Evaluation of Patients With Pulmonary Nodules: When Is It Lung Cancer?*

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

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Background: **Pulmonary nodules are spherical radiographic opacities that measure up to 30 mm in diameter. Nodules are extremely common in clinical practice and challenging to manage, especially small, "subcentimeter" nodules. Identification of malignant nodules is important because they represent a potentially curable form of lung cancer.**

Methods: **We developed evidence-based clinical practice guidelines based on a systematic literature review and discussion with a large, multidisciplinary group of clinical experts and other stakeholders.**

Results: **We generated a list of 29 recommendations for managing the solitary pulmonary nodule (SPN) that measures at least 8 to 10 mm in diameter; small, subcentimeter nodules that measure < 8 mm to 10 mm in diameter; and multiple nodules when they are detected incidentally during evaluation of the SPN. Recommendations stress the value of risk factor assessment, the utility of imaging tests (especially old films), the need to weigh the risks and benefits of various management strategies (biopsy, surgery, and observation with serial imaging tests), and the importance of eliciting patient preferences.**

Conclusion: **Patients with pulmonary nodules should be evaluated by estimation of the probability of malignancy, performance of imaging tests to characterize the lesion(s) better, evaluation of the risks associated with various management alternatives, and elicitation of patient preferences for treatment.**

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Key words: emission CT; granulomas; lung metastasis; lung neoplasms; needle biopsy; pulmonary coin lesion; radiograph CT; thoracic radiography; thoracic surgery

Abbreviations: ACCP = American College of Chest Physicians; CXR = chest radiography; FDG = F-18 fluorodeoxyglucose; HU = Hounsfield unit; NSCLC = non-small cell lung cancer; OR = odds ratio; PET = positron emission tomography; SCLC = small cell lung cancer; SPN = solitary pulmonary nodule; TTNA = transthoracic needle aspiration/biopsy

Pulmonary nodules are small, focal, radiographic opacities that may be solitary or multiple. By definition, the solitary pulmonary nodule (SPN) is a single, spherical, well-circumscribed, radiographic opacity that measures ≤ 3 cm in diameter and is surrounded

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completely by aerated lung. There are no associated atelectasis, hilar enlargement, or pleural effusion.[1,2] The term *coin lesion* should be discouraged because nodules are spherical and not coin shaped. Patients with solitary nodules typically have no symptoms. Focal pulmonary lesions that are >3 cm in diameter are called *lung masses* and are presumed to represent bronchogenic carcinoma until proved otherwise. The diagnosis and management of lung masses and symptomatic nodules are discussed in other chapters in these guidelines.

We further distinguish small, subcentimeter nodules from the classical SPN because, compared with larger nodules, nodules that measure <8 to 10 mm in diameter are much less likely to be malignant, typically defy accurate characterization by imaging tests, and are often difficult to approach by needle biopsy. Throughout this chapter, we reserve the term *SPN* for nodules that measure at least 8 to 10 mm in diameter and use the term *subcentimeter* to refer to smaller nodules. We use the term *indeterminate* to describe a nodule that is not calcified in a benign pattern and that has not been shown to be stable after >2 years of follow-up. We do not distinguish screen-detected nodules from nodules that are detected incidentally or distinguish nodules that are detected by chest radiography (CRX) vs chest CT. When treating patients with lung nodules, it is more important to consider the number (solitary vs multiple), size, and morphology of the lesion(s), as well as the presence of symptoms and risk factors for malignancy. In contrast to the patient with an SPN, patients with multiple lung nodules often have symptoms and typically require systemic therapy for an underlying infectious, inflammatory, or neoplastic diseases.

We begin this chapter by discussing recommendations for the patient with an SPN that measures at least 8 to 10 mm in diameter. Next, we discuss recommendations for managing the increasingly common problem of the subcentimeter nodule. Finally, we discuss patients with multiple lung nodules and other special circumstances. Most of the interventions described in this chapter are diagnostic tests. Although there have been many high-quality studies of diagnostic accuracy, few randomized, controlled trials or outcomes studies have been performed. As a result, many of the recommendations in this chapter are based on evidence that is relatively low in quality.

Materials and Methods

To update previous recommendations on the evaluation of patients with pulmonary nodules,[3] guidelines on lung cancer diagnosis and management that were published between 2002 and May 2005 were identified by a systematic review of the literature (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter). Those guidelines, which include recommendations that are specific to the treatment of patients with pulmonary nodules, were identified for inclusion in this chapter. Supplemental material that is appropriate to this topic was obtained by literature search of a computerized database (MEDLINE), as described in the chapter of these guidelines by Wahidi et al.[4] In addition, we identified articles by searching our own files and by reviewing reference lists provided by the Thoracic Oncology NetWork of the American College of Chest Physicians (ACCP). A multidisciplinary writing committee composed of three pulmonologists, two thoracic surgeons, and two radiologists developed the recommendations and graded the strength of the recommendations and the quality of the supporting evidence by using a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter). The resulting guideline was reviewed by all members of the lung cancer guidelines panel before approval by the Thoracic Oncology NetWork, the Health and Science Policy Committee, and the Board of Regents of the ACCP.

Results

SPNs

The SPN is commonly encountered in both primary care and specialty settings. Most lung nodules are detected incidentally on CXRs or CT scans that are obtained for some other purpose. In one study[5] from the 1950s, an SPN was found in 1 of 500 CXRs (0.2%) that were obtained in community settings. More recently, almost 7% of 1,000 healthy volunteers in New York who participated in the Early Lung Cancer Action Project[6] were found to have between one and three nodules on baseline screening CXR. In most of these volunteers (76%), the largest nodule measured <1 cm in diameter. Perhaps not surprising, an even larger number of the participants in this study (almost 25%) were found to have between one and six lung nodules (many of which were subcentimeter nodules) on a low-dose spiral CT scan of the chest. Of note, more than half of the nodules that were detected by CXR were false-positive findings; the presence of the nodule was not confirmed by low-dose CT. In other studies[4] of screening with low-dose CT, nodules were identified in 8 to 51% of participants at the time of baseline screening.

The prevalence of malignancy in patients with SPN varies widely across studies. In studies[4] of positron emission tomography (PET) with F-18 fluorodeoxyglucose (FDG), the prevalence of malignancy ranged from 46 to 82%. In screening studies,[4] the prevalence of malignant SPN was much lower, roughly 2 to 13% in those with nodules. Most of the screening-detected nodules measured <10 mm in diameter. In a study[4] of patients with either screening-detected or incidentally detected lung nodules, the prevalence of malignancy was 33 to 60% in nod-

ules that measured 11 to 20 mm in diameter and 64 to 82% in nodules that measured > 20 mm in diameter.

The SPN is important because malignant nodules represent a potentially curable form of bronchogenic carcinoma. In stark contrast to patients who present with more advanced lung cancer, > 60% of patients with clinical stage IA (T1N0M0) tumors will still be alive 5 years after they receive treatment.[7] It is not clear to what extent the malignant SPN represents "early" lung cancer vs "slowly growing" lung cancer, but it should be acknowledged that many patients who present with a malignant SPN probably have tumors that are less aggressive biologically than tumors in patients who present with more advanced stages of lung cancer.[8] Despite this, many cancerous SPNs clearly do not behave in a "benign" or indolent manner: up to 20% of patients with clinical stage IA tumors will have occult mediastinal lymph node metastasis identified by mediastinal biopsy or thoracotomy.[9,10]

Differential Diagnosis: In studies[11–20] of PET imaging, most of which were performed in the United States, the most common causes of benign SPN were healed or nonspecific granulomas, accounting for 25% of all benign causes. Another 15% of benign nodules were caused by active granulomatous infections, including tuberculosis, coccidioidomycosis, histoplasmosis, cryptococcosis, and aspergillosis. Hamartomas comprised an additional 15% of benign lesions. Less common miscellaneous causes of benign nodules included nonspecific inflammation and fibrosis, lung abscesses, round pneumonia, round atelectasis, bronchogenic cysts, healed pulmonary infarcts, focal hemorrhage, hemangiomas, and arteriovenous malformations. Because bronchopneumonia is a very uncommon cause of SPN and unnecessary use of antibiotics encourages the development of resistant strains of bacteria, we strongly discourage the use of empirical antibiotics in patients who have lung nodules with no symptoms. In addition, a trial of antibiotics contributes to avoidable delays in the diagnosis and treatment of patients with malignant nodules.

The most common causes of malignant SPN in studies[11–20] of PET imaging were adenocarcinoma (47%), squamous cell carcinoma (22%), solitary metastasis (8%), undifferentiated non-small cell carcinoma (NSCLC) [7%], small cell lung cancer (SCLC) [4%], and bronchioloalveolar cell carcinoma (4%). Less common causes of malignant SPN included large cell carcinoma, carcinoid tumors, intrapulmonary lymphomas, adenosquamous carcinoma, adenoid cystic carcinoma, and malignant teratomas.

