CLINICAL PRACTICE

The Solitary Pulmonary Nodule

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 60-year-old man undergoes chest radiography during an evaluation for pneumonia, and a nodule 1.5 cm in diameter is discovered. He is a heavy smoker but has no history of lung disease. The results of a physical examination are unremarkable. How should he be evaluated?

THE CLINICAL PROBLEM

A solitary pulmonary nodule is noted on 0.09 to 0.20 percent of all chest radiographs.[1,2] An estimated 150,000 such nodules are identified each year. Although the causes may include many benign conditions, bronchogenic carcinoma as a cause of solitary nodules has been increasing, especially in the elderly. In patients with resected malignant nodules, survival may be as high as 80 percent at five years[3]; in contrast, survival rates at five years among those with advanced malignant disease remain below 5 percent. Ideally, diagnostic approaches to pulmonary nodules would permit definitive resection when possible and avoid resection in patients with benign disease. Recent developments in the approach to pulmonary nodules include improvements in radiographic imaging, techniques to distinguish benign from malignant nodules without surgery, lung-cancer screening, and minimally invasive surgical approaches.[3,4]

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STRATEGIES AND EVIDENCE

DEFINITION

A solitary pulmonary nodule, or "coin lesion," is an approximately round lesion that is less than 3 cm in diameter and that is completely surrounded by pulmonary parenchyma, without other abnormalities. Lesions larger than 3 cm are called masses and are often malignant. The incidence of cancer in patients with solitary nodules ranges from 10 to 70 percent.[4,5] Infectious granulomas cause about 80 percent of the benign lesions, and hamartomas about 10 percent.[6,7] Only biopsy can definitively diagnose a lesion.

IMPROVEMENTS IN RADIOGRAPHIC IMAGING

Pulmonary nodules are usually discovered incidentally. Although chest radiography traditionally provided information regarding the margin characteristics, calcification pattern, size, and growth rate of these lesions, computed tomographic (CT) imaging has improved physicians' ability to assess each of these features and is now critical in the evaluation of the lesions.

Two patterns of the margins of a nodule are relatively specific for cancer. One is the corona radiata sign, consisting of very fine linear strands extending 4 to 5 mm outward from the nodule, originally described on plain tomographs[8]; they have a spiculated appearance on plain radiographs[2] (Fig. 1A and 1B). A scalloped border is associated with

