Solitary pulmonary nodule

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The solitary pulmonary nodule remains a common and challenging clinical problem. The goal of diagnosis is to establish the cause of the pulmonary nodule by the least invasive means. The authors thus review the scope of the problem, the differential diagnosis of the solitary pulmonary nodule, the available radiographic diagnostic techniques, and the available tissue sampling techniques.

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Solitary pulmonary nodules are frequent because the incidence of lung cancer in the United States continues to rise. American Cancer Society data suggest that 150,000 new lung cancers came to clinical attention in 1987. Data from a representative series show that 31% of these new lung cancers present as a nodule or mass on the initial chest radiograph,[1] indicating that 46,500 new malignant solitary pulmonary nodules should have developed. Considering that only 35% of all solitary pulmonary nodules are bronchogenic cancer (*Table 1*), the estimated 1987 incidence of new solitary nodules was 133,900. This figure rivals the yearly incidence of other major pulmonary problems in the United States, namely lung cancer and the adult respiratory distress syndrome.[2]

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Table 1. Estimated 1987 incidence of solitary pulmonary nodules

- 150,000 new lung cancers
- 31% present as nodule/mass on initial chest radiograph
- 46,500 new malignant solitary pulmonary nodules
- 35% of all solitary pulmonary nodules are bronchogenic cancer
- 133,900 estimated new solitary nodules

Table 2. Selected differential diagnosis of the solitary pulmonary nodule

Malignant tumors
Bronchogenic carcinoma
Metastatic tumors
Carcinoid
Miscellaneous
Hamartomas
Granulomas
Tuberculosis
Histoplasmosis
Coccidioidomycosis
Cryptococcosis
Aspergillosis
Blastomycosis
Miscellaneous lesions
Bronchial cyst
Subpleural lymph nodes
Arteriovenous fistula
Localized anthrosilicosis
Echinococcus cyst
Dirofilaria immitis
Enlarged pulmonary artery
Hemangiopericytoma
Fibroma
Rheumatoid nodule
Infarct
Hematoma
Lung disease
Sarcoidosis
Rounded atelectasis
Pseudotumor (loculated fluid)
Bronchopulmonary sequestration

Differential diagnosis of the solitary pulmonary nodule

The differential diagnosis of the solitary pulmonary nodule is extensive (*Table 2*) and includes various granulomas, hamartomas, malignancies (most of which are bronchogenic carcinomas), and a variety of miscellaneous lesions including vascular abnormalities (e.g., arteriovenous fistulas, vascular aneurysms) and congenital abnormalities of the lung (including bronchopulmonary sequestrations and bronchial cysts). Lesions that may simulate solitary pulmonary nodules should also be considered, such as pulmonary pseudotumors (collections of fluid loculated within the fissures of the lung) and rounded atelectasis (commonly believed to be an involution of the lung as surrounding pleural fluid is resorbed). Recognizing vascular lesions and pseudotumors is important as it will allow the clinician to avoid inappropriate biopsy procedures.

Table 3 presents the frequency distribution of solitary pulmonary nodules in 13 of the largest available series,[3–15] each of which contains more than 100 patients. Clearly, the range of frequencies for each cause of the solitary pulmonary nodule is quite broad. For example, malignant lesions made up between 10% and 67% of all solitary pulmonary nodules in these 13 series. This wide range in frequency is probably due to differences in the source populations and in study inclusion criteria. Overall, however, malignant lesions comprised 44% of all solitary pulmonary nodules and most (35%) were bronchogenic carcinomas. Benign lesions made up the remaining 56%, of which granulomas were most common.

To examine the frequency distribution of solitary pulmonary nodules at The Cleveland Clinic Foundation, we reviewed the pathology of 67 recently resected pulmonary nodules (*Table 4*). A total of 154 thoracotomies for pulmonary lesions performed between January 1 and December 31, 1986 were reviewed to identify the subset of resected solitary pulmonary nodules. Nodules in patients not referred for resection were not included in this series. Of the 67 total nodules, 46 (69%) were malignant lesions and 21 (31%) were benign. As in the other 13 large series (*Table 3*), bronchogenic carcinomas constituted most of the malignant solitary pulmonary nodules (39, or 58% of the total); solitary pulmonary metastases and unusual pulmonary neoplasms (e.g., carcinoid tumors) made up the remainder. Also in keeping with other series, granulomas were the most frequent cause of benign solitary nodules (10, or 15% of the total). However, the frequency distribution in our series varied from the frequencies in the pooled series in two striking ways:

1. The malignancies (and especially bronchogenic cancers) constituted most (69%) of all resected nodules at the Cleveland Clinic. Notably, this is in spite of our extensive referral from areas in which histoplasmosis is prevalent (e.g., the

Table 3. Distribution of malignant and benign solitary pulmonary nodules in 13 series

Series	Year	Number of cases	All malignant lesions (%)	Bronchogenic cancers (%)	All bening lesions (%)	All granulomas (%)
Bernatz and Clagett[3]	1953	180	34	30	66	36
Good et al[4]	1953	156	35	16	65	42
Paulson[5]	1956	180	44	34	56	37
Gerrits[6]	1956	210	54	47	46	9
Davis et al[7]	1956	215	47	37	53	38
Good and Wilson[8]	1958	184	52	33	48	31
Taylor et al[9]	1958	236	10	8	90	78
Cartwright et al[10]	1959	296	40	32	60	49
Perasalo and Tala[11]	1959	159	62	51	38	26
Steele[12]	1963	887	36	32	64	53
Walske[13]	1966	217	36	34	64	54
Nandi et al[14]	1981	239	67	65	33	25
Toomes et al[15]	1983	955	49	38	51	24
Total		4,114				
Mean (range)			44 (10–67)	35 (8–65)	56 (38–90)	37 (9–78)

Ohio River valley). We suspect that the excess of malignancies among all pulmonary nodules reflects the Cleveland Clinic's tertiary referral pattern as well as the surgical source of this series—a patient group from which patients with evidently benign lesions (e.g., by pathognomonic calcification or no