO | 26 | | 58 (15/26) BAC; 0 (0/26) AAH; 42 (11/26) Ad | |
| Suzuki et al[30]/2002 | 69 | 69 | Pure GGO | 38 | | 84 (32/38) BAC; 16 (6/38) Ad | NR |
| | | | Complex GGO (mixed GGO) | 31 | | 48 (15/31) BAC; 52 (16/31) Ad | |
| Wantanabe et al[31]/2002 | 20 | 20 | Pure GGO | 20 | 7.9 ± 1.9 mm | 15 (3/20) AAH; 85 (17/20) BAC | NR |
| Hasegawa et al[10]/2000 | 61 | 61 | Pure GGO | 19 | 9.9 ± 4.8 | 100 (19/19) WD Ad | VDT, 813 ± 375 d |
| | | | Mixed GGO | 19 | 11.4 ± 4.4 | 74 (14/19) WD Ad; 26 (5/19) MD Ad | VDT, 457 ± 260 d |
| | | | Solid | 23 | 15.6 ± 5.6 | 22 (5/23)WD Ad; 9 (2/23) MD Ad; 17 (4/23) PD Ad; 35 (8/23) Sq 17 (4/23) small cell | VDT, 149 ± 125 d |
| | | | Size < 10 mm | 22 | | NR | VDT, 536 ± 283 d |
| | | | Size 10–15 mm | 23 | | NR | VDT, 466 ± 481 d |
| | | | Size 16–20 mm | 9 | | NR | VDT, 325 ± 353 d |
| | | | Size > 20 mm | 7 | | NR | VDT, 299 ± 273 ds |
| Wang et al[32]/2000 | 12 | 12 | Soft-tissue density (solid) | 9 | | 11 (1/9) WD Ad; 33 (3/9) MD Ad; 11 (1/9) PD Ad; 11 (1/9) Sq; 33 (3/9) small cell | NR |
| | | | GGO | 3 | | 100 (3/3) WD Ad | |
| | | | Smooth | 7 | | 29 (2/7) MD Ad; 14 (1/7) PD Ad; 14 (1/7) Sq; 43 (3/7) small cell | |
| | | | Irregular | 5 | | 80 (4/5) WD Ad; 20 (1/5) MD Ad; | |
| | | | Spiculation | 6 | | 17 (1/6) WD Ad; 17 (1/6) MD Ad; 17 (1/6) PD Ad; 17 (1/6) Sq; 33 (2/6) small cell | |
| | | | Lobulation | 7 | | 29 (2/7) MD Ad; 14 (1/7) PD Ad; 14 (1/7) Sq; 29 (3/7) small cell | |

**Table 5—*Continued***

| Study/Year | Participants, No. | Nodules, No. | Nodule Characteristic | Nodules With Characteristic, No. | Mean Size, mm | Histology, % (No./Total) | Growth Rate |
|---|---|---|---|---|---|---|---|
| Aoki et al[33]/2000 | 34 | 34 | Solid (no GGO) | 12 | | 58 (7/12) BAC; 42 (5/12) AD | VDT reported per tumor type, not by nodule characteristics; BAC range 42–1,486 AD; range 124–402; mean 252 |
| | | | Minimal GGO (< 10%) | 5 | | 60 (3/5) BAC; 40 (2/5) AD | |
| | | | Moderate GGO (10–50%) | 11 | | 100 (11/11) BAC | |
| | | | Mostly GGO (> 50%) | 6 | | 100 (6/6) BAC | |

*AAH = atypical adenomatous hyperplasia; Ad = adenocarcinoma; MD = moderately differentiated; PD = poorly differentiated; Sq = squamous cell carcinoma. See previous tables for other abbreviations.

specificity, 54 to 93%; Table 7).[25,51–56] The point on the summary receiver operating characteristic curve that corresponded to the median specificity reported in seven studies of dynamic CT with enhancement had a sensitivity of 96% and a specificity of 75%.

In 11 studies[38,57–66] of CT-guided needle biopsy, nondiagnostic results were recorded in 4 to 41% of cases (median, 21%). Nondiagnostic biopsy results were seen in approximately 44% of patients with benign nodules (range, 0 to 89%) and 8% of patients with malignant nodules (range, 0 to 22%). In patients with biopsy results that revealed a specific malignant or benign diagnosis, sensitivity ranged from 82 to 100% (median, 97.5%). However, when nondiagnostic biopsy results were included in the false-negative column, sensitivity ranged from 65 to 94% (median, 90%). Although all but one study reported perfect specificity, some studies assumed that all positive biopsy results were true positive (Table 8). In the 11 studies,[38,57–66] the risk for pneumothorax ranged from 15 to 43% (median, 26.5%), and 4 to 18% (median, 5%) of patients required chest tube placement.

