Managing the Small Pulmonary Nodule Discovered by CT*

Daniel M. Libby, MD, FCCP; James P. Smith, MD, FCCP; Nasser K. Altorki, MD, FCCP; Mark W. Pasmantier, MD; David Yankelevitz, MD; and Claudia I. Henschke, PhD, MD

Objectives: To review the Early Lung Cancer Action Project experience and the medical literature from 1993 to 2003 on detection of the small, noncalcified pulmonary nodule by CT in order to formulate a management algorithm for these nodules.

Design: Prospective noncomparative study of smokers without prior malignancy and a review of the medical literature of CT screening of lung cancer.

Interventions: Chest CT and, where appropriate, CT observation for nodule growth, antibiotics, CT-guided fine-needle aspiration (FNA) biopsy, fiberoptic bronchoscopy, and video-assisted thoracoscopic surgery (VATS).

Results: The following factors influence the probability of malignancy in a CT-detected, small, noncalcified pulmonary nodule: size, change in size, age, smoking history, density, number of nodules, gender, circumstance of the CT, spirometry, occupational history, and endemic granulomatous disease. The two diagnostic techniques most useful in evaluating the CT-detected, small, noncalcified nodule are short-term observation of nodule growth by CT and CT-guided FNA. Due to small nodule size and the frequent finding of nonsolid or part-solid nodules, positron emission tomography, fiberoptic bronchoscopy, and VATS were less useful.

Conclusions: Pulmonologists are frequently asked to evaluate the CT-detected, small, noncalcified nodule invisible on standard chest radiography. Immediate biopsy is justified if the likelihood of cancer is high, but if that likelihood is low or intermediate, a period of observation by CT is appropriate. VATS or thoracotomy are rarely necessary for a diagnosis of lung cancer in the CT-detected small pulmonary nodule.

Key words: CT-detected pulmonary nodule; early lung cancer detection; management

Abbreviations: CXR = chest radiography; ELCAP = Early Lung Cancer Action Project; FNA = fine-needle aspiration; PET = positron emission tomography; 3D = three dimensional; VATS = video-assisted thoracoscopic surgery

Although lung cancer is not the most common type of cancer, it is the leading cause of cancer death in the United States.1 This may result from intrinsic aggressive biological behavior, late diagnosis and, until recently, little attention to screening for lung cancer. As with other epithelial cancers, there is likely a wide range of biological behaviors intrinsic to lung cancer. In patients whose lung cancer is detected in stage I, the cure rate is 70%.2 However, trials to determine if screening reduced lung cancer mortality in the 1970s and 1980s, utilizing the best technology of the day, chest radiography (CXR), and sputum cytology, did not demonstrate a decrease in lung cancer mortality, perhaps because only 30% of lung cancers discovered with CXR screening were in stage I.3–6 Fewer than 10% of patients whose lung cancer was discovered by the development of symptoms (no screening) were stage I.4 Over the past 10
years, lung cancer screening studies using CT have detected up to 85% of lung cancers in stage I, offering promise in what has been a disease with a dismal outlook.7–14

Physicians are therefore increasingly asked to diagnose, manage, and treat ever-smaller pulmonary nodules discovered on CT performed either for lung cancer detection, coronary artery disease screening, or for other reasons. This is a review of the principles of diagnosis and management of small pulmonary nodules gained through our experience in patients with the Early Lung Cancer Action Project (ELCAP) and the subsequent projects (New York ELCAP and International ELCAP).15,16

**Materials and Methods**

We reviewed our experience with lung cancer screening by CT in patients without prior malignancy at the Weill Medical College of Cornell University ELCAP from 1993 to the present, and performed a review of the literature using MEDLINE to evaluate all published studies of CT screening for lung cancer to determine the best approach to the diagnosis and management of the small pulmonary nodule. A small pulmonary nodule was defined as an opacity in the pulmonary parenchyma the small pulmonary nodule. A small pulmonary nodule was discovered on CT performed either for lung tissue. The resulting analysis was organized into two sections: factors influencing the probability of lung cancer in a pulmonary nodule, and techniques utilized in the diagnosis of the small pulmonary nodule detected by CT.