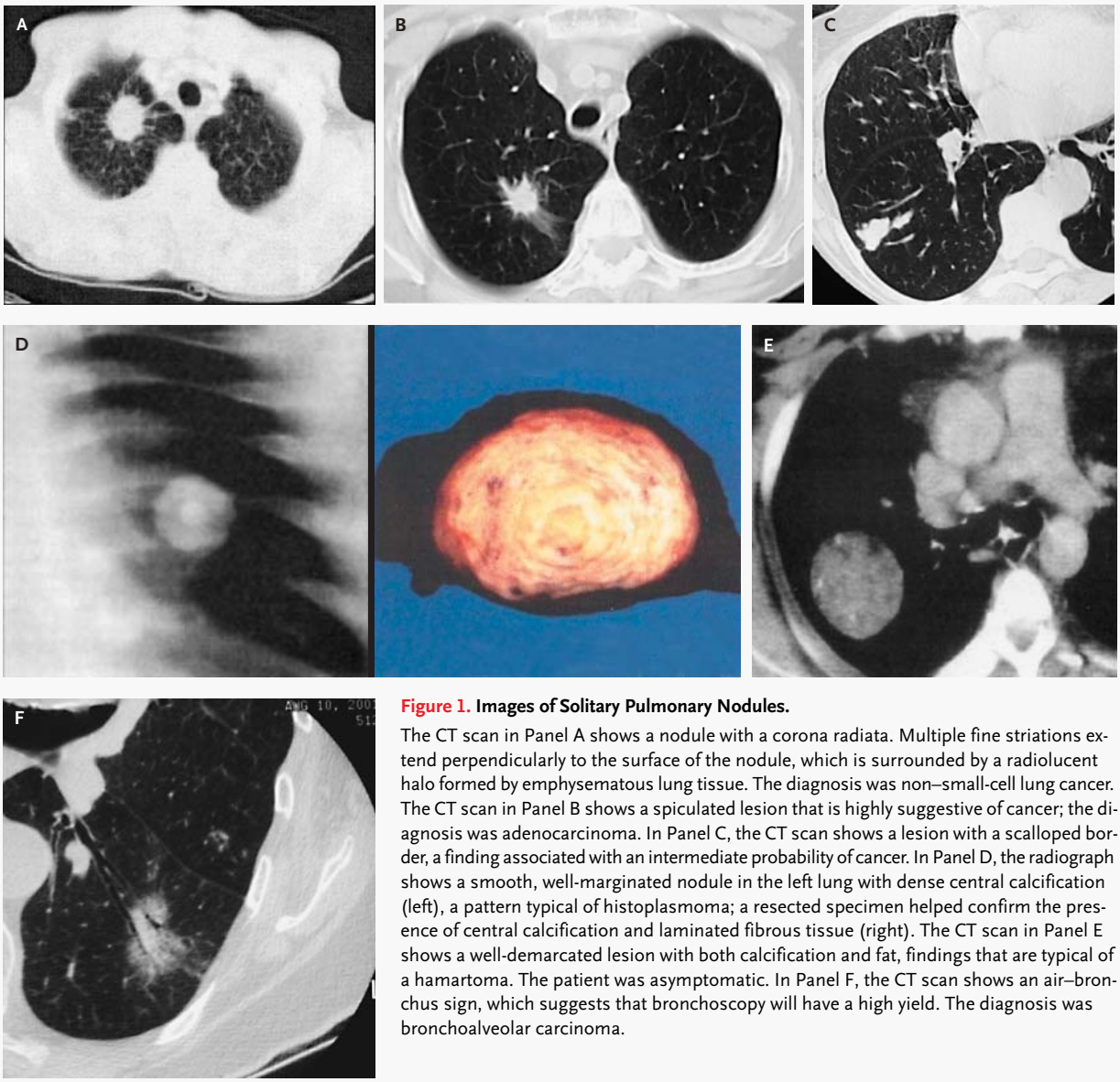

Figure 1. Images of Solitary Pulmonary Nodules.

The CT scan in Panel A shows a nodule with a corona radiata. Multiple fine striations extend perpendicularly to the surface of the nodule, which is surrounded by a radiolucent halo formed by emphysematous lung tissue. The diagnosis was non–small-cell lung cancer. The CT scan in Panel B shows a spiculated lesion that is highly suggestive of cancer; the diagnosis was adenocarcinoma. In Panel C, the CT scan shows a lesion with a scalloped border, a finding associated with an intermediate probability of cancer. In Panel D, the radiograph shows a smooth, well-marginated nodule in the left lung with dense central calcification (left), a pattern typical of histoplasmoma; a resected specimen helped confirm the presence of central calcification and laminated fibrous tissue (right). The CT scan in Panel E shows a well-demarcated lesion with both calcification and fat, findings that are typical of a hamartoma. The patient was asymptomatic. In Panel F, the CT scan shows an air–bronchus sign, which suggests that bronchoscopy will have a high yield. The diagnosis was bronchoalveolar carcinoma.

an intermediate probability of cancer, whereas a smooth border is more suggestive of a benign diagnosis.

Calcification within a nodule suggests that it is a benign lesion. Patterns of calcification are more easily observed on CT scans than on plain-film radiographs.[9] With CT considered the reference standard, plain-film radiographs of the chest have a sensitivity, specificity, and positive predictive value of 50, 87, and 93 percent, respectively, for identifying calcification. A laminated or central pattern is typical of a granuloma, whereas a classic "popcorn" pattern is most often seen in hamartomas. In approximately half the cases of hamartoma, high-resolution CT can show a definitive pattern of fat and cartilage. Calcification patterns that are stippled or eccentric have been associated with cancer.