Pretest Probability: Although clinical and radiographic characteristics cannot reliably distinguish between benign and malignant nodules in most patients, it nevertheless is important to estimate the clinical "pretest" probability of malignancy before ordering imaging tests or biopsy procedures. Estimating pretest probability facilitates the selection and interpretation of subsequent diagnostic tests. Common sense suggests that different management approaches are called for in a 30-year-old nonsmoker with a 1-cm, smooth-bordered nodule, and a 70-year-old heavy smoker with a 2.5-cm spiculated nodule. Most patients with SPNs have characteristics that fall somewhere between these two extremes. Although many clinicians estimate pretest probability intuitively, several quantitative models[21–23] have been developed to assist in this task. One validated model[22,24] was developed by investigators at the Mayo Clinic, who used multiple logistic regression analysis to identify six independent predictors of malignancy in 419 patients with noncalcified nodules that measured between 4 and 30 mm in diameter on CXR. Independent predictors of malignancy included older age (odds ratio [OR], 1.04 for each year), current or past smoking (OR, 2.2), history of extrathoracic cancer > 5 years before nodule detection (OR, 3.8), nodule diameter (OR, 1.14 for each millimeter), spiculation (OR, 2.8), and upper-lobe location (OR, 2.2). The prediction model is described by the following equations:

$$\text{Probability of malignancy} = e^x/(1 + e^x)$$

$$x = -6.8272 + (0.0391 \times \text{age}) + (0.7917 \times \text{smoke}) + (1.3388 \times \text{cancer}) + (0.1274 \times \text{diameter}) + (1.0407 \times \text{spiculation}) + (0.7838 \times \text{location})$$

where e is the base of natural logarithms, age is the patient's age in years, smoke = 1 if the patient is a current or former smoker (otherwise = 0), cancer = 1 if the patient has a history of an extrathoracic cancer that was diagnosed > 5 years ago (otherwise = 0), diameter is the diameter of the nodule in millimeters, spiculation = 1 if the edge of the nodule has spicules (otherwise = 0), and location = 1 if the nodule is located in an upper lobe (otherwise = 0).

Of note, the accuracy of this model for predicting malignancy was similar to the accuracy of expert clinicians.[25] Other investigators have attempted to predict malignancy by using the likelihood ratio form of Bayes theorem[21,23] and neural networks.[26–28]

Recommendation

1. In every patient with an SPN, we recommend that clinicians estimate the pretest probability of malignancy either qualitatively by using clinical judgment or quantitatively by using a validated model. Grade of recommendation, 1C

Imaging Tests: Pulmonary nodule diagnosis begins with imaging studies. CXR and CT are useful and widely available. Recent attention has focused on contrast-enhanced CT and FDG-PET. MRI plays a limited role, if any, in most patients.

CXR: SPN diagnosis should begin with a careful review of the CXR. Nodules located within the chest should be seen in more than one radiographic view, although it is sometimes difficult to visualize nodules in the lateral projection. Occasionally, nipple shadows or articular surfaces of ribs can masquerade as pulmonary nodules. In these cases, the use of nipple markers or apical lordotic projections may help to distinguish normal anatomic structures from abnormal nodular parenchymal lesions.

Depending on the location of the lesion and the sharpness of its borders, nodules as small as 5 to 6 mm in diameter can sometimes be visualized by plain CXR.[29] However, many larger solitary nodules are often missed by even experienced chest radiologists. For example, in the Mayo Lung Project,[30] 45 of 50 screening-detected peripheral carcinomas were visible on previous radiographs when reviewed in retrospect. All but one of the tumors measured at least 1 cm in diameter. In another study,[31] 19% of NSCLCs were identified retrospectively on previous CXRs that were interpreted as being normal. Patients with missed lesions had smaller nodules, more superimposing structures, and more indistinct border edges than patients with tumors that were not missed. In a more recent retrospective study[32] of 40 patients with NSCLCs that initially were missed on CXR, the median diameter was 1.9 cm, and 85% of the lesions were peripheral in location. Missed cancers were most commonly located on the right side and in the upper lobes, especially in the apical and posterior segments. A clavicle obscured 22% of the missed lesions.

The recent introduction of dual-energy subtraction digital CXR systems substantially increases the ability to detect nodules. This technique provides markedly enhanced contrast resolution, especially in previously difficult-to-evaluate regions of the lung, including behind the heart and below the diaphragms.[33] It is also possible, by use of both single- and dual-exposure techniques, to vary radiation exposure (kilovolt peak) and thereby facilitate detection of noncalcified nodules.[34] As the use of these newer techniques becomes more widespread in clinical practice, it is likely that fewer lung nodules will escape detection.

In all patients with an SPN, it is essential to compare the current CXR with previous chest films. This point cannot be emphasized strongly enough because nodules that have been stable for at least 2 years usually do not require further evaluation. If the nodule is seen with the benefit of hindsight on the previous CXR, then growth rate of it can be estimated. The growth rate is typically expressed in terms of the doubling time, or the time it takes for the nodule to double in volume. Because the volume of a sphere equals $4\Pi r^3/3$, one doubling in tumor volume corresponds approximately to an increase in nodule diameter of 26%. The doubling time can be calculated by using the formula $dt = (t \times \log 2)/\{3 \times [\log (d_2/d_1)]\}$, where dt is the doubling time in days, t is the time in days between CXRs, d_2 is the diameter of the nodule at the time of the current CXR, and d_1 is the diameter of the nodule at the time of the previous CXR.[35] Doubling times for malignant nodules are highly variable but are generally thought to fall between 20 and 300 days.[36–38] However, older studies of lung cancer growth rates selectively enrolled patients who were more likely to have benign-appearing nodules or nodules that initially escaped detection, biasing the results in favor of longer doubling times. Indirect epidemiologic evidence suggests that most malignant nodules encountered in clinical practice have tumor doubling times that are well < 100 days.[39] Malignant nodules with longer doubling times can grow for many years before symptoms develop. For example, assuming exponential growth, a malignant nodule that measures 10 mm in diameter and has a tumor volume doubling time of 300 days will require > 4 years (approximately five doubling times) to reach a size that is commonly associated with symptoms (32 mm).

Because doubling times for malignant SPN rarely are > 300 days (except in screening studies), 2-year radiographic stability strongly suggests a benign etiology. Some authors[40] have questioned the validity of this rule, especially as it relates to smaller, screening-detected nodules, which may have longer doubling times when cancerous. Many of these nodules have a pure ground-glass appearance, which often represents slowly growing bronchioloalveolar cell carcinoma. Because some ground-glass opacities eventually take on a more aggressive phenotype, longer follow-up for patients with these lesions should be considered.[41,42] However, there is no evidence that extending follow-up beyond 2 years identifies a sizable number of malignant nodules or improves patient outcomes.

Occasionally, a presumptive benign diagnosis can be established when a characteristic pattern of calcification is noted on the CXR. Diffuse, central, laminated, and popcorn patterns of calcification are considered to be benign,[43,44] although the presence of intranodular fat density is more sensitive for identifying a hamartoma than popcorn calcification.[45] If one of these patterns of calcification is clearly evident on the CXR, no additional evaluation is necessary. However, other patterns of calcification, including the stippled and eccentric patterns, do not exclude malignancy. Further evaluation of these nodules is mandatory. Studies[46] have documented that, compared with routine CXR and standard digital radiography, dual-energy digital subtraction radiography improves detection of intranodular calcification.

Recommendations

2. In every patient with an SPN that is visible on CXR, we recommend that previous CXRs and other relevant imaging test be reviewed. Grade of recommendation, 1C

3. In patients who have an SPN that shows clear evidence of growth on imaging tests, we recommend that tissue diagnosis be obtained unless specifically contraindicated. Grade of recommendation, 1C

4. In a patient with an SPN that is stable on imaging tests for at least 2 years, we suggest that no additional diagnostic evaluation be performed, except for patients with pure ground-glass opacities on CT, for whom a longer duration of annual follow-up should be considered. Grade of recommendation, 2C

5. In a patient with an SPN that is calcified in a clearly benign pattern, we recommend no additional diagnostic evaluation. Grade of recommendation, 1C

Chest CT: Because of lack of superimposition of normal structures, CT is both more sensitive and more specific than CXR for detecting nodules. The likelihood of nodule detection increases with use of thinner slice thickness. Single-arm prospective studies[6,47] of CT screening in high-risk participants found one or more nodules in approximately 25% of participants when 10-mm collimation was used. In contrast, approximately 50% of participants were found to have one or more nodules when 1.25- to 5-mm collimation was used for screening.[48–50]

As is true for nodules identified by CXR, all previous CT scans should be reviewed when a nodule is first identified by CT. Chest CT provides more specific information about the location, density, and edge characteristics of nodules that have been detected. In addition, CT sometimes identifies unsuspected lymphadenopathy, synchronous parenchymal lesions, or invasion of the chest wall or mediastinum. Selected morphologic characteristics are described next. We discuss nodule size and attenuation characteristics (solid vs semisolid vs ground-glass) in greater detail in a subsequent section on small, subcentimeter nodules.