**Results**

**Factors Influencing the Probability of Lung Cancer in a Pulmonary Nodule**

**Size:** Since CXR studies have shown the likelihood of cancer in solitary pulmonary nodules, it has been recognized that nodule size correlates with the risk of cancer,17 but until CT there were little data on nodules < 1.5 to 2.0 cm in diameter (Table 1).18 It is difficult to recognize lung cancer by CT in nodules < 5 mm in diameter among the many nodules of this size. Lung cancer appears to be rare in nodules < 5 mm in size, and it is safe to repeat the CT at 1 year in these patients (Fig 1, top).7,8 The importance of size in determining the likelihood of lung cancer in a pulmonary nodule is influenced by the age of the subject and the circumstance of the study. For example, in ELCAP, as we lowered the minimum age for lung cancer screening from 60 to 40 years, we found lung cancer incidence in nodules < 15 mm in diameter on baseline screening to be as low as 5%. Thus, immediate biopsy is no longer recommended for nodules < 15 mm found on baseline screening. A period of radiographic observation for growth (with or without antibiotics, depending on the clinical circumstances) is appropriate (Fig 1, top).19 New nodules discovered on a 1-year repeat CT more frequently contain cancer and at smaller size than on the baseline CT.7,8

**Change in Size:** A nodule that increases in size is assumed to be active; if it doubles in volume in < 1 month, its growth rate is uncharacteristic of lung cancer. A nodule that grows at a rate consistent with cancer (doubling time of 30 to 360 days) should be sampled for biopsy or resected,20 although slower-growing lung cancers have been described. It is important to remember that CT offers a two-dimensional view, unless three-dimensional (3D) software is available. If such software is not available, estimates of nodule growth must rely on diameter rather than direct measurement of volume in assessment of doubling time, which is less accurate.

**Number of Nodules:** In the initial ELCAP report, a positive finding was defined as one to six noncalcified pulmonary nodules; more than six nodules were thought to indicate inflammatory lung disease, and this has been confirmed after years of follow-up.7 Synchronous lung cancers are increasingly recognized as CT screening has become more prevalent, and multifocal bronchoalveolar cell or adenocarcinoma is often the histology, particularly in women who never smoked or quit cigarette smoking many years earlier. We follow up any new nodule on repeat screening and all nodules ≥5 mm on baseline.

**Density:** While CXR only permits identification of solid nodules, the use of CT led to increasing recognition of subsolid (nonsolid and part-solid) nodules (Fig 2).21 A nonsolid nodule (previously termed ground-glass opacity) is a density through which aerated lung parenchyma is visible. A part-solid nodule contains a solid component that obliterates the aerated lung and also contains a nonsolid

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**Table 1—Factors Influencing the Probability of Cancer in a Pulmonary Nodule**

<table>
<thead>
<tr>
<th>Size</th>
<th>Change in size (growth)</th>
<th>Number</th>
<th>Density</th>
<th>Circumstance of CT</th>
<th>Patient age</th>
<th>Gender</th>
<th>Cigarette smoking history</th>
<th>Spirometry</th>
<th>Occupational history</th>
<th>Endemic granulomatous disease</th>
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component. Nonsolid nodules possess a relatively low risk of cancer (approximately 15%); as their size rises > 1.5 cm, the risk of malignancy, particularly adenocarcinoma with bronchoalveolar cell features, rises. Part-solid nodules are the most likely of nodules < 1.5 cm in diameter to contain lung cancer (approximately 40 to 50%), and the risk of cancer rises as the size of the nodule, particularly the solid component, increases. Although solid nodules are the most common, a lower proportion are cancer. Inflammatory diseases of the lung, particularly tuberculosis (typical and atypical) and mycoses, generally produce solid nodules that can be expected to eventually calcify, permitting their designation as benign. Only approximately 15% of solid nodules < 1 in diameter contain cancer, but as solid nodule size increases, the proportion that is cancer increases. Despite the lower proportion of solid nodules that are cancer, because there are many more solid than subsolid nodules, most lung cancers are found in solid nodules. There appears to be a progression from nonsolid to part-solid to solid nodule. The nonsolid nodule may represent, in some instances, inflammatory disease; in others, it may contain premalignant lesions such as atypical adenomatous hyperplasia or bronchoalveolar hyperplasia. The nonsolid nodule may also represent bronchoalveolar carcinoma or invasive adenocarcinoma with bronchoalveolar cell features. Noguchi et al devised a histopathologic classification (types A to D) describing progressively greater malignant potential and propensity to locoregional metastases. The part-solid lesion often contains invasive adenocarcinoma in the solid component. Solid nodules containing cancer may contain adenocarcinoma or other cell types such as epidermoid, large-cell anaplastic, neuroendocrine, carcinoid (typical or atypical) or, least likely, small-cell carcinoma.