The growth rate of a nodule can be estimated if previous images are available to allow accurate measurement of changes in its size. The volume-doubling time for malignant bronchogenic tumors is rarely less than a month or more than a year. If lesions are considered spherical, a 30 percent increase in diameter represents a doubling of volume. A nod-

ule that was not present on a radiograph obtained less than two months before the current image is therefore not likely to be malignant.

Traditionally, stability of findings on chest radiographs for two years has been considered a sign that a lesion is benign, although bronchoalveolar-cell carcinomas and typical carcinoids occasionally appear to be stable for two or more years.[10] However, this two-year rule has been questioned. The initial studies investigating two-year stability as an indicator of a benign process were retrospective and reviewed only cases in which resection had been performed. One such study[11] examined 156 solitary pulmonary nodules and masses ranging in size from 1 to 14 cm. Previous plain films were available in 74 of these cases. In 26, there was a previously documented nodule with no growth; 9 of them were malignant. The absence of appreciable growth over a two-year period had a predictive value of 65 percent for a benign lesion.[11] Thus, the dictum that two-year stability on plain-film radiography indicates a benign process should be used with caution.

The use of stability as an indicator of a benign process is predicated on accurate measurement of growth and thus on the resolution of the imaging technique used. Thin-section high-resolution CT allows improved estimation of nodule size and growth characteristics. Small nodules, those with indistinct borders, or those obscured by ribs or other structures may be difficult to assess on a standard chest radiograph; the limit of detectable changes in size on standard radiography has been estimated to be 3.0 to 5.0 mm, whereas high-resolution CT has a resolution of 0.3 mm. Thus, it still seems reasonable to use two-year stability on high-resolution CT as a practical guideline for predicting a benign process.

Although the optimal frequency of follow-up imaging is not known, the traditional standard of imaging at three-month intervals during the first year after a nodule is discovered and then at six-month intervals during the next year is logical, provided that high-resolution CT is used, rather than plain-film radiography. Preliminary experience with two-dimensional, multicriterion, segmentation CT algorithms, which create a virtual-reality image of the nodule, and repeated CT scanning to assess growth in all dimensions are promising approaches, but they are still experimental. Preliminary data suggest that a single repeated CT scan obtained 30 days after the first scan may allow detection of growth in tumors as small as 5 mm.[12] Even with this technique, the optimal approach to the imaging of nodules less than 5 mm in diameter remains to be determined, since there is a paucity of data indicating which imaging strategies are best in this situation.

NONSURGICAL APPROACHES TO DIAGNOSIS

Nonsurgical tests to help distinguish benign from malignant nodules include CT densitometry, contrast-enhanced CT, bronchoscopy, transthoracic fine-needle aspiration biopsy, and more recently, positron-emission tomography (PET).

CT Densitometry

CT densitometry involves the measurement of attenuation values, expressed in Hounsfield units, as compared with a reference "phantom." Attenuation values are usually higher for benign nodules than they are for malignant nodules. CT phantoms allow the identification of 35 to 55 percent of all subsequently identified benign lesions. In one large, multicenter trial that used CT densitometry, only 1 nodule among 66 identified as benign was later found to be malignant.[13] In that study, the cutoff point used was 264 Hounsfield units; lesions with greater density were considered to be benign. In other investigations, however, a more conventional cutoff point of 185 Hounsfield units yielded a higher false negative rate. Local expertise varies with this technique, and it has not become widely used.

Contrast-Enhanced CT

In a newer technique, the degree of enhancement on spiral CT after the injection of intravenous contrast material is used to differentiate benign from malignant lesions. In one study, in which an increase in attenuation of 20 Hounsfield units was considered the threshold for the detection of a malignant process, the sensitivity and specificity of the technique were 95 to 100 percent and 70 to 93 percent, respectively.[14] This technique, although promising, awaits further validation.