Morphologic characteristics on chest CT that suggest malignancy include spiculated margins,[51–53] vascular convergence (which suggests vascular and/or lymphatic invasion),[54] and the finding of either a dilated bronchus leading into the nodule[55] or the presence of pseudocavitation, a "bubbly" appearance thought to represent air bronchiolograms.[53] True cavitation, especially when associated with a thick and irregular wall, is a strong predictor of malignancy. One study[56] found that whereas only 5% of all cavitated nodules with thin walls (< 5 mm) were malignant, the probability of malignancy was $> 85\%$ when maximum wall thickness was > 15 mm.

Morphologic clues can sometimes lead to a presumptive benign diagnosis. For example, arteriovenous fistulas often demonstrate the presence of a feeding artery and a draining vein. A fungus ball can be identified as a solitary nodule within a cavity, although this appearance does not exclude the possibility of malignancy. Acute pulmonary infarcts typically appear on CT as wedge-shaped densities that abut the pleura, involve the lower lobes, and contain air bronchograms, but chronic infarcts may be more difficult to distinguish from a peripheral carcinoma. Rounded atelectasis is characterized by a quartet of CT features, including volume loss, a juxtapleural location, associated pleural thickening, and a dense "comet tail" of bronchovascular structures that points toward the hilum. Although classically associated with asbestos-related pleural disease, this entity may be the result of any process that causes marked focal pleural fibrosis.[57]

Initially described in severely immunocompromised patients with marked neutropenia, the CT halo sign (defined as a zone of ground-glass attenuation surrounding a solid dense core) is strongly associated with the presence of an invasive fungal infection, with the halo caused by hemorrhage surrounding a focal pulmonary infarct.[58] It should be emphasized, however, that other infectious and noninfectious entities may be associated with a positive halo sign, including mycobacterial infections.[59–61]

In the past, CT densitometry was performed by comparing the density of a given nodule with the density of a standardized "reference phantom."[52,62] Relatively sensitive but not specific, this technique is no longer used because of limited reliability.

However, smaller (< 20 mm in diameter), smooth-bordered nodules that contain fat density (< 25 Hounsfield units [HU]) can be confidently diagnosed as a hamartoma, provided appropriate caution is taken to avoid misinterpreting partial volume artifacts as actual fat.[63]

CT with dynamic contrast enhancement has proved to be highly sensitive but nonspecific for identifying malignant nodules.[4] A multicenter study[64] enrolled 356 participants with normal renal function and noncalcified nodules that measured 0.5 to 4 cm in diameter, 48% of which were malignant. Using a threshold for enhancement of 15 HU, the sensitivity and specificity of contrast-enhanced CT were 98% and 58%, respectively. Absence of lung nodule enhancement was strongly predictive of a benign diagnosis; the negative predictive value was 96.5%. Allowing for slight differences in technique, nearly identical results have been reported by others.[65–69]

Risks associated with CT include radiation exposure and adverse effects as a result of administration of iodinated contrast material. The magnitude of the risk associated with radiation exposure from a single CT scan is likely to be small, but in patients who require multiple follow-up scans, low-dose techniques should be used whenever possible to minimize the uncertain risk associated with repeated radiation exposure.[70] IV contrast should not be used in patients with renal insufficiency or allergy to iodine, and it is usually not necessary to administer contrast when performing follow-up CT scans to identify growth.

Recommendations

6. In every patient with an indeterminate SPN that is visible on CXR, we recommend that CT of the chest be performed, preferably with thin sections through the nodule. Grade of recommendation, 1C

7. In every patient with an indeterminate SPN that is visible on chest CT, we recommend that previous imaging tests be reviewed. Grade of recommendation, 1C

8. In a patient with normal renal function and an indeterminate SPN on CXR or chest CT, we recommend that CT with dynamic contrast enhancement be considered in centers that have experience performing this technique. Grade of recommendation, 1B

MRI: MRI has a very limited role in the evaluation of the SPN. Dynamic gadolinium-enhanced MRI of lung nodules has been shown to be nearly comparable to contrast-enhanced CT for differentiating benign from malignant nodules: however, this technique remains experimental because of a lack of consensus regarding standardization.[71,72] Consequently, MRI is not indicated in the workup of the SPN outside investigational settings.

FDG-PET: In this chapter, recommendations address the use of FDG-PET for characterizing SPNs. Recommendations regarding the related issue of when to use FDG-PET for lung cancer staging are presented in these guidelines in the "Noninvasive Staging of Non-small Cell Lung Cancer" chapter.

FDG-PET is a noninvasive functional imaging test that is widely used in clinical oncology for tumor diagnosis, disease staging, and evaluation of treatment response.[73,74] FDG is taken up selectively by malignant tumor cells, which overexpress the glucose transporter protein. FDG subsequently accumulates within the cell because the radiolabeled glucose analog is phosphorylated once but not metabolized further. FDG is a positron-emitting radionuclide that undergoes an annihilation reaction after colliding with a nearby electron, resulting in the simultaneous release of two high-energy (511 kiloelectron volts) photons in opposite directions. Annihilation photons are coincidentally detected by a ring of crystals in the PET scanner. Electronic circuits and computer software subsequently localize the abnormality, register the intensity of uptake, and reconstruct cross-sectional images for display.[75]

In 17 studies[4] of diagnostic accuracy identified in the evidence chapter for this guideline, PET characterized pulmonary nodules with fairly high sensitivity (80 to 100%) and variable specificity (40 to 100%); using a summary receiver operating characteristic curve method, point estimates for pooled sensitivity and specificity were 87% and 83%, respectively. Slightly more favorable estimates were reported in a previous metaanalysis.[76] PET seems to be less sensitive for nodules that measure < 8 to 10 mm in diameter,[77] so its use in such nodules should be discouraged outside investigational settings. Preliminary evidence suggests that FDG-PET can help characterize screening-detected nodules that measure at least 8 to 10 mm in diameter, but a troubling number of false-negative and occasional false-positive findings have been reported in this situation.[78–80]

False-negative findings on PET can be seen in patients with bronchioloalveolar cell carcinoma, carcinoid tumors, and mucinous adenocarcinomas.[18,81] In theory, uncontrolled hyperglycemia may also cause false-negative results,[82] but the influence of hyperglycemia in clinical settings is uncertain. False-positive findings are often the result of infections or inflammatory conditions, including (but not limited to) endemic mycoses, tuberculosis, rheumatoid nod-

ules, and sarcoidosis.[11,83] Paradoxically, false-positive PET results can be helpful sometimes because they alert the clinician to the presence of an active infectious or inflammatory condition that might require specific treatment. In some circumstances, FDG-PET can be helpful by directing tissue biopsy.[84] As a "metabolic biopsy tool," PET can identify which lesions or portions of lesions are metabolically active and most likely to yield a definitive tissue result.

Use of FDG-PET may be most cost-effective when clinical pretest probability and CT results are discordant, especially when pretest probability is relatively low and CT characteristics are indeterminate (*ie*, not clearly benign).[85] In patients with indeterminate nodules (by CT) and high pretest probability, negative PET results do not reliably exclude malignancy. However, patients with nonhypermetabolic malignant tumors may have a favorable prognosis even when definitive surgical treatment is delayed by a period of observation as long as 238 days.[86,87] Hence, patients with negative PET results should be followed up with serial imaging tests for at least 2 years to confirm a benign diagnosis. A more cautious approach would be to perform needle biopsy in high-probability patients with negative PET results.

Integrated PET-CT scanners combine CT and FDG imaging capability in a single patient gantry, facilitating the precise localization of areas of FDG uptake to normal structures or abnormal soft-tissue masses. Accordingly, PET-CT can help to distinguish between hilar and mediastinal lymph nodes and identify invasion of the chest wall or mediastinal structures, but the role of PET-CT scanners in the management of SPN has not been well defined.[88,89] FDG-PET imaging is associated with minimal risk to the patient, because radiation doses are extremely low.