**Circumstance of the CT Study:** If chest CT is performed to screen for lung cancer, the initial baseline study may contain nodules resulting from prior inflammatory disorders or lung cancer. In the ELCAP series of 1,000 subjects undergoing the initial baseline screen CT, 233 subjects (23.3%) had one to six noncalcified pulmonary nodules. However, the number of new nodules discovered on the repeat screening study a year later was only 30 (2.5% of 1,184 repeat screenings). For a new nodule discovered on the 1-year interval screening study, a course of antibiotics has been suggested (with a repeat diagnostic CT 4 to 6 weeks later); indeed, it was found that in 12 of the 30 patients, the new repeat screen CT-diagnosed nodules resolved 4 to 6 weeks later. Of the 18 patients with new persistent nodules on the 1-year interval screening study, 7

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**Figure 1.** Top: Prebiopsy algorithm for management. Bottom: Postbiopsy algorithm for management.
subjects (39%) had lung cancer, a much higher proportion than was found at baseline (27 of 233 subjects [12%]). Thus, a baseline screening CT is much more likely to have a false-positive result than the 1-year interval screening study. Chest CT performed incidentally in an individual without respiratory signs or symptoms probably possesses the same chance of containing a pulmonary nodule as a baseline screening study (23%); given the same risk profile of age and smoking history, the nodules discovered would contain the same proportion of lung cancers as a baseline screening study (12%).

**Age:** Lung cancer is rare before the age of 40 years, but its incidence increases steadily from 40 to 80 years.\(^1\) This depends, however, on the age when smoking started. After age 80 years, the incidence of lung cancer levels off and may decline. Studies of CT screening for lung cancer from Japan\(^9,10,12,13\) that included patients aged \(\geq 40\) years had a much lower incidence of cancer in pulmonary nodules than did screening studies\(^7,8\) from the United States that included patients \(> 60\) years old.

**Gender:** As cigarette smoking has increased in women, the incidence of lung cancer has risen.\(^24\) Women may be at higher risk than equally smoking men of the same age, perhaps related to genetically linked differences in enzymes involved in the detoxification of carcinogens in cigarette smoke.

**Cigarette Smoking History:** The incidence of lung cancer directly correlates with the pack-years of cigarettes smoked.\(^25\) While it had been thought that smoking cessation produced a progressive drop in lung cancer incidence, this concept has been questioned.\(^26\) It appears that the incidence of lung cancer stops increasing after smoking cessation, but it does not drop to the levels of individuals who never smoked. Consequently, it is common to encounter patients with newly diagnosed lung cancer who stopped smoking many years or decades earlier. The change in smoking habits in the United States toward low-tar and filter cigarettes has influenced the clinical presentation of lung cancer. Changing smoking habits are associated with the rise of adenocarcinoma to the most common histologic subtype.\(^27\) Small-cell carcinoma, the cell type most closely associated with cigarette smoking, has become the least common histology. The location of the primary tumor has mirrored these changes in histology and smoking habits, for peripheral adenocarcinomas have become much more common than large airway lesions. It is thought that smokers of low-tar, filter cigarettes inhale more deeply and retain smoke in more pe-
 Spirometric Findings: There is a statistically significant association between a spirometrically demonstrated obstructive ventilatory impairment and lung cancer. After controlling for the number of cigarettes smoked, smokers with reduced FEV1/FVC ratios have a higher risk of acquiring lung cancer, particularly lung cancer involving large airways, than smokers without an obstructive ventilatory impairment. This has led to the recommendation that the spirometric finding of an obstructive ventilatory impairment should be present with equal frequency (stratification) in studies comparing screening with no screening and in lung cancer prevention studies. In order to study the highest risk group possible (and thereby limit the false-positive rate of the screening test), some investigators have included, along with age and smoking history, an FEV1/FVC of < 0.7 as an entry criteria. Although this provides for a higher risk group, it biases these studies toward including a higher percentage of patients with large airway cancers.

Occupational History: Asbestos exposure, after a latency period of 20 to 40 years, predisposes to lung cancer acting synergistically with the risk posed by cigarette smoking. Workers exposed to respirable radioactive gas in the production and disposal of fissionable materials have an increased risk of lung cancer, although the risk has not been as well quantified as the asbestos risk. International ELCAP is currently studying this group with CT. Uranium miners and individuals working with heavy metals such as cadmium and nickel are known to have an increased lung cancer risk. Individuals with idiopathic pulmonary fibrosis and pneumoconioses probably have an increased risk of acquiring adenocarcinoma or bronchoalveolar cell carcinoma.