Bronchoscopy

The sensitivity of bronchoscopy for detecting a malignant process in a solitary pulmonary nodule ranges from 20 to 80 percent, depending on the size of the nodule, its proximity to the bronchial tree, and the prevalence of cancer in the study population.[15] For nodules that are less than 1.5 cm in diameter, the sensitivity is 10 percent, and for those that are 2.0 to 3.0 cm in diameter, it is 40 to 60 percent.[16] When CT reveals a bronchus leading to the lesion, bron-

choscopy has a 70 percent sensitivity.[17] Ultrathin bronchoscopy, which involves the use of fiberoptic technology in thin bronchoscopes that can reach beyond eighth-generation bronchi, has been used experimentally to allow direct visualization of peripheral lesions.

Transthoracic Fine-Needle Aspiration Biopsy

Transthoracic fine-needle aspiration biopsy identifies peripheral pulmonary lesions as malignant or benign in up to 95 percent of cases. For malignant lesions, the sensitivity is 80 to 95 percent and the specificity is 50 to 88 percent. The positive predictive value in one study involving more than 200 patients was 98.6 percent; the negative predictive value was 96.6 percent.[18] Even for lesions that are less than 2 cm in diameter, transthoracic fine-needle aspiration biopsy has a sensitivity of more than 60 percent for detecting a malignant process.[19] However, the false negative rate is 3 to 29 percent. Complication rates are higher than those for bronchoscopy, with an incidence of pneumothorax of up to 30 percent, although in most cases, treatment is not required.

AREAS OF UNCERTAINTY

POSITRON-EMISSION TOMOGRAPHY

In PET, the uptake of fludeoxyglucose F 18 is used to measure glucose metabolism. Because of increased metabolic activity, most lung tumors have greater uptake of fludeoxyglucose F 18 than normal tissue. This technique is becoming widely used for differentiating benign from malignant nodules.[20] According to a recent meta-analysis, its estimated sensitivity for identifying a malignant process is 96.8 percent and its specificity is 77.8 percent.[21] Some gamma cameras can now have PET capability added to them, but the question of whether these modified gamma cameras have the same ability to detect malignant processes as equipment manufactured specifically for PET requires further study. False negative results can occur, most notably in association with bronchioloalveolar carcinoma, carcinoids, and tumors less than 1 cm in diameter.[22,23] False positive results also occur, usually in association with infectious or inflammatory processes.

PET may also provide staging information. Up to 14 percent of patients otherwise eligible for surgery have occult extrathoracic disease on whole-body PET imaging.[24] For example, the sensitivity and specificity of CT scans for detecting mediastinal lymph-node involvement are 55 to 88 percent and 76 to 85 percent, respectively.[25] The sensitivity and specificity of PET in the presence of abnormal lymph nodes on CT scanning are 94 percent and 82 percent, respectively. In one prospective study, the diagnostic accuracy of CT was 64 percent, that of PET 88 percent, and that of the combination of CT and PET 96 percent.[26]

A decision-analysis model constructed to assess cost effectiveness showed that a strategy of CT combined with PET for staging was often superior to conventional approaches, since it reduced the number of patients requiring surgery by 15 percent. Estimated cost savings of the combined strategy ranged from $91 to $2,200 per patient.[27]

SELECTING A DIAGNOSTIC STRATEGY

The pretest probability of cancer determines the most cost-effective strategy for the diagnosis of a solitary nodule. In one decision analysis, estimation of the incremental cost-effectiveness ratio suggested that the preferred strategy is radiographic follow-up when the probability of cancer is low (<12 percent), CT and PET scanning when the probability is intermediate (12 to 69 percent), CT followed by either biopsy or surgery when the probability is high (>69 to 90 percent), and surgery when the probability is very high (>90 percent).[27]