In one study[67] of 118 patients with nodules that measured up to 4 cm in diameter, a combined strategy of tissue sampling (percutaneous and bronchoscopic) and radiographic observation with repeat sampling as needed yielded a sensitivity and a specificity of 100%. Further studies are needed to reproduce these promising results.

## Results

### *What Is the Prevalence of SPNs?*

The prevalence of SPNs (8 to 51%) and the prevalence of malignancy in patients with SPNs (1.1 to 12%) varied significantly across studies. This variation stems from the inconsistency among studies in method, enrolled population, and reporting of results.

### *What Is the Prevalence of Malignancy in Nodules With Varying Characteristics (Size, Morphology, and Type of Opacity)?*

The prevalence of malignancy in SPNs increased in proportion to 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[9,21–25] 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%).

### *What Are the Relationships Between Growth Rates, Histology, and Other Nodule Characteristics?*

BAC is the most common histologic subtype in nodules with purely or primarily ground-glass attenuation on HRCT (range, 70 to 100%). Limited data exist on the VDT of malignant SPNs.

**Table 6—*Performance Characteristics and Complication Rates of Tests for SPN Diagnosis: PET With 18-Fluorodeoxyglucose**

| Study/Year | Participants, No. | Age, Mean ± SD, Range, Mean, or Mean (Range), yr | Pulmonary Nodules, No. | Lesion Diameter, Mean, Mean ± SD, or Mean (Range), cm | Prevalence of Malignancy in SPNs, % | Reference Test | Sensitivity for Malignancy, % (No./Total) | Specificity for Malignancy, % (No./Total) |
|---|---|---|---|---|---|---|---|---|
| Kubota et al[34]/ 1990† | 22 | 35.0–75.0 | 13 | 0.5–6.0 | 46 | Surgery, n = 8; bronchoscopy, n = 4; needle biopsy, n = 1 | 67 (4/6) | 86 (6/7) |
| Gupta et al[35]/ 1992† | 20 | 70.8 (39.0–85.0) | 19 | 0.6–6.0 | 63 | Thoracotomy, n = 9; needle biopsy, n = 8; bronchoscopy, n = 1; observation, n = 1 | 100 (12/12) | 100 (7/7) |
| Dewan et al[36]/ 1993‡ | 30 | 65.3 (38.0–89.0) | 31 | 0.6–3.0 | 68 | Thoracotomy, n = 21; needle biopsy, n = 8; bronchoscopy, n = 1; observation, n = 1 | 90 (19/21) | 80 (8/10) |
| Patz et al[37]/1993† | 51 | 60.0 (19.0–80.0) | 38 | 38 nodules < 4 cm; 5 masses > 4 cm; 8 poorly defined opacities | 66 | Bronchoscopy, n = 21; open lung biopsy, n = 14; needle biopsy, n = 14 | 100 (25/25) | 100 (13/13) |
| Dewan et al[38]/ 1995†§ | 33 | 65.2 (41.0–88.0) | 22 | 1–6 | 73 | Thoracotomy or needle biopsy, n = 31; observation, n = 2 | 100 (16/16) | 83 (5/6) |
| Duhaylongsod et al[39]/1995†‖ | 100 | 58.0 ± 4.0 | 47 | 2.2 ± 0.8 for 79 SPNs; 5.2 ± 0.8 for 11 masses; 10 ill-defined infiltrates | 66 | Bronchoscopy or needle biopsy, n = 49; open biopsy, n = 35 | 100 (31/31) | 81 (13/16) |
| Duhaylongsod et al[40]/1995† | 53 | 61.0 ± 4.0 | 39 | 39 nodules 4 cm; 14 masses > 4 cm | 56 | | 95 (21/22) | 88 (15/17) |
| Gupta et al[41]/ 1996¶ | 61 | 65.0 (24.0–89.0) | 42 | 0.6–3.0 | 79 | Thoracotomy, n = 43; needle biopsy, n = 13; bronchoscopy, n = 4; observation, n = 1 | 91 (30/33) | 78 (7/9) |
| Dewan et al[42]/ 1997# | 52 | 63.6 ± 11.3 | 26 | 3 | 65 | Thoracotomy, n = 36; needle biopsy, n = 9; bronchoscopy, n = 3; mediastinoscopy, n = 3; observation, n = 1 | 100 (17/17) | 100 (9/9) |
| Gupta et al[43]/ 1998 | 19 | 32.0–78.0 | 19 | 1.0–3.5 | 63 | Needle biopsy, n = 10; thoracotomy, n = 8; bronchoscopy, n = 1 | 100 (12/12) | 100 (7/7) |
| Lowe et al[44]/ 1998† | 89 | 63.0 ± 9.5 | 77 | 0.7–4.0 | 66 | Needle biopsy or open-lung biopsy | 98 (50/51) | 69 (18/26) |
| Orino et al[45]/ 1998 | 23 | 64.6 | 23 | 1.0–2.8 | 74 | VATS, n = 16; bronchoscopy, n = 4; needle biopsy, n = 3 | 88 (15/17) | 67 (4/6) |
| Präuer et al[46]/ 1998** | 50 | 59.0 (27.0–84.0) | 54 | 1.8 ± 0.7 (0.3–3.0) | 57 | Surgery | 90 (28/31) | 83 (19/23) |