Recommendations

9. In patients with low-to-moderate pretest probability of malignancy (5 to 60%) and an indeterminate SPN that measures at least 8 to 10 mm in diameter, we recommend that FDG-PET imaging be performed to characterize the nodule. Grade of recommendation, 1B

10. In patients with an SPN that has a high pretest probability of malignancy (> 60%) or patients with a subcentimeter nodule that measures < 8 to 10 mm in diameter, we suggest that FDG-PET not be performed to characterize the nodule. Grade of recommendation, 2C

Management Strategies: Once imaging tests have been performed, management alternatives include surgery, transthoracic needle or bronchoscopic biopsy, and observation with serial radiographs, or "watchful waiting." Each of these approaches has advantages and disadvantages. Surgery is the diagnostic "gold standard" and the definitive treatment for malignant nodules, but surgery should be avoided in patients with benign nodules. Biopsy often establishes a specific benign or malignant diagnosis, but biopsy is invasive, potentially risky, and frequently nondiagnostic. Observation with serial imaging tests avoids unnecessary surgery in patients with benign nodules, but observation delays diagnosis and treatment in cases of malignancy. A decision analysis found that the choice of management strategy was "a close call" across a range of probabilities for malignancy.[90] In this analysis, observation was favored when the probability of malignancy was $< 3\%$, and surgery was preferred when the probability was $> 68\%$. Biopsy was the recommended strategy when the probability of malignancy fell between 3% and 68%. A generic management algorithm that is based on this analysis and a subsequent cost-effectiveness analysis[85] is presented in Figure 1. More specific recommendations are outlined next.

Patients with SPN may have underlying comorbidities that preclude surgical intervention. Preoperative risk assessment is discussed in detail in the chapter on "Physiologic Evaluation of the Patient With Lung Cancer Being Considered for Resectional Surgery" in these guidelines, and evaluation of patients who refuse surgery or who are poor candidates for surgery is discussed later in this chapter.

Shared Decision Making and Patient Preferences: Because different management strategies are associated with similar expected outcomes in many patients with lung nodules, patient preferences should be elicited and used to guide decisions. Some patients may be uncomfortable with adopting a strategy of observation when told that a potentially cancerous lung nodule is present. Others are similarly risk averse about undergoing surgery unless they are certain that cancer is present. All patients should be provided with an estimate of the probability of cancer and informed about the specific risks and benefits associated with alternative management strategies. Clinicians should elicit preferences for management and be sensitive to the preferred participatory decision-making style of the patient.[91,92]

Recommendation

11. In every patient with an SPN, we recommend that clinicians discuss the risks and ben-

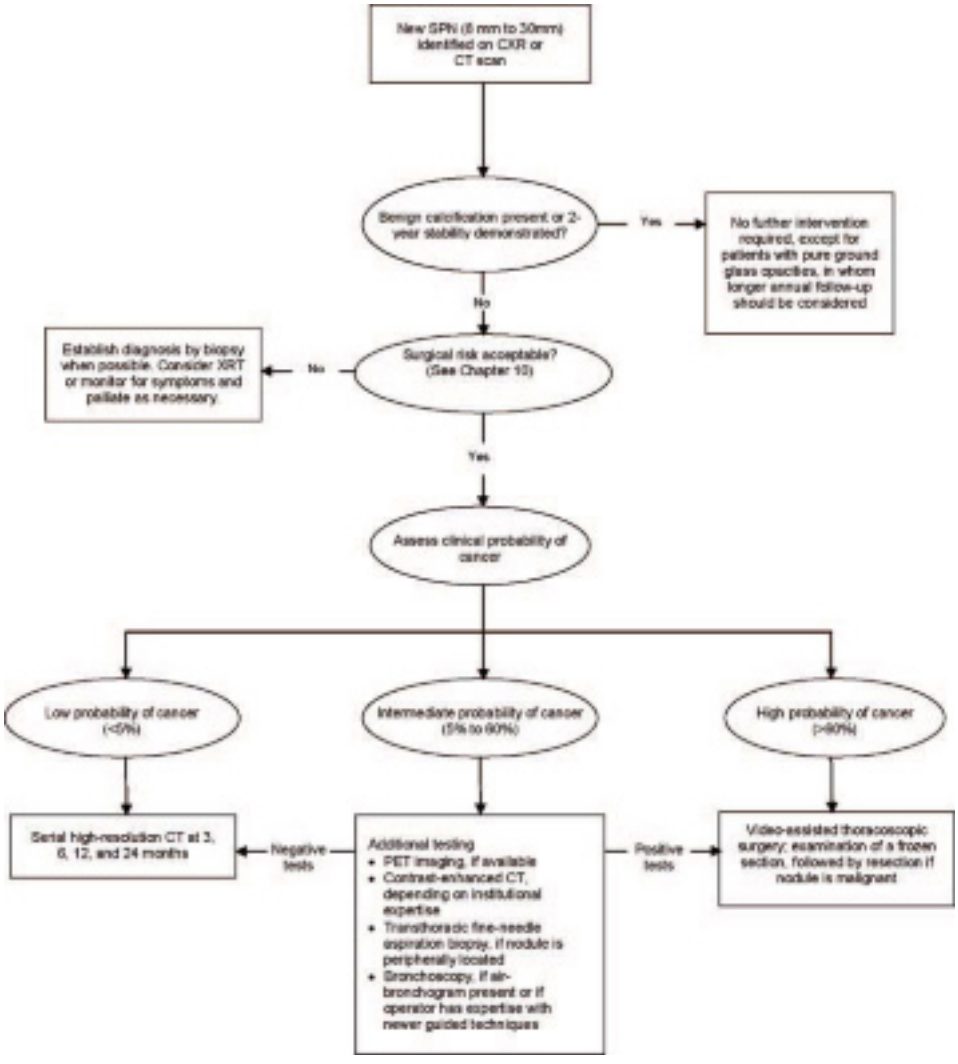

FIGURE 1. Recommended management algorithm for patients with SPNs that measure 8 to 30 mm in diameter. Adapted from Ost et al.[2]

efits of alternative management strategies and elicit patient preferences. Grade of recommendation, 1C

Observation or Watchful Waiting: In some patients with lung nodules, observation with serial imaging tests may be used as a diagnostic tool. When this strategy is used, detection of growth at any time is presumptive evidence of malignancy, and surgical resection should be performed in patients who are operative candidates. Two-year radiographic stability is strong presumptive evidence of a benign cause. Because it may be difficult to detect growth in nodules on plain CXRs, CT is usually preferred. Although it may be possible to detect growth on serial CXRs when the nodule is large (> 1.5 to 2 cm) and has sharp, clearly demarcated borders, the observation strategy is seldom used in operative candidates with nodules of this size, because of the relatively high probability of malignancy. The optimal time interval between imaging tests has not been determined for patients with SPN, but the standard clinical practice is to obtain follow-up CT scans at least at 3, 6, 12, and 24 months. More frequent follow-up may be considered in patients who are at higher risk for malignancy. Less frequent follow-up is indicated in patients with small, subcentimeter nodules.

The disadvantage of the observation strategy is that it potentially delays diagnosis and treatment in patients with malignant nodules. Depending on the growth rate and metastatic potential of the nodule and the length of observation, some malignant tumors will progress from resectable to unresectable disease during the observation period, and opportunities for surgical cure will be missed. Empirical data relevant to the hazard of delay

are scarce, although a Scottish study[93] found that maximum cross-sectional tumor area increased by > 50% in almost 25% of patients who had delays in radiotherapy treatment lasting between 18 and 131 days. Therefore, the observation strategy should be selected with caution. It is most appropriate in patients with a very low risk for malignancy and/or those who are at high risk for complications of surgical resection and/or nonsurgical biopsy.

Recommendations

12. In patients who have an indeterminate SPN that measures at least 8 to 10 mm in diameter and are candidates for curative treatment, observation with serial CT scans is an acceptable management strategy in the following circumstances: (1) when the clinical probability of malignancy is very low (< 5%); (2) when clinical probability is low (< 30 to 40%) and the lesion is not hypermetabolic by FDG-PET or does not enhance > 15 HU on dynamic contrast CT; (3) when needle biopsy is nondiagnostic and the lesion is not hypermetabolic by FDG-PET; (4) when a fully informed patient prefers this nonaggressive management approach. Grade of recommendation, 2C

13. In patients who have an indeterminate SPN that measures at least 8 to 10 mm in diameter and undergo observation, we suggest that serial CT scans be repeated at least at 3, 6, 12, and 24 months. Grade of recommendation, 2C

Transthoracic Needle Aspiration Biopsy: Needle biopsy of the SPN is usually performed under the guidance of fluoroscopy or, more common, CT. Few studies of needle biopsy have been performed under fluoroscopic guidance and limited enrollment to participants with pulmonary nodules. In one study[94] with a very high prevalence of malignancy, a diagnosis was made by fluoroscope-guided needle biopsy in 84% of patients with nodules that measured 2 to 4 cm in diameter. However, in two other studies[95,96] with a lower prevalence of malignancy, the diagnostic yield was only 36 to 43%.