However, determining the probability of cancer in patients with solitary pulmonary nodules remains an inexact science; data concerning risk factors for cancer are summarized in Table 1.[2,28-30] Previous research has used either Bayesian techniques or multivariate logistic-regression models with some success.[28,29] A multivariate model incorporating age, cigarette-smoking status, the presence or absence of a history of cancer, the diameter of the nodule, the presence or absence of spiculation, and the location of the nodule (upper lobe vs. lower lobe) has proved similar to expert physician judgment in predicting cancer.[2,29]

IMPLICATIONS OF LUNG-CANCER SCREENING FOR DIAGNOSTIC APPROACHES

CT screening for lung cancer raises the question of how any small nodules that are identified should best be evaluated. The Early Lung Cancer Action Project investigators reported the value of low-dose CT of the chest for the detection of lung cancer.[31] Of 1000 patients at high risk who were screened, 233 (23 percent) had noncalcified nodules on CT scanning; 27 of the nodules (12 percent) were ma-

lignant. Many of these lesions were less than 1 cm in diameter. Currently available PET techniques would have been of limited value for detecting these small nodules. In that trial,[31] strategies of transthoracic fine-needle aspiration biopsy for larger (≥1 cm) and more suspicious lesions and serial CT scanning at three-month intervals for smaller lesions were used, with good results. Biopsy was performed for only one benign nodule, whereas biopsy and resection were performed for the 27 malignant nodules. A cost-effectiveness analysis showed that the estimated cost of the program was $93,000 per life saved.[32] Although definitive data are not yet available to help determine the nodule size that should prompt aggressive evaluation, these results suggest that the 1-cm threshold may be a practical preliminary guideline.

In a study at the Mayo Clinic, 1520 patients were evaluated with low-dose spiral CT at base line (prevalence screening), with another evaluation to take place at one year (incidence screening). Twenty-two cases of lung cancer were identified during prevalence screening.[33] Among the 1464 patients who underwent incidence screening, new nodules were identified in 191 (13 percent); in 3 of them the lesions were subsequently identified as malignant. Seven of 29 nodules that were resected turned out to be benign.

A European trial in which more than 700 heavy smokers underwent low-dose CT scanning found small nodules (<1 cm in diameter) in 40 percent of the participants; larger lesions (≥1 cm in diameter) were present in only 3 percent.[34] The smaller lesions were not resected and were monitored with low-dose CT. Of the larger lesions, eight proved to be malignant.

On the basis of the preliminary data available so far, it seems reasonable to pursue a strategy of careful observation with serial high-resolution CT scanning in patients with small nodules (<1 cm in diameter) and to use transthoracic fine-needle aspiration biopsy in those with larger lesions (≥1 cm) or lesions that have a more suspicious morphologic appearance.[27,28,32,33]

Table 1. Assessment of the Risk of Cancer in Patients with Solitary Pulmonary Nodules.

Variable	Risk of Cancer		
	Low	Intermediate	High
Diameter of nodule (cm)	<1.5	1.5–2.2	≥2.3
Age (yr)	<45	45–60	>60
Smoking status	Never smoked	Current smoker (≤20 cigarettes/day)	Current smoker (>20 cigarettes/day)
Smoking-cessation status	Quit ≥7 yr ago or never smoked	Quit <7 yr ago	Never quit
Characteristics of nodule margins	Smooth	Scalloped	Corona radiata or spiculated

Table 2. American College of Radiology Recommendations for the Testing of Solitary Pulmonary Nodules.*

Level of Clinical Suspicion	Size of Nodule on Plain-Film Radiography	
	<1 cm	≥1 cm
Low		
Initial evaluation	High-resolution CT	High-resolution CT or transthoracic fine-needle aspiration biopsy
Follow-up	Follow-up CT	Follow-up CT
Moderate to high	Transthoracic fine-needle aspiration biopsy	Contrast-enhanced high-resolution CT

* The information is based on data from Henschke et al.[31] CT denotes computed tomography.