**Table 6—*Continued***

| Study/Year | Participants, No. | Age, Mean ± SD, Range, Mean, or Mean (Range), yr | Pulmonary Nodules, No. | Lesion Diameter, Mean, Mean ± SD, or Mean (Range), cm | Prevalence of Malignancy in SPNs, % | Reference Test | Sensitivity for Malignancy, % (No./Total) | Specificity for Malignancy, % (No./Total) |
|---|---|---|---|---|---|---|---|---|
| Hung et al[47]/2001 | 26 | 60.0 (27.0–79.0) | 26 | 2.5 ± 0.8 | 77 | Pathology examinations n = 26 | 95 (19/20) | 50 (3/6) |
| Croft et al[48]/2002 | 90 | 63.0 (34.0–86.0) | 91 | 4.4 (0.7–17.0) | 82 | Mediastinoscopy, TBB, thoracoscopy, thoracotomy, or craniotomy, n = 90 | 93 (65/70) | 40 (6/15) |
| Matthies et al[49]/2002 | 36 | 67.0 (36.0–88.0) | 38 | 2.7 ± 1.2 (0.6–6.0) | 53 | Biopsy or resection, n = 19; no histology, n = 1 | 80 (16/20) | 94 (15/16) |
| Herder et al[50]/2004 | 35 | 61.0 ± 0.0 | 36 | < 3.0 | 67 | Histology, n = 15; observation, n = 21 | 93 (13/14) | 77 (17/22) |

*TBB = transbronchial biopsy; VATS = video-assisted thoracoscopic surgery. See previous tables for other abbreviations.
†These studies included participants with pulmonary nodules and mass lesions; results presented are for pulmonary nodules.
‡Data include findings as reported for 30 nodules and a second nodule in patient 19 that was false positive but not initially reported, as described by Gould et al.[1]
§Data exclude four patients with SPNs (patients 17, 23, 27, and 28) for whom findings were reported previously in 1993 study.
‖Results presented for nodules ≤ 3 cm in diameter.
¶Data exclude 19 patients for whom findings were reported previously in 1992 study, as described by Gould et al.[1]
#Data exclude 26 patients for whom findings were reported previously in 1993 and 1995 studies.
**Four participants had two pulmonary nodules each.

*What Are the Performance Characteristics and Complication Rates of Tests for SPN Diagnosis?*

The sensitivity of PET imaging for identifying malignant SPNs 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, sensitivity and specificity were excellent when biopsy yielded a specific benign or malignant results, but nondiagnostic results were seen approximately 20% of the time.

## Discussion

In patients with incidentally detected SPNs, treatment goals include prompt identification of malignant nodules to permit timely surgical resection and avoidance of surgery (when possible) in patients with benign nodules. Patients with SPNs and their clinicians confront challenging treatment decisions and must weigh the risks and benefits of various treatment strategies. Our report sought answers to key questions that are frequently posed when an SPN is encountered.

Our first question addressed the prevalence of SPNs. Between-study variation in the prevalence of SPNs (Table 1) may be partially explained by the use of different radiographic techniques (*eg*, section thickness on CT), the varying percentage of smokers (former, current, and heavy) included in each study population, and the diverse geographic location of the studies (United States, Japan, Germany, and Italy). Other factors that can affect the prevalence of lung nodules include the technical quality of the scan and interobserver variation related to radiologists' interpretation of the images. On the basis of nodules found on follow-up scans, Swensen et al[12] reexamined baseline scans and retrospectively diagnosed new nodules in 26% of patients. Several studies commented on the appearance of new nodules and resolution of previously seen nodules during scheduled follow-up scans, further complicating the accurate determination of SPN prevalence.

Another important consideration is that these studies screened populations at higher risk for malignancy and therefore did not address the prevalence of SPN in the population at large. It remains unclear whether or how the prevalence of SPN is affected by age and smoking.