Several studies of CT-guided needle biopsy limited enrollment to patients with pulmonary nodules that measured < 4 cm in diameter.[4] As expected, the specificity of needle biopsy for identifying malignancy was very high. However, nondiagnostic biopsy results were seen in 4 to 41% of patients (median, 21%). It is interesting that nondiagnostic biopsies were more common in nodules that proved to be benign (approximately 44% of all benign nodules) than in those that were malignant (approximately 8% of all malignant nodules). The sensitivity of transthoracic needle aspiration biopsy (TTNA) depends on the size of the nodule, the size of the needle (especially for identifying lymphoma or benign disease), the number of needle passes, and the presence of on-site cytopathology examination. Complications include minor pneumothorax in approximately 25% of procedures and major pneumothorax that requires chest tube drainage in approximately 5% of procedures. Identified risk factors for pneumothorax include smaller lesion size, deeper location, proximity to fissures, the presence of emphysema, lateral pleural puncture site, and a smaller angle of entry between the needle and the pleura. Risk factors for chest tube drainage include emphysema, proximity to fissures, and the need to traverse aerated lung.[97–99]

Use of needle biopsy is probably most appropriate when there is discordance among the clinical probability of cancer, imaging test results, patient preferences, and/or the risk for surgical complications, as described in recommendation 14. It is important to emphasize that a nondiagnostic needle biopsy result does not rule out the possibility of malignancy.

Bronchoscopy: Bronchoscopy is an excellent tool for sampling central airway lesions, mediastinal nodes, and parenchymal masses. Traditionally, bronchoscopy has played a limited role in SPN management outside investigational settings. Diagnostic yields with fluoroscope-guided bronchoscopy for malignant, peripheral pulmonary nodules that measure < 2 cm in diameter have consistently been in the range of 10 to 50%.[100–103] The likelihood of obtaining a specific benign diagnosis is even lower. The presence of an air bronchogram in a pulmonary nodule is associated with an increased yield, especially if this provides a specific road map as to the bronchial location.[104,105] Likewise, bronchoscopy with multiplanar CT or endobronchial ultrasound guidance seems to be an improvement over bronchoscopy under standard fluoroscopic guidance.[105–108]

A newer technique, electromagnetic navigation, combines simultaneous CT virtual bronchoscopy with real-time fiberoptic bronchoscopy and shows promise as another tool for guiding biopsy of peripheral nodules.[109,110] Although these new methods seem to improve diagnostic yields over fluoroscopic guidance, results still do not compare favorably with those from a recent series that evaluated TTNA in patients with small peripheral nodules.[111] Until further progress is made in guidance of bronchoscopy, peripheral nodules that do not have a CT-bronchus sign should be pursued with TTNA. In addition, routine preoperative bronchoscopy is not recom-

mended in the patient with an SPN, because it has been shown rarely to change stage and obviate the need for surgery.[112]

Older retrospective series[113] reported major complications of bronchoscopy in < 1% of procedures, including bleeding, respiratory depression, cardiorespiratory arrest, arrhythmia, and pneumothorax. Mortality has been considered rare, with a reported death rate of 0.01 to 0.03% in > 70,000 procedures.[114,115] However, a more recent prospective, multicenter study[116] suggested that complications and mortality are more frequent than previously recognized. Bechara et al[116] reported adverse events in 35% of 300 bronchoscopies performed that included at least two endobronchial biopsies. Severe adverse events occurred in 10% of patients, 4 of whom died (2%). However, two of the deaths occurred 1 week after the procedure and seemed to be unrelated.

Recommendation

14. In patients who have an indeterminate SPN that measures at least 8 to 10 mm in diameter and are candidates for curative treatment, it is appropriate to perform a transthoracic needle biopsy or bronchoscopy in the following circumstances: (1) when clinical pretest probability and findings on imaging tests are discordant; for example, when the pretest probability of malignancy is high and the lesion is not hypermetabolic by FDG-PET; (2) when a benign diagnosis that requires specific medical treatment is suspected; (3) when a fully informed patient desires proof of a malignant diagnosis before surgery, especially when the risk for surgical complications is high. In general, we suggest that transthoracic needle biopsy be the first choice for patients with peripheral nodules, unless the procedure is contraindicated or the nodule is inaccessible. We suggest that bronchoscopy be performed when an air bronchogram is present or in centers with expertise in newer guided techniques. Grade of recommendation, 2C

Surgery: Surgical resection is the "gold standard" diagnostic test and can often be therapeutic. However, only one flawed and inconclusive randomized, controlled trial[117–119] has compared surgery alone with an alternative treatment in patients with resectable lung cancer. The decision to include surgery as part of the diagnostic strategy for the SPN must take into account the benefits of definitive diagnosis and treatment when compared with the surgical risk. Video-assisted thorascopic surgery, thoracotomy, and mediastinoscopy may be used alone or in combination in patients with SPNs, depending on the clinical circumstances. Video-assisted thorascopic surgery is commonly used to diagnose peripheral SPN. Thoracotomy is sometimes necessary to make the diagnosis. If the nodule proves to be a primary lung malignancy, then therapeutic resection and staging are often completed in a single operative procedure.

Thoracoscopy is usually the favored surgical approach for nodules located in the peripheral third of the lung. It is a minimally invasive technique with a sensitivity and specificity approaching 100%,[120–122] with an associated mortality of approximately 1%.[123–128] The rate of conversion to thoracotomy is approximately 12%. As thorascopic techniques mature, resection of smaller nodules (< 5 mm) is becoming possible. Localizing techniques can be used to aid the surgeon in finding these lesions. Wire localization, methylene dye injection, fluoroscopy, and intrathoracic and extrathoracic ultrasound each have been reported as useful allies in locating small nodules.[129–134]

The diagnosis is most often established by intraoperative consultation with pathology. Frozen-section analysis is sensitive and specific for diagnosis of malignancy; however, the technique has limitations that the surgeon should understand. In one recent study,[135] the sensitivity for identifying malignancy was 86.9% for nodules that measured < 1.1 cm in diameter and 94.1% for nodules that measured between 1.1 and 1.5 cm. The specificity of frozen-section analysis was 100%. The technique has limitations in distinguishing bronchioloalveolar carcinoma from atypical adenomatous hyperplasia and reactive pneumocyte hyperplasia. It is limited in establishing a specific cell type in NSCLC. It is limited in recognizing small peripheral carcinoid tumors. Lesions that measure < 5 mm should probably not be used for frozen-section analysis unless there is other material available for permanent studies.[135]

For the surgical candidate with an SPN that is proved to be NSCLC, lobectomy and systematic mediastinal lymph node dissection are the standard of care for complete oncologic resection and staging.[136] Thoracotomy is the standard approach for resection, with a morbidity and mortality of approximately 34% and 4%, respectively.[137–145] Thoracoscopic resection and lymph node dissection for staging is an option in experienced hands.[143,146–148] For patients with marginal cardiac performance or limited pulmonary reserve, limited resection can be considered acceptable treatment, although limited resection is associated with a higher rate of local recurrence and a statistically nonsignificant trend toward reduced 5-year survival.[149,150]

An oncologic resection is not complete without staging the mediastinum. Recommendations for intraoperative staging can be found in the "Treatment of Non-small Cell Lung Cancer-Stage IIIA" in these guidelines.

Recommendations

15. In surgical candidates with an indeterminate SPN that measures at least 8 to 10 mm in diameter, surgical diagnosis is preferred in most circumstances, including the following: (1) when the clinical probability of malignancy is moderate to high (> 60%); (2) when the nodule is hypermetabolic by FDG-PET imaging; (3) when a fully informed patient prefers undergoing a definitive diagnostic procedure. Grade of recommendation, 1C

16. In patients who have an indeterminate SPN in the peripheral third of the lung and choose surgery, we recommend that thoracoscopy be performed to obtain a diagnostic wedge resection. Grade of recommendation, 1C

17. In a patient who chooses surgery for an indeterminate SPN that is not accessible by thoracoscopy, bronchoscopy, or TTNA, we recommend that a diagnostic thoracotomy be performed. Grade of recommendation, 1C

18. In patients who undergo thoracoscopic wedge resection for an SPN that is found to be cancer by frozen section, we recommend that anatomic resection with systematic mediastinal lymph node sampling or dissection be performed during the same anesthesia. Grade of recommendation, 1C

19. In patients who have an SPN and are judged to be marginal candidates for lobectomy, we recommend definitive treatment by wedge resection/segmentectomy (with systematic lymph node sampling or dissection). Grade of recommendation, 1B

Patients Who Are Not Surgical Candidates: Management is uncertain in patients who have an SPN and refuse surgery or are judged to be at unacceptably high risk for complications from even a limited pulmonary resection. No randomized trials have compared early treatment before the development of symptoms vs later treatment when symptoms develop. Discussion of potential risks and benefits with patients is limited by the paucity of data. For patients who prefer treatment, the diagnosis of lung cancer should first be confirmed by biopsy whenever possible. Although external-beam radiation therapy with curative intent is the current standard of care, experimental alternatives for these patients include stereotactic radiosurgery and radiofrequency ablation.