THORACOTOMY AND VIDEO-ASSISTED THORACOSCOPIC SURGERY

Nearly all solitary nodules are resectable. Lobectomy in patients with malignant disease is associated with an operative mortality rate of 3 to 7 percent or less, according to results in selected series.[35,36] Resection of benign nodules is associated with a mortality rate of less than 1 percent, largely because only a small wedge resection is required.

Video-assisted thoracoscopic surgery offers the potential for lower morbidity and a shorter hospital stay than conventional thoracotomy. This procedure involves the use of general anesthesia with a double-lumen tube to allow separate ventilation of each lung, followed by discontinuation of mechanical ventilation to the side with the nodule. Partial pneumothorax is then induced by insufflation of carbon dioxide in the affected side. A trocar is inserted through the seventh intercostal space to create access for the thoracoscope. Additional trocars are

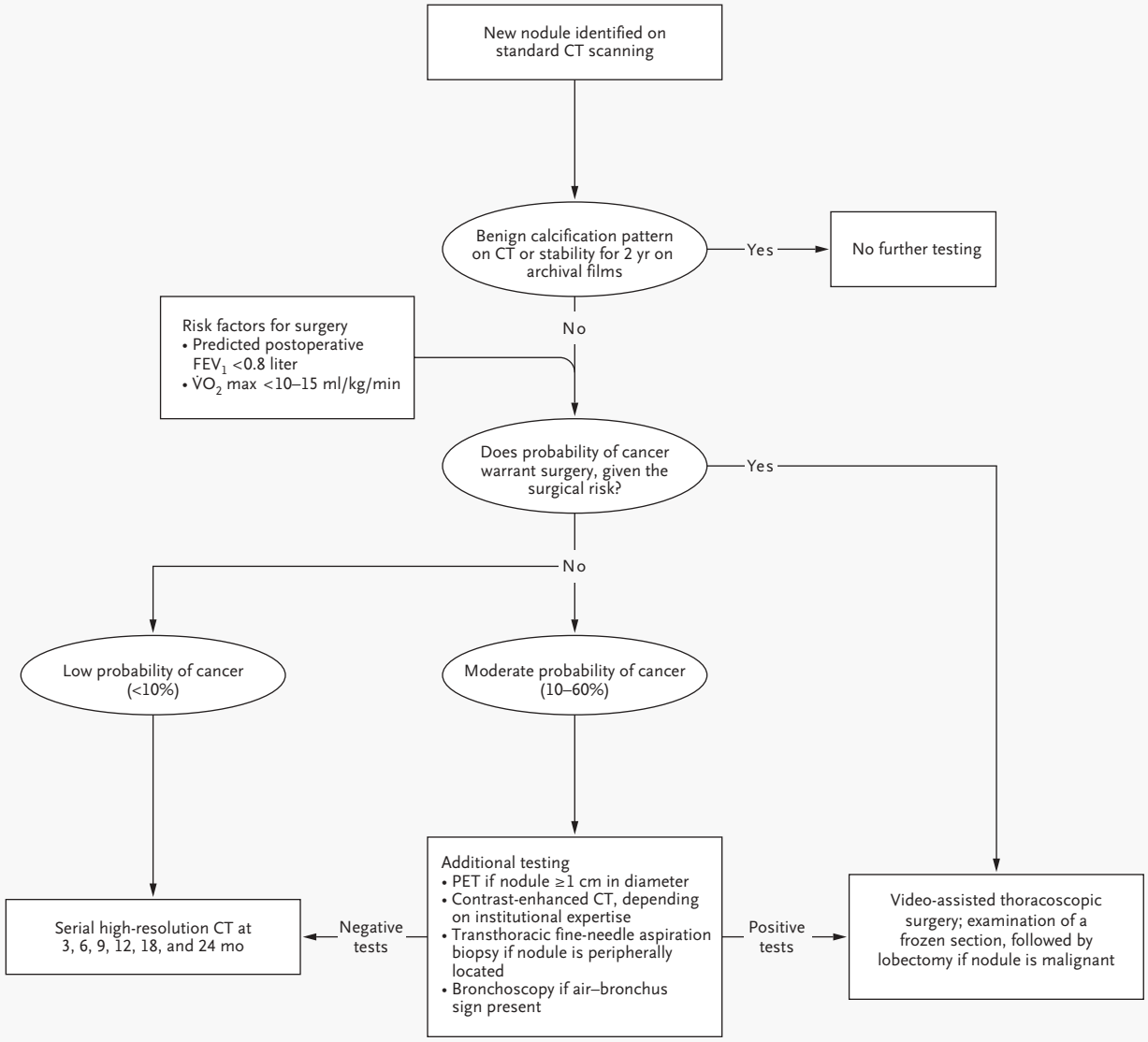

Figure 2. Approach to the Management of Solitary Pulmonary Nodules.

Management approaches vary according to several factors, including the degree of surgical risk, the presence or absence of coexisting conditions, the patient's preferences, and local radiologic and surgical expertise. The probabilities of cancer shown are approximations. CT denotes computed tomography, FEV_1 forced expiratory volume in one second, $\dot{V}O_2$ max maximal oxygen consumption, and PET positron-emission tomography.

placed so that other instruments, such as lasers and stapling devices, can be used. Video-assisted thoracoscopic surgery may be most successful for the treatment of peripheral lesions and some central lesions in the lower lobe. An initial, frozen section can be examined to assist in the decision about whether to proceed with a full lobectomy. As surgical morbidity and mortality decline, the strategy of proceeding directly to video-assisted thoracoscopic surgery becomes more effective than other diagnostic approaches.

GUIDELINES

No evidence-based guidelines completely address the approach to solitary pulmonary nodules.[7,28,35]