For obtaining reproducible information, it is important that future studies of SPN prevalence exclude patients with multiple nodules, as well as patients with masses that measure > 3 cm in diam-

**Table 7—*Performance Characteristics and Complication Rates of Tests for SPN Diagnosis: Dynamic CT With Nodule Enhancement**

| Study/Year | Participants, No. | Nodules or Masses, No. | Prevalence of Malignancy, % | Reference Test | Definition of Positive Test Result (Malignancy) | Sensitivity for Malignancy, % (No./Total) | Specificity for Malignancy, % (No./Total) |
|---|---|---|---|---|---|---|---|
| Swensen et al[51]/1992† | 52 | 30 | 73 | Tissue diagnosis or observation | Enhancement > 19 HU | 100 (23/23) | 86 (6/7) |
| Swensen et al[25]/1995‡§ | 163 | 163 | 68 | Tissue diagnosis, n = 132; observation, n = 31 | Enhancement > 19 HU | 100 (111/111) | 77 (40/52) |
| Yamashita et al[52]/1995‖ | 32 | 32 | 56 | Surgical resection or biopsy | Enhancement > 20 HU | 100 (18/18) | 93 (13/14) |
| Swensen et al[53]/1996¶ | 107 | 107 | 49 | Tissue diagnosis, n = 63; observation, n = 44 | Enhancement > 19 HU | 98 (51/52) | 73 (40/55) |
| Potente et al[54]/1997# | 40 | 25 | 68 | Thoracotomy, n = 18; needle biopsy, n = 6; bronchoscopy, n =1 | Enhancement > 19 HU | 100 (17/17) | 75 (6/8) |
| Swensen et al[55]/2000** | 356 | 356 | 48 | Tissue diagnosis, n = 237; observation, n = 119 | Enhancement > 15 HU | 98 (167/171) | 58 (107/185) |
| Yi et al[56]/2004 | 198 | 131 | 53 (70/131) | TTNB, n = 39; surgery, n = 70; observation, n = 22 | Enhancement > 30 HU | 99 (69/70) | 54 (33/61) |

*HU = Hounsfield units; TTNB = transthoracic needle biopsy. See previous tables for other abbreviations.

†Twenty-two nodules were excluded because the final diagnosis was not established (n = 22) or CT was technically inadequate (n = 3).

‡Includes 30 participants reported previously.[3]

§Fifty-five participants were excluded because the final diagnosis was not established (n = 34) or CT was technically inadequate (n = 21).

‖Fifteen participants were excluded because benign calcification was present on standard CT (n = 5), the final diagnosis was not established (n = 7), or CT was technically inadequate (n = 3).

¶Forty-nine participants were excluded because the final diagnosis was not established (n = 41) or CT was technically inadequate (n = 8).

#Fifteen participants were excluded because iodinated contrast material was contraindicated (n = 2), thin-section CT showed calcification (n = 8), CT was technically inadequate (n = 3), or plain CT was typical for acute granuloma (n = 2).

**A total of 169 participants were excluded because the final diagnosis was not established (n = 147), CT was technically inadequate (n = 19), needle biopsy was recently performed (n = 1), an incorrect dosage of contrast material was administered (n = 1), or the nodule diameter (3 mm) was the same size as the CT collimation (n = 1).

eter. For accurate calculation of SPN prevalence, the number of patients with at least one SPN must be reported, instead of the number of total nodules or the number of abnormal CT scans. An ideal study design would enroll a large cross-section of the population and analyze SPN rates in the overall population as well as subgroup of subjects with risk factors for lung cancer, such as smoking status, age, and sex. A study restricted to a specific geographic location would be of greatest interest to physicians in that area. Alternatively, a multicenter study could be stratified by location.

The prevalence of malignancy in detected nodules also varied across studies. A key factor that may account for these differences is the dissimilarity in the sizes of the pulmonary opacities included in each study, with larger nodules having a higher probability of malignancy.

Our second question dealt with the prevalence of malignancy in nodules with varying characteristics. A consistent finding among studies was the association between increasing nodule size and the likelihood of malignancy, as well as the exceedingly low incidence of malignancy in nodules $< 5$ mm in size. On the basis of this observation, the Fleischner Society[3] recommends that no follow-up is necessary in patients with nodules that measure up to 4 mm in size, provided that they have no risk factors for lung cancer.

On the basis of current data, the edge and morphology characteristics of a nodule are less instructive in determining the probability of malignancy. Although there is a trend toward a lower incidence of malignancy in smooth and solid nodules, no firm conclusions can be drawn, primarily because of the lack of a standardized terminology to describe SPN morphology and the resulting inconsistency between studies.

Our third question addressed the histologic type and growth rate of small pulmonary nodules with varying characteristics. Once again, definitions, classification systems, and results differed across studies. The pure ground-glass malignant pulmonary nodule stood out as an entity that has a long VDT and is predominantly caused by BAC.