Endemic Granulomatous Disease: In studies of CXR screening for lung cancer in the 1950s and 1960s, most lung nodules were due to Mycobacterium tuberculosis. As the nationwide incidence of tuberculosis has declined, except notably in immigrants from endemic areas and in HIV-positive individuals, M tuberculosis has become a less common etiology of pulmonary nodules. When CT screening for lung cancer was performed in the Midwest United States, an area endemic with histoplasmosis, a high false-positive rate was observed. Similarly, in studies currently underway in China, a higher false-positive rate will be an expected finding due to the high incidence of tuberculosis. Atypical mycobacterial infection, usually due to Mycobacterium avium intracellulare or Mycobacterium kansasii, has been observed in apparently healthy people, older women in particular, and is often associated with peripheral bronchiectasis and mucoid impaction.

Diagnostic Techniques for Managing the Small Pulmonary Nodule Detected by CT

CT Assessment of Nodule Growth: Assessment of nodule growth by CT has become such an important predictive parameter, with or without the use of 3D software, that it may circumvent the need for other diagnostic techniques (see below). A nodule < 5 mm in diameter or a nonsolid nodule 5 to 9 mm in diameter possess a very low risk of malignancy, so ELCAP recommends a repeat CT in 1 year (Table 2). Part-solid or solid nodules 5 to 9 mm in size and some nodules > 10 mm in size have an intermediate likelihood of malignancy; therefore, a repeat CT in 6 weeks to assess for nodule growth or resolution (with or without antibiotics) may be useful (Fig 1, top). Further CT assessment for nodule growth after 3 months is reasonable for those nodules that are “nonspecific benign” on fine-needle aspiration (FNA) and for those nodules that partially resolve or do not change after antibiotics on the 6-week CT. If doubling times (estimated by conventional CT or 3D software) are in the range of 30 to 360 days, biopsy or resection may be reasonable options. If a nodule does not grow in volume in 6 months, the risk of malignancy is very small (< 10%). Volumetric assessment of nodule size may permit estimation of doubling times within 6 to 12 weeks when change in size is not apparent on standard two-dimensional CT.

Table 2—Low-Risk Noncalcified Pulmonary Nodules Detected by CT

<table>
<thead>
<tr>
<th>Nodule with specific benign diagnosis after biopsy</th>
<th>Patients with nodules that have resolved with or without antibiotics</th>
<th>Nodules &lt; 5 mm in diameter</th>
<th>Nonsolid nodules 5 to 9 mm in diameter</th>
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images. The medical risks of biopsy by FNA, video-assisted thoracoscopic surgery (VATS), or surgery, and the financial expense of positron emission tomography (PET) may be avoided by rapid and accurate assessment of nodule growth.

**Percutaneous FNA Biopsy:** FNA has been used in the diagnosis of pulmonary nodules for > 25 years (Fig 1). Fluoroscopically guided FNA was popularized in Sweden in the 1970s. Biplanar fluoroscopy and the introduction of biopsy needles procuring a core of tissue for histopathologic evaluation were further refinements. With CT, nodules of 5 to 15 mm in diameter are found, and CT-guided FNA has become a very important diagnostic technique, although its sensitivity and specificity in the very small CT-detected nodules 5 to 10 mm in diameter need verification. In institutions where CT-guided FNA is not performed, there will likely be greater reliance on CT assessment of nodule growth. VATS and thoracotomy will probably be performed for benign nodules with somewhat greater frequency if CT-guided biopsy of the small, noncalcified nodule is not available.

Three types of results may be obtained from FNA: malignant, specific benign, and nonspecific benign. The treatment implications of a malignant diagnosis such as carcinoma or lymphoma are clear. Specific benign diagnoses such as tuberculosis (typical or atypical), mycoses, nocardia, hamartoma, or benign intrapulmonary lymph node do not require surgery and may be medically treatable or safe to observe. A nonspecific benign diagnosis, however, requires careful clinical and radiographic follow-up. Nonspecific benign diagnoses might include atypical bronchoalveolar hyperplasia, inflammation (granulomatous or other, without organisms on smear or culture), atypical cells, etc. If further growth occurs after a nonspecific benign diagnosis is obtained from FNA, repeat biopsy or resection are indicated.

**PET:** PET using fluorodeoxyglucose is useful in assessing the likelihood of malignancy in a pulmonary nodule, particularly if it is solid and > 1 cm in diameter. False-positive PET findings in active granulomatous disease and benign tumors have been described. A standard uptake value > 3 is sensitive and specific for cancer, but if the nodule is subsolid or < 1 cm in diameter, sensitivity and specificity decline. PET has limited usefulness in early lung cancer detection where many nodules are < 1 cm in diameter and may be subsolid. The sensitivity of PET in adenocarcinoma with alveolar cell features has also been questioned. Once a diagnosis of lung cancer has been established in a solid nodule, particularly if there is high fluorodeoxyglucose uptake, PET may be helpful in detecting mediastinal lymph node metastases even when the nodes are not enlarged on CT. Clinically occult extrathoracic metastases or synchronous extrathoracic primary malignancies may be discovered by PET.