Recommendations

20. For the patient who has an SPN and is not a surgical candidate and prefers treatment, we recommend that the diagnosis of lung cancer be confirmed by biopsy, unless contraindicated. Grade of recommendation, 1C

21. For the patient who has a malignant SPN and is not a surgical candidate and prefers treatment, we recommend referral for external-beam radiation or to a clinical trial of an experimental treatment such as stereotactic radiosurgery or radiofrequency ablation. Grade of recommendation, 2C

Small Subcentimeter Pulmonary Nodules

Subcentimeter nodules measure < 8 to 10 mm in diameter, can be solitary or multiple, and are usually detected incidentally on a CT scan that has been ordered for some other reason. As is true for larger nodules, the likelihood of malignancy depends on patient risk factors, nodule size, and certain morphologic characteristics.

Predictors of Malignancy: Patient characteristics have been incompletely studied as predictors of malignancy in individuals with subcentimeter nodules. In the Lung Screening Study,[151] abnormal findings on a single low-dose CT screening examination were more common in current smokers and individuals who were at least 65 years of age. The likelihood of malignancy is probably highest in current smokers and lowest in nonsmokers who have nodules that are comparable in size. Extrapolation from studies in patients with larger nodules would suggest that the risk for malignancy probably increases with age.[21–23]

Size: Studies of CT screening in volunteers at risk for lung cancer confirm a strong association between nodule diameter and the likelihood of malignancy.[4] Data from baseline screening in three US trials[49,151,152] of low-dose CT show that the probability of malignancy is extremely low (< 1%) in prevalent nodules that measure < 5 mm in diameter. For nodules that measure 5 to 9 mm in diameter, the prevalence of malignancy varies from 2.3 to 6%.[151,152] In one Japanese study,[130] the prevalence of malignancy in subcentimeter nodules was > 20%, considerably higher than in the US studies.

Similar results have been reported in nonscreened populations evaluated by CT. One retrospective review[153] of 3,446 consecutive chest CT scans at a single institution identified 87 patients with non–screening-detected lung nodules that measured < 10 mm in diameter and definitive 2-year follow-up. Whereas 10 of these nodules were malignant (11%), 9 nodules proved to be metastases in patients with known extrathoracic malignancies (who composed 56% of the study population). More recently, in a retrospective review[154] of 414 patients with no history of neoplasm, infection, fibrosis, or immune deficiency and one or more noncalcified lung nodules that measured < 5 mm, none of the nodules was observed to grow at > 3 to 24 months of follow-up. The upper boundaries of the 95% confidence intervals for the probability of growth in these small nodules were 0.9, 1.0, and 1.3% at 3, 6, and 12 months, respectively.

Morphology: In the past decade, we have witnessed a remarkable change in CT terminology to describe the morphology of lung nodules. Morphologic characteristics of small nodules can be visualized by high-resolution CT with thin (approximately 1 mm) slices through the target nodule. On the basis of observations from recent lung cancer screening trials,[4] it is now appreciated that nodules may be characterized as solid, partly solid, or pure ground-glass opacities (defined as focal densities in which underlying lung morphology is preserved). These categories can help to distinguish benign from malignant nodules. In two small studies,[155,156] almost 60% of pure ground-glass opacities were malignant, although the percentage was lower (18%) in another study.[42] The likelihood of malignancy was similarly high in partly solid lesions but much lower (< 10%) in solid nodules.[42,156]

Ground-glass nodules often represent either atypical adenomatous hyperplasia or true bronchoalveolar cell carcinoma.[54,157–164] When malignant, partly solid or solid nodules usually represent adenocarcinoma but can also be caused by squamous cell carcinoma or small cell carcinoma. Of note, observed growth rates are often very slow for malignant ground-glass opacities, intermediate for partly solid nodules, and relatively fast for solid nodules.[4]

Management Strategies: The optimal approach to the management of subcentimeter nodules remains problematic. Expert consensus-based guidelines for radiographic follow-up in patients with small pulmonary nodules were published by members of the Fleischner Society,[165] who concluded that the follow-up should be less frequent and often shorter in duration than in patients with larger nodules.

Decisions about the frequency and duration of follow-up for patients with subcentimeter nodules need to weigh multiple considerations, including clinical risk factors (*eg*, age, smoking history, exposure to secondhand smoke and other lung carcinogens); nodule size; the probable rate of nodule growth as reflected by CT morphology[41,158,163]; the limited accuracy of available techniques for establishing growth by cross-sectional and/or volumetric measurements, especially for nodules that measure < 5 mm in size[166–168]; concerns regarding radiation dose[70,169,170]; risk factors for surgical complications; and cost. There is no evidence that early identification of subcentimeter malignant lung nodules improves lung cancer mortality rates (see "Screening for Lung Cancer"), providing additional justification for a less aggressive management approach. In patients who are not considered to be surgical candidates (especially those with limited life expectancy), the utility of follow-up is questionable, and even less aggressive management alternatives (including no follow-up) should be considered.

In general, we agree with the consensus recommendations of the Fleischner Society that are outlined in Recommendations 22 to 25 and in Figure 2, although more frequent follow-up of small lung nodules should be considered in fully informed patients who prefer a more aggressive approach. It should also be noted that controversy remains regarding how long follow-up should be continued for both partly solid and especially pure ground-glass nodules.[41,158,163] As a consequence, longer follow-up extending over years may be appropriate in some patients, especially when there is an antecedent history of lung cancer. Follow-up studies should be performed with the lowest possible radiation dose (ideally between 40 and 100 mA) to minimize cumulative radiation exposure in individuals who require multiple follow-up CT examinations.

Recommendations

22. For surgical candidates who have subcentimeter nodules and no risk factors for lung cancer, the frequency and duration of follow-up (preferably with low-dose CT) should depend on the size of the nodule. We suggest the following: (1) that nodules that measure up to 4 mm in diameter not be followed up, but the patient must be fully informed of the risks and benefits of this approach; (2) that nodules that measure > 4 to 6 mm be reevaluated at 12 months without additional follow-up if unchanged; (3) that nodules that measure > 6 to 8 mm be followed up sometime between 6 and 12

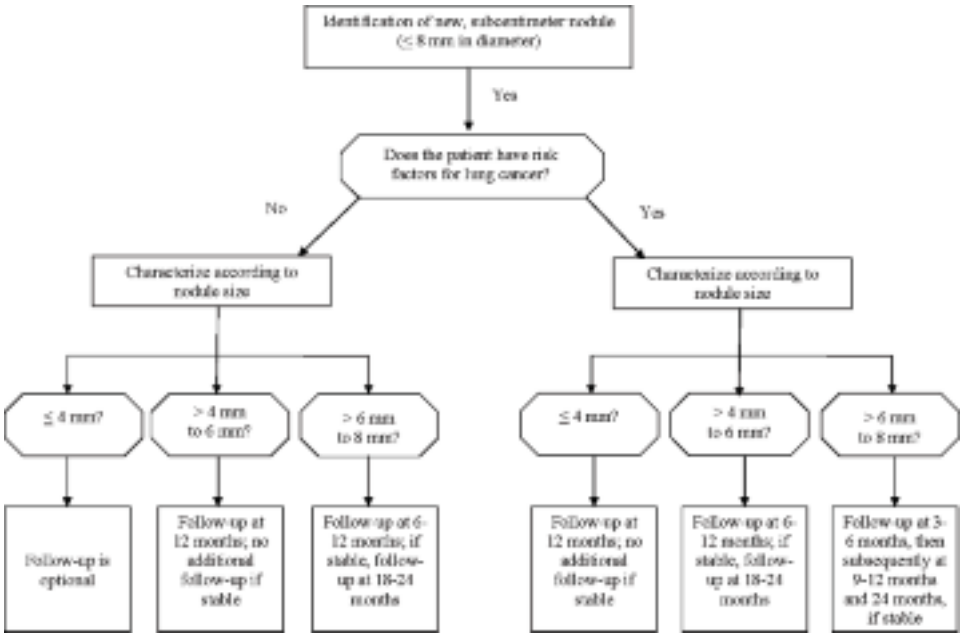

FIGURE 2. Recommended management algorithm for patients with subcentimeter pulmonary nodules that measure ≤ 8 mm in diameter.