The study by Hasegawa et al[10] showed that a lesion that has ground-glass attenuation and seems to be stable over a 2-year period could still be malignant,

**Table 8—*Performance Characteristics and Complication Rates of Tests for SPN Diagnosis: CT-guided Needle Biopsy**

| Study/Year | Participants, No. | Procedures, No. | Prevalence of Malignancy, % | Reference Test | Nondiagnostic Biopsies, % (Malignant, No./Benign, No.) | Sensitivity of Diagnostic Biopsy for Malignancy, % (No./Total) | Specificity of Diagnostic Biopsy for Malignancy, % (No./Total) | Complications, % |
|---|---|---|---|---|---|---|---|---|
| van Sonnenberg et al[57]/1988 | 145† | 107 | 78 | NS | 20 (7/8)‡ | 100 (76/76) | 100 (10/10) | 43 (pneumothorax) |
| García Río et al[58]/1994 | 84 | 84 | 80 | Transbronchial biopsy, thoracotomy, mediastinoscopy, necropsy, response to therapy, or observation | 20 (13/4)§ | 94 (51/54) | 100 (13/13) | 14 (pneumothorax) |
| Dewan et al[38]/1995 | 33‖ | 22 | 73 | Needle biopsy or thoracotomy, n = 21; 2-yr clinical follow-up, n = 1 | 41 (4/5) | 100 (12/12) | 100 (1/1) | 41 (pneumothorax); 18 (chest tube) |
| Li et al[59]/1996 | 27 | 27 | 85 | Surgery or autopsy | 26 (5/2)¶ | 83 (15/18) | 100 (2/2) | 22 (pneumothorax) |
| Santambrogio et al[60]/1997 | Group A: 110# | Group A: 110 | Group A: 62 | Surgery (n = 217) and clinical follow-up over 15 mo (n = 3) | Group A: 0 | Group A: 99 (67/68) | Group A: 100 (42/42) | Pneumothorax: (26, group A; 21, group B) |
| | Group B: 110# | Group B: 110 | Group B: 65 | | Group B: 6 | Group B: 90 (63/70) | Group B: 96 (26/27) | Chest tube: (6, group A; 5, group B) |
| Wescott et al[61]/1997 | 62** | 75 | 67 | Surgery, biopsy from other site, or clinical follow-up | 19 (3/11) | 100 (40/40) | 100 (21/21) | 27 (pneumothorax); 4 (chest tube); 9 (hemoptysis) |
| Yankelevitz et al[62]/1997 | 114 | 114 | 75 | NS | 27 (5/26) | 100 (80/80) | 100 (3/3) | 20 (pneumothorax) |
| Hayashi et al[63]/1998 | 52 | 52 | 72 | Surgery, biopsy from other site, autopsy, culture, or clinical follow-up | 4 (0/2) | 100 (35/35) | 100 (15/15) | 37 (pneumothorax) |
| Laurent et al[64]/2000 | 66†† | 67 | 71 | Surgery or clinical follow-up | 21 (4/10) | 100 (43/43) | 100 (9/9) | 15 (pneumothorax) |
| Wallace et al[65]/2002 | 61 | 57 | 76 | Surgery, biopsy, or clinical follow-up | 23 (6/14) | 82 (32/39) | 100 (18/18) | 31 (pneumothorax) |
| Yamagami et al[66]/2003 | 108 | 110 | 79 | Surgery, biopsy, or clinical follow-up | 6 (6/0) | 95 (77/81) | 100 (23/23) | 34 (pneumothorax); 4 (chest tube); 6 (hemoptysis) |

*See other tables for abbreviations.
†A total of 145 participants had 107 pulmonary lesions, 31 mediastinal lesions, and 12 pleural lesions; data presented are for pulmonary lesions.
‡The final diagnosis was not reported for six additional patients with nondiagnostic biopsies.
§Five of 13 nondiagnostic (malignant) biopsies were suspicious for malignancy.
‖Thirty-three participants had 22 pulmonary nodules ≤ 3 cm, 9 masses > 3 cm, 3 hilar lesions, and 1 case of multiple pulmonary nodules; data presented are for SPNs.
¶In five cases, needle biopsy results were suspicious for malignancy but not diagnostic.
#In group A (n = 110), a cytologist assessed sample adequacy and the biopsy was repeated when necessary; in group B (*n* = 110), immediate cytologic assessment was not performed.
**Sixty-two participants with 64 nodules underwent 75 biopsy procedures; 5 procedures were performed under fluoroscopic guidance.
††Sixty-seven biopsy procedures were performed in 66 participants; results reported for 66 procedures.

challenging the time-honored rule of 2-year radiographic stability as a sign of a benign process. Whether such lesions represent clinically important cases of lung cancer or "overdiagnosed" cases of indolent lung cancer is a question that has not been resolved.