**Flexible Fiberoptic Bronchoscopy:** Flexible fiberoptic bronchoscopy has limited usefulness in the diagnosis of small peripheral nodules, although transbronchial needle aspiration biopsy increases the sensitivity. Fiberoptic bronchoscopy has an important role in the uncommon circumstance of endobronchial lesions discovered on screening CT, and it can be helpful in diagnosing infectious diseases presenting with focal pulmonary nodules such as tuberculosis (typical or atypical) or mycoses.

**VATS:** VATS may be useful in the diagnosis of peripheral pulmonary nodules eluding diagnosis by other techniques. It is most accurate in peripheral (within 2 cm of the pleura) solid lesions; nonsolid lesions often produce a normal appearance on surgical inspection and may prove difficult to localize during VATS.

**DISCUSSION**

Lung cancer is common and, under present “routine care,” commonly fatal. In CXR screening, less than one third of lung cancers were discovered in stage I. While this represents a great improvement over no screening, it is not sufficient. CT finds lung cancer in stage I 85% of the time, a fact documented in many thousands of patients in the United States, Europe, and Japan.

Faced with a small, CT-detected pulmonary nodule, the physician must first assess the likelihood of lung cancer. Utilizing the parameters of age, nodule size, smoking history, spirometric findings, occupational history, endemic granulomatous disease, the circumstances of the CT (baseline screen, interval 1-year screen, or study performed for other reasons), the number of nodules, the presence of radiographic or clinical signs of inflammatory lung disease such as bronchiectasis or atypical tuberculosis, and the density of the nodule (solid, nonsolid, or part solid), an initial clinical impression is formulated (Table 1, Fig 1). If lung cancer is highly suspect and the patient is considered fit for thoracic surgery, biopsy should be undertaken. If the nodule is judged to have an intermediate likelihood of being lung cancer, either PET or a period of radiographic observation with a repeat CT in 6 to 12 weeks should be suggested. For a nodule known to be new by CT, an infectious etiology may be present, and empiric antibiotics may
be justified. Widespread use of antibiotics for CT-detected, small pulmonary nodules may not be a wise practice, as it may exacerbate the problem of antibiotic resistance. If resolution of the nodule occurs, no further evaluation is warranted; if it grows, biopsy should then be done. If no change occurs, depending on clinical factors, either biopsy or follow-up CT may be reasonable. If a nodule fails to change over a 2-year period on CT, it is most likely benign; if it continues to grow despite benign biopsy findings, particularly if nonspecific benign, it must still be viewed with suspicion and either sampled again for biopsy or resected. As technologic advances are applied to CT, particularly the widespread application of volumetric analysis capable of estimating doubling times in 6 to 8 weeks and the development of multislice scanners capable of producing extremely thin slices, specific management recommendations are likely to change.

Cytopathologic analysis of FNA specimens and histopathologic study of resected lesions have changed our concept of the natural history of some lung cancers, and radiologic-pathologic correlations have emerged. Some lung cancers appear to begin in areas of bronchoalveolar hyperplasia and subsequently develop features of bronchoalveolar carcinoma and, finally, invasive adenocarcinoma. This may be analogous to the pathologic progression in breast, colorectal, and cervical carcinomas. Nonsolid nodules commonly contain premalignant bronchoalveolar hyperplasia, while part-solid nodules are more commonly bronchoalveolar carcinoma and solid nodules are invasive adenocarcinoma. As the size of any of these radiologic types of nodule increases, the risk of cancer in the nodule also increases.

CT-guided FNA has been a great advance in the diagnosis of small pulmonary nodules. Nodules > 5 mm in diameter may be amenable to biopsy by this technique, depending on the skill and experience of the radiologist and cytopathologist. When the result of the biopsy is clearly malignant or when a specific benign diagnosis is made from the FNA, management decisions are clear. However, nonspecific benign findings such as inflammation, cellular atypia, bronchoalveolar hyperplasia, blood, bronchial cells, and granuloma without organisms on special stains must be viewed with suspicion, and clinical and radiographic follow-up are essential. By combining careful radiographic follow-up by CT, PET, and the judicious use of empiric antibiotics and biopsy, patients are spared unnecessary surgery. While a definitive answer to the question of whether CT screening reduces lung cancer mortality may not be forthcoming for several years, physicians will be increasingly asked to manage the small pulmonary nodules discovered by CT in clinical practice.

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