months and then again between 18 and 24 months if unchanged. Grade of recommendation, 2C

RECOMMENDATIONS

23. For surgical candidates who have subcentimeter nodules and one or more risk factors for lung cancer, the frequency and duration of follow-up (preferably with low-dose CT) should depend on the size of the nodule. We suggest the following: (1) that nodules that measure up to 4 mm in diameter be reevaluated at 12 months without additional follow-up if unchanged; (2) that nodules that measure > 4 to 6 mm be followed up sometime between 6 and 12 months and then again between 18 and 24 months if unchanged; (3) that nodules that measure > 6 to 8 mm be followed up initially sometime between 3 and 6 months then subsequently between 9 and 12 months and again at 24 months if unchanged. Grade of recommendation, 2C

24. For surgical candidates with subcentimeter nodules that display unequivocal evidence of growth during follow-up, we recommend that definitive tissue diagnosis be obtained by surgical resection, transthoracic needle biopsy, or bronchoscopy. Grade of recommendation, 1C

25. For individuals who have subcentimeter nodules and are not candidates for curative treatment, we recommend limited follow-up (in 12 months) or follow-up when symptoms develop. Grade of recommendation, 1C

Multiple Nodules

Multiple nodules and the solitary nodule have similar causes, although for multiple nodules, metastatic disease is the most likely malignant diagnosis and active infectious or inflammatory granulomatous disease is the most likely benign cause. A detailed discussion of diagnosis and treatment in these patients is beyond the scope of this chapter; however, the diagnosis can usually be established by a combination of serologic testing, sputum analysis, bronchoscopy with biopsy or bronchoalveolar lavage, transthoracic needle biopsy, and/or open surgical biopsy. Treatment should be directed at the specific underlying cause. An inherent assumption in the evaluation of many patients with multiple nodules is that all of the nodules identified represent the same diagnosis. This is usually true in a patient with multiple nodules that measure ≥ 1 cm in diameter but often not the case when a dominant nodule and one or more additional diminutive nodules are present.

Patients With One or More Additional Nodules Detected During SPN Evaluation: In patients with a known or suspected lung cancer on CXR, CT will frequently identify one or more additional nodules.

Studies indicate that most of these additional nodules are benign. A study[171] from Japan showed that 10% of patients with suspected lung cancer had a second nodule detected during subsequent evaluation, and 60% of these were benign at surgery. Similarly, Keogan et al[172] reported that CT detected a second, indeterminate nodule in 16% of patients with clinically operable stage I to IIIA NSCLC. The nodules ranged in size from 4 to 12 mm, and although many of the nondominant nodules were unavailable for follow-up, > 85% of those with a definite diagnosis were benign.

Screening studies provide additional evidence that patients with a malignant nodule will not uncommonly have additional benign nodules. In the Early Lung Cancer Action Project,[6] 30% of the participants with cancer identified during baseline (prevalence) screening had one or more additional nodules at the time of detection. None of these was reported to be malignant after follow-up.[173] In the Mayo Clinic screening study,[174] > 50% of the 31 participants with prevalent cancers had other nodules detected, and all but one (a carcinoid tumor) proved to be benign by absence of growth during follow-up. In these studies, the majority of "secondary" nodules measured < 4 mm, which suggests a very low risk for malignancy. Therefore, although the likelihood of finding one or more additional nodules increases with the use of smaller slice thickness on CT, the vast majority of additional nodules will be benign.

When confronted with one or more additional nodules during SPN evaluation, it is prudent to consider each nodule individually, rather than assuming that the additional nodules are either metastatic or benign. Preoperative PET scanning may help to decide whether more than one nodule is likely malignant and guide further evaluation, although many of these nodules will be too small to be reliably characterized by PET. Above all, candidates for curative treatment who have known or suspected malignant nodules and have one or more additional nodules present should not be denied curative therapy unless metastasis is confirmed by histopathology. The evaluation and treatment of a synchronous cancer in a separate lobe, satellite cancers in the same lobe, and metachronous cancers is discussed in the "Bronchioloalveolar Lung Cancer" chapter in these guidelines.

Recommendation

26. In patients who are candidates for curative treatment for a dominant SPN and one or more additional small nodules, we recommend that each nodule be evaluated individually, as necessary, and curative treatment not be denied unless there is histopathologic confirmation of metastasis. Grade of recommendation, 1C

Solitary Metastasis

In patients with an active or previous extrapulmonary cancer, the SPN can represent a metastasis, a primary lung cancer, or benign disease. Determining the cause of the nodule is important so that appropriate therapy can be offered.

Pulmonary metastasectomy has been offered to selected patients who have an SPN in the setting of an extrapulmonary malignancy because of the potential for cure.[175–184] In this group, 60 to 80% of nodules will be malignant, and 20 to 50% will be due to bronchogenic carcinoma.[185–187] Distinguishing patients with metastatic disease from those with a primary lung cancer is the task, and treatment for cure is the goal. Chronic benign processes and infectious causes are a consideration; however, malignancy must be aggressively pursued, and tissue diagnosis is required.

The site and histology of the primary tumor influence both the likelihood of metastasis[188–192] and the prognosis after metastasectomy.[183,193,194] Of 5,206 procedures included in the International Registry of Lung Metastases, the most common malignant diagnoses were sarcoma (42%), colon cancer (14%), breast cancer (9%), renal cell carcinoma (8%), germ cell tumors (7%), melanoma (6%), and head and neck cancer (5%). In a combined series,[183] 5-year survival after metastasectomy was 80% for patients with germ cell tumors, 53% for gynecologic cancers, 44% for head and neck tumors, 43% for renal cell carcinoma, 38% for colon cancer, 34% for sarcoma, 34% for breast cancer, and 16% for melanoma. Overall survival after metastasectomy ranges from 25 to 45%.[188,195] Prognosis is best for patients with longer disease-free intervals (> 36 months), solitary metastases, and germ cell or Wilms tumors. A diagnosis of melanoma confers the worst prognosis.[196,197]

Metastasectomy should be considered in surgical candidates who have disease that is otherwise controlled without evidence of extrapulmonary involvement, for whom no better therapy is available. If these criteria are met, then the surgical strategy must be directed at completeness of resection with minimal morbidity and mortality. The "gold standard" is argued to be complete resection with an approach that will allow thorough palpation of the lung.[198,199] Thoracotomy is appropriate for this approach. It has been reported that 30 to 50% of metastases will present as bilateral disease that is not apparent on CT scan, and exploration of both lungs may be justified.[198,199] This approach would require bilateral thoracotomies, median sternotomy, or bilateral ante-

rior thoracotomy with transverse sternotomy (clamshell incision) to explore both lungs completely. However, some believe that equal benefits can be achieved when only radiographically visible disease is resected. Thoracoscopy can be used to achieve this objective.[200–202]

Recommendation

27. In surgical candidates with a solitary pulmonary metastasis, we recommend that pulmonary metastasectomy be performed when there is no evidence of extrapulmonary malignancy and there is no better available treatment. Grade of recommendation, 1C

Solitary Nodule Caused by Small Cell Carcinoma

SCLCs represent approximately 15 to 20% of all primary lung cancers,[203] and 90% of these patients have regional lymph node involvement or metastatic disease at initial presentation.[204] Infrequently, surgical resection of an undiagnosed lung nodule reveals the presence of SCLC. Surgery should also be considered in patients who have known SCLC and present with an SPN and no evidence of regional or distant metastasis. In one older study,[205] multimodality treatment with surgery and adjuvant chemotherapy resulted in a 5-year survival rate of 59% in patients with T1N0M0 tumors caused by small cell carcinoma. Other series[206–210] confirmed that cure was possible in surgically resected, limited-stage small cell carcinoma. Three factors contributed to favorable outcomes: small tumor size, no lymph node involvement, and candidacy for lobectomy.[211] A patient who has small cell carcinoma and presents with an SPN falls into this category and should be considered for surgery.

Recommendations

28. In surgical candidates with an SPN that has been diagnosed as SCLC, we recommend surgical resection with adjuvant chemotherapy, provided that noninvasive and invasive staging exclude the presence of regional or distant metastasis. Grade of recommendation, 1C

29. In patients who have an SPN and in whom SCLC is diagnosed intraoperatively, we recommend anatomic resection (with systematic mediastinal lymph node sampling or dissection) under the same anesthesia when there is no evidence of nodal involvement and when the patient will tolerate resection. Surgery should be followed by adjuvant chemotherapy. Grade of recommendation, 1C

Conclusions

The classical SPN is a common and vexing problem. Patients with an SPN should be evaluated by review of old films, estimation of the probability of malignancy, performance of imaging tests to characterize the nodule better, evaluation of the risks associated with various treatment alternatives, and elicitation of patient preferences for treatment. Subcentimeter nodules are becoming increasingly prevalent, and we still have much to learn about their biology and behavior, although it is already apparent that the growth rates of small malignant nodules vary widely and that morphologic characteristics provide clues about the likelihood of malignancy and the rate of growth. In this guideline, we endorsed recent expert consensus-based recommendations for performing follow-up CT scans in patients with subcentimeter nodules that balance the potential benefits of careful follow-up with the potential risks associated with radiation exposure from CT. In the future, as imaging tests and other diagnostic technologies improve, the prevalence of pulmonary nodules will likely increase, as will our ability to distinguish malignant from benign nodules before surgery.