Our last question addressed the performance characteristics and complication rates of tests for SPN diagnosis. The accurate measurement of the sensitivity and specificity of a diagnostic test requires the use of an appropriate reference standard and depends on disease prevalence. Surgical excision of a suspected malignant nodule remains the "gold standard," but the associated risk and expense demand a search for an alternative diagnostic test that is minimally invasive and accurate. At present, the most extensively studied diagnostic test is the PET scan. Data convincingly showed that PET imaging was relatively sensitive for identifying malignancy, but specificity was more variable and often poor to fair. CT-guided tissue sampling yields specific malignant diagnoses but suffers from sampling bias, which dictates additional workup if biopsy results are nondiagnostic in patients with a high pretest probability of malignancy. The associated pneumothorax rate, albeit high, infrequently leads to significant morbidity.

## Conclusions

Our report sought evidence related to the prevalence of SPNs, the prevalence of malignancy in patients with SPNs, characteristics of SPNs associated with malignancy, and accuracy of tests that are used for SPN diagnosis. It is clear that further research is needed to address vital questions such as the prevalence of SPNs in the population at large, the characteristics that indicate malignancy, and the best management strategy. Essential steps toward more rigorous research must include the establishment of consensus on classification schema for radiographic opacities, especially with regard to size and morphology, and collaboration among researchers to conduct large-scale clinical trials.

## References


1 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; 285:914–924

2 Gould MK, Sanders GD, Barnett PG, et al. Cost-effectiveness of alternative management strategies for patients with solitary pulmonary nodules. Ann Intern Med 2003; 138:724–735

3 MacMahon H, Austin JH, 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

4 Veronesi G, Bellomi M, Spaggiari L, et al. Low dose spiral computed tomography for early diagnosis of lung cancer: results of baseline screening in 5,000 high-risk volunteers; ASCO Annual Meeting Proceedings Part I. J Clin Oncol 2006; 24(suppl):7029

5 Henschke CI, Yankelevitz DF, Naidich DP, et al. CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. Radiology 2004; 231:164–168

6 Gohagan J, Marcus P, Fagerstrom R, et al. Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of the National Cancer Institute. Chest 2004; 126:114–121

7 Li F, Sone S, Abe H, et al. Malignant versus benign nodules at CT screening for lung cancer: comparison of thin-section CT findings. Radiology 2004; 233:793–798

8 Li F, Sone S, Abe H, et al. Lung cancers missed at low-dose helical CT screening in a general population: comparison of clinical, histopathologic, and imaging findings. Radiology 2002; 225:673–683

9 Takashima S, Sone S, Li F, et al. Small solitary pulmonary nodules (≤1 cm) detected at population-based CT screening for lung cancer: reliable high-resolution CT features of benign lesions. AJR Am J Roentgenol 2003; 180:955–964

10 Hasegawa M, Sone S, Takashima S, et al. Growth rate of small lung cancers detected on mass CT screening. Br J Radiol 2000; 73:1252–1259

11 Sone S, Li F, Yang ZG, et al. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. Br J Cancer 2001; 84:25–32

12 Swensen SJ, Jett JR, Hartman TE, et al. Lung cancer screening with CT: Mayo Clinic experience. Radiology 2003; 226:756–761

13 Swensen SJ, Jett JR, Sloan JA, et al. Screening for lung cancer with low-dose spiral computed tomography. Am J Respir Crit Care Med 2002; 165:508–513

14 Nawa T, Nakagawa T, Kusano S, et al. Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. Chest 2002; 122:15–20

15 Henschke CI, Yankelevitz DF, Libby DM, et al. Early Lung Cancer Action Project: annual screening using single-slice helical CT. Ann NY Acad Sci 2001; 952:124–134

16 Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999; 354:99–105

17 Macbeth F, Toy E, Coles B, et al. Palliative radiotherapy regimens for non-small cell lung cancer. Cochrane Database Syst Rev 2001 (3): CD002143

18 Diederich S, Wormanns D, Lenzen H, et al. Screening for asymptomatic early bronchogenic carcinoma with low dose CT of the chest. Cancer 2000; 89(suppl):2483–2484

19 Henschke CI, Yankelevitz DF, Mirtcheva R, et al. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 2002; 178:1053–1057

20 Suzuki K, Nagai K, Yoshida J, et al. Video-assisted thoracoscopic surgery for small indeterminate pulmonary nodules: indications for preoperative marking. Chest 1999; 115:563–568

21 Zerhouni EA, Stitik FP, Siegelman SS, et al. CT of the pulmonary nodule: a cooperative study. Radiology 1986; 160:319–327