The American College of Radiology has published criteria for choosing the most appropriate tests in given circumstances, according to available evidence and expert opinion (Table 2).[30] Lesions are categorized on the basis of size (<1 cm vs. ≥1 cm in diameter) and the level of clinical suspicion for cancer (low vs. moderate to high). Unfortunately, these guidelines do not delineate the probability of cancer that is associated with a low, moderate, or high level of suspicion or how best to assess probability. In addition, variations among patients in terms of surgical risk are not included in the guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The approach to a patient with a pulmonary nodule should be based on an estimate of the probability of cancer, determined according to the size of the nodule, the presence or absence of a history of smoking, the patient's age, and characteristics of the nodule's margins on CT imaging (Fig 2).[28,29] When the probability of cancer is low, the nodule should be monitored with serial high-resolution CT. A standard approach consisting of high-resolution CT at three-month intervals during the first year and at six-month intervals the next year is logical. When the probability of cancer is high, surgical resection is warranted, assuming the surgical risk is acceptable.

For patients in whom the probability of cancer is estimated to be between 10 percent and 60 percent, additional testing is warranted. Options include PET, contrast-enhanced CT, transthoracic fine-needle aspiration biopsy, and bronchoscopy. For the patient described in the clinical vignette, appropriate strategies would include PET, since the nodule is 1.5 cm in diameter, or transthoracic fine-needle aspiration biopsy if it is peripherally located, or video-assisted thoracoscopic surgery if the margin is spiculated and thus strongly suggestive of a malignant process and the patient is deemed to be at low surgical risk.

For patients with indeterminate nodules, we favor the use of PET scanning to allow precise risk stratification. If the PET scan is negative for cancer, a strategy of follow-up with high-resolution CT is warranted. If the PET scan is positive for cancer, then the surgical risk may be acceptable. In patients who have a relatively high risk of cancer but no coexisting conditions, early video-assisted thoracoscopic surgery is still an option. In other cases, there may be little difference among the strategies in terms of their relative risks and benefits. The patient's preference is a very important factor, especially if the potential difference among strategies is likely to be small.

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