Summary of Recommendations

1. In every patient with an SPN, we recommend that clinicians estimate the pretest probability of malignancy either qualitatively by using their clinical judgment or quantitatively by using a validated model. Grade of recommendation, 1C

2. In every patient with an SPN that is visible on CXR, we recommend that previous CXRs and other relevant imaging tests be reviewed. Grade of recommendation, 1C

3. In patients who have an SPN that shows clear evidence of growth on imaging tests, we recommend that tissue diagnosis be obtained unless specifically contraindicated. Grade of recommendation, 1C

4. In a patient with an SPN that is stable on imaging tests for at least 2 years, we suggest that no additional diagnostic evaluation be performed, except for patients with pure ground-glass opacities on CT, in whom a longer duration of annual follow-up should be considered. Grade of recommendation, 2C

5. In a patient with an SPN that is calcified in a clearly benign pattern, we recommend no additional diagnostic evaluation. Grade of recommendation, 1C

6. In every patient with an indeterminate SPN that is visible on CXR, we recommend that CT of the chest be performed, preferably with thin sections through the nodule. Grade of recommendation, 1C

7. In every patient with an indeterminate SPN that is visible on chest CT, we recommend that previous imaging tests be reviewed. Grade of recommendation, 1C

8. In a patient with normal renal function and an indeterminate SPN on CXR or chest CT, we recommend that CT with dynamic contrast enhancement be considered in centers that have experience performing this technique. Grade of recommendation, 1B

9. In patients with low-to-moderate pretest probability of malignancy (5 to 60%) and an indeterminate SPN that measures at least 8 to 10 mm in diameter, we recommend that F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging be performed to characterize the nodule. Grade of recommendation, 1B

10. In patients with an SPN that has a high pretest probability of malignancy (> 60%) or patients with a subcentimeter nodule that measures < 8 to 10 mm in diameter, we suggest that FDG-PET not be performed to characterize the nodule. Grade of recommendation, 2C

11. In every patient with an SPN, we recommend that clinicians discuss the risks and benefits of alternative management strategies and elicit patient preferences. Grade of recommendation, 1C

12. In patients who have an indeterminate SPN that measures at least 8 to 10 mm in diameter and are candidates for curative treatment, observation with serial CT scans is an acceptable management strategy in the following circumstances: (1) when the clinical probability of malignancy is very low (< 5%); (2) when clinical probability is low (< 30 to 40%) and the lesion is not hypermetabolic by FDG-PET or does not enhance > 15 Hounsfield units (HU) ondynamic contrast CT; (3) when needle biopsy is nondiagnostic and the lesion is not hypermetabolic by FDG-PET; (4) when a fully informed patient prefers this nonaggressive management approach. Grade of recommendation, 2C

13. In patients who have an indeterminate SPN that measures at least 8 to 10 mm in diameter and undergo observation, we suggest that serial CT scans be repeated at least at 3, 6, 12, and 24 months. Grade of recommendation, 2C

14. In patients who have an indeterminate SPN that measures at least 8 to 10 mm in diameter and are candidates for curative treatment, it is appropriate to perform a transthoracic needle biopsy or bronchoscopy in the following circumstances: (1) when clinical pretest probability and findings on imaging tests are discordant; for example, when the pretest probability of malignancy is high and the lesion is not hypermetabolic by FDG-PET; (2) when a benign diagnosis that requires specific medical treatment is suspected; (3) when a fully informed patient desires proof of a malignant diagnosis before surgery, especially when the risk for surgical complications is high. In general, we suggest that transthoracic needle biopsy be the first choice for patients with peripheral nodules, unless the procedure is contraindicated or the nodule is inaccessible. We suggest that bronchoscopy be performed when an air bronchogram is present or in centers with expertise in newer guided techniques. Grade of recommendation, 2C

15. In surgical candidates with an indeterminate SPN that measures at least 8 to 10 mm in diameter, surgical diagnosis is preferred in most circumstances, including the following: (1) when the clinical probability of malignancy is moderate to high (> 60%); (2) when the nodule is hypermetabolic by FDG-PET imaging; (3) when a fully informed patient prefers undergoing a definitive diagnostic procedure. Grade of recommendation, 1C

16. In patients who have an indeterminate SPN in the peripheral third of the lung and choose surgery, we recommend that thoracoscopy be performed to obtain a diagnostic wedge resection. Grade of recommendation, 1C

17. In a patient who chooses surgery for an indeterminate SPN that is not accessible by thoracoscopy, bronchoscopy, or transthoracic needle aspiration, we recommend thata diagnostic thoracotomy be performed. Grade of recommendation, 1C

18. In patients who undergo thoracoscopic wedge resection for an SPN that is found to be cancer by frozen section, we recommend that anatomic resection with systematic mediastinal lymph node sampling or dissection be performed during the same anesthesia. Gradeof recommendation, 1C

19. In patients who have an SPN and are judged to be marginal candidates for lobectomy, we recommend definitive treatment by wedge resection/segmentectomy (with systematic lymph node sampling or dissection). Grade of recommendation, 1B

20. For the patient who has an SPN and is not a surgical candidate and prefers treatment, we recommend that the diagnosis of lung cancer be confirmed by biopsy, unless contraindicated. Grade of recommendation, 1C

21. For the patient who has a malignant SPN and is not a surgical candidate and prefers treatment, we recommend referral for external-beam radiation or to a clinical trial of an experimental treatment such as stereotactic radiosurgery or radiofrequency ablation. Grade of recommendation, 2C

22. For surgical candidates who have subcentimeter nodules and no risk factors for lung cancer, the frequency and duration of follow-up (preferably with low-dose CT) should depend on the size of the nodule. We suggest the following: (1) that nodules that measure up to 4 mm in diameter not be followed up, but the patient must be fully informed of the risks and benefits of this approach; (2) that nodules that measure > 4 to 6 mm be reevaluated at 12 months without additional follow-up if unchanged; (3) that nodules that measure > 6 to 8 mm be followed up sometime between 6 and 12 months and then again between 18 and 24 months if unchanged. Grade of recommendation, 2C

23. For surgical candidates who have subcentimeter nodules and one or more risk factors for lung cancer, the frequency and duration of follow-up (preferably with low-dose CT) should depend on the size of the nodule. We suggest the following: (1) that nodules that measure up to 4 mm in diameter be reevaluated at 12 months without additional follow-up if unchanged; (2) that nodules that measure > 4 to 6 mm be followed up sometime between 6 and 12 months and then again between 18 and 24 months if unchanged; (3) that nodules that measure > 6 to 8 mm be followed up initially sometime between 3 months and 6 months then subsequently between 9 and 12 months and again at 24 months if unchanged. Grade of recommendation, 2C

24. For surgical candidates with subcentimeter nodules that display unequivocal evidence of growth during follow-up, we recommend that definitive tissue diagnosis be obtained by surgical resection, transthoracic needle biopsy, or bronchoscopy. Grade of recommendation, 1C

25. For individuals who have subcentimeter nodules and are not candidates for curative treatment, we recommend limited follow-up (in 12 months) or follow-up when symptoms develop. Grade of recommendation, 1C

26. In patients who are candidates for curative treatment for a dominant SPN and one or more additional small nodules, we recommend that each nodule be evaluated individually, as necessary, and curative treatment not be denied unless there is histopathologic confirmation of metastasis. Grade of recommendation, 1C

27. In surgical candidates with a solitary pulmonary metastasis, we recommend that pulmonary metastasectomy be performed when there is no evidence of extrapulmonary malignancy and there is no better available treatment. Grade of recommendation, 1C

28. In surgical candidates with an SPN that has been diagnosed as SCLC, we recommend surgical resection with adjuvant chemotherapy, provided that noninvasive and invasive staging exclude the presence of regional or distant metastasis. Grade of recommendation, 1C

29. In patients who have an SPN and in whom SCLC is diagnosed intraoperatively, we recommend anatomic resection (with systematic mediastinal lymph node sampling or dissection) under the same anesthesia when there is no evidence of nodal involvement and when the patient will tolerate resection. Surgery should be followed by adjuvant chemotherapy. Grade of recommendation, 1C

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