22 Siegelman SS, Khouri NF, Leo FP, et al. Solitary pulmonary nodules: CT assessment. Radiology 1986; 160:307–312

23 Tozaki M, Ichiba N, Fukuda K. Dynamic magnetic resonance imaging of solitary pulmonary nodules: utility of kinetic

patterns in differential diagnosis. J Comput Assist Tomogr 2005; 29:13–19
24 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; 157:849–855
25 Swensen SJ, Brown LR, Colby TV, et al. Pulmonary nodules: CT evaluation of enhancement with iodinated contrast material. Radiology 1995; 194:393–398
26 Asamura H, Suzuki K, Watanabe S, et al. A clinicopathological study of resected subcentimeter lung cancers: a favorable prognosis for ground glass opacity lesions. Ann Thorac Surg 2003; 76:1016–1022
27 Kishi K, Homma S, Kurosaki A, et al. Small lung tumors with the size of 1cm or less in diameter: clinical, radiological, and histopathological characteristics. Lung Cancer 2004; 44:43–51
28 Nakamura H, Saji H, Ogata A, et al. Lung cancer patients showing pure ground-glass opacity on computed tomography are good candidates for wedge resection. Lung Cancer 2004; 44:61–68
29 Nakata M, Sawada S, Saeki H, et al. Prospective study of thoracoscopic limited resection for ground-glass opacity selected by computed tomography. Ann Thorac Surg 2003; 75:1601–1605
30 Suzuki K, Asamura H, Kusumoto M, et al. "Early" peripheral lung cancer: prognostic significance of ground glass opacity on thin-section computed tomographic scan. Ann Thorac Surg 2002; 74:1635–1639
31 Watanabe S, Watanabe T, Arai K, et al. Results of wedge resection for focal bronchioloalveolar carcinoma showing pure ground-glass attenuation on computed tomography. Ann Thorac Surg 2002; 73:1071–1075
32 Wang JC, Sone S, Feng L, et al. Rapidly growing small peripheral lung cancers detected by screening CT: correlation between radiological appearance and pathological features. Br J Radiol 2000; 73:930–937
33 Aoki T, Nakata H, Watanabe H, et al. Evolution of peripheral lung adenocarcinomas: CT findings correlated with histology and tumor doubling time. AJR Am J Roentgenol 2000; 174:763–768
34 Kubota K, Matsuzawa T, Fujiwara T, et al. Differential diagnosis of lung tumor with positron emission tomography: a prospective study. J Nucl Med 1990; 31:1927–1932
35 Gupta NC, Frank AR, Dewan NA, et al. Solitary pulmonary nodules: detection of malignancy with PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology 1992; 184:441–444
36 Dewan NA, Gupta NC, Redepenning LS, et al. Diagnostic efficacy of PET-FDG imaging in solitary pulmonary nodules: potential role in evaluation and management. Chest 1993; 104:997–1002
37 Patz EF Jr, Lowe VJ, Hoffman JM, et al. Focal pulmonary abnormalities: evaluation with F-18 fluorodeoxyglucose PET scanning. Radiology 1993; 188:487–490
38 Dewan NA, Reeb SD, Gupta NC, et al. PET-FDG imaging and transthoracic needle lung aspiration biopsy in evaluation of pulmonary lesions: a comparative risk-benefit analysis. Chest 1995; 108:441–446
39 Duhaylongsod FG, Lowe VJ, Patz EF Jr, et al. Detection of primary and recurrent lung cancer by means of F-18 fluorodeoxyglucose positron emission tomography (FDG PET). J Thorac Cardiovasc Surg 1995;110:130–139; discussion 139–140
40 Duhaylongsod FG, Lowe VJ, Patz EF Jr, et al. Lung tumor growth correlates with glucose metabolism measured by fluoride-18 fluorodeoxyglucose positron emission tomography. Ann Thorac Surg 1995; 60:1348–1352
41 Gupta NC, Maloof J, Gunel E. Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. J Nucl Med 1996; 37:943–948
42 Dewan NA, Shehan CJ, Reeb SD, et al. Likelihood of malignancy in a solitary pulmonary nodule: comparison of Bayesian analysis and results of FDG-PET scan. Chest 1997; 112:416–422
43 Gupta N, Gill H, Graeber G, et al. Dynamic positron emission tomography with F-18 fluorodeoxyglucose imaging in differentiation of benign from malignant lung/mediastinal lesions. Chest 1998; 114:1105–1111
44 Lowe VJ, Fletcher JW, Gobar L, et al. Prospective investigation of positron emission tomography in lung nodules. J Clin Oncol 1998; 16:1075–1084
45 Orino K, Kawamura M, Hatazawa J, et al. Efficacy of F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scans in diagnosis of pulmonary nodules [in Japanese]. Jpn J Thorac Cardiovasc Surg 1998; 46:1267–1274
46 Prauer HW, Weber WA, Romer W, et al. Controlled prospective study of positron emission tomography using the glucose analogue [18f]fluorodeoxyglucose in the evaluation of pulmonary nodules. Br J Surg 1998; 85:1506–1511
47 Hung GU, Shiau YC, Tsai SC, et al. Differentiation of radiographically indeterminate solitary pulmonary nodules with. Jpn J Clin Oncol 2001; 31:51–54
48 Croft DR, Trapp J, Kernstine K, et al. FDG-PET imaging and the diagnosis of non-small cell lung cancer in a region of high histoplasmosis prevalence. Lung Cancer 2002; 36:297–301
49 Matthies A, Hickeson M, Cuchiara A, et al. Dual time point 18F-FDG PET for the evaluation of pulmonary nodules. J Nucl Med 2002; 43:871–875
50 Herder GJ, Golding RP, Hoekstra OS, et al. The performance of (18)F-fluorodeoxyglucose positron emission tomography in small solitary pulmonary nodules. Eur J Nucl Med Mol Imaging 2004; 31:1231–1236
51 Swensen SJ, Morin RL, Schueler BA, et al. Solitary pulmonary nodule: CT evaluation of enhancement with iodinated contrast material; a preliminary report. Radiology 1992; 182: 343–347
52 Yamashita K, Matsunobe S, Tsuda T, et al. Solitary pulmonary nodule: preliminary study of evaluation with incremental dynamic CT. Radiology 1995; 194:399–405
53 Swensen SJ, Brown LR, Colby TV, et al. Lung nodule enhancement at CT: prospective findings. Radiology 1996; 201:447–455
54 Potente G, Iacari V, Caimi M. The challenge of solitary pulmonary nodules: HRCT evaluation. Comput Med Imaging Graph 1997; 21:39–46
55 Swensen SJ, Viggiano RW, Midthun DE, et al. Lung nodule enhancement at CT: multicenter study. Radiology 2000; 214:73–80
56 Yi CA, Lee KS, Kim EA, et al. Solitary pulmonary nodules: dynamic enhanced multi-detector row CT study and comparison with vascular endothelial growth factor and microvessel density. Radiology 2004; 233:191–199
57 van Sonnenberg E, Casola G, Ho M, et al. Difficult thoracic lesions: CT-guided biopsy experience in 150 cases. Radiology 1988; 167:457–461
58 Garcia Rio F, Diaz Lobato S, Pino JM, et al. Value of CT-guided fine needle aspiration in solitary pulmonary nodules with negative fiberoptic bronchoscopy. Acta Radiol 1994; 35:478–480
59 Li H, Boiselle PM, Shepard JO, et al. Diagnostic accuracy and safety of CT-guided percutaneous needle aspiration biopsy of the lung: comparison of small and large pulmonary nodules. AJR Am J Roentgenol 1996; 167:105–109
60 Santambrogio L, Nosotti M, Bellaviti N, et al. CT-guided

fine-needle aspiration cytology of solitary pulmonary nodules: a prospective, randomized study of immediate cytologic evaluation. Chest 1997; 112:423–425
61 Westcott JL, Rao N, Colley DP. Transthoracic needle biopsy of small pulmonary nodules. Radiology 1997; 202:97–103
62 Yankelevitz DF, Henschke CI, Koizumi JH, et al. CT-guided transthoracic needle biopsy of small solitary pulmonary nodules. Clin Imaging 1997; 21:107–110
63 Hayashi N, Sakai T, Kitagawa M, et al. CT-guided biopsy of pulmonary nodules less than 3 cm: usefulness of the spring-operated core biopsy needle and frozen-section pathologic diagnosis. AJR Am J Roentgenol 1998; 170:329–331
64 Laurent F, Latrabe V, Vergier B, et al. CT-guided transthoracic needle biopsy of pulmonary nodules smaller than 20 mm: results with an automated 20-gauge coaxial cutting needle. Clin Radiol 2000; 55:281–287
65 Wallace MJ, Krishnamurthy S, Broemeling LD, et al. CT-guided percutaneous fine-needle aspiration biopsy of small (≤1-cm) pulmonary lesions. Radiology 2002; 225: 823–828
66 Yamagami T, Iida S, Kato T, et al. Usefulness of new automated cutting needle for tissue-core biopsy of lung nodules under CT fluoroscopic guidance. Chest 2003; 124: 147–154
67 Welker JA, Alattar M, Gautam S. Repeat needle biopsies combined with clinical observation are safe and accurate in the management of a solitary pulmonary nodule. Cancer 2005; 103:599–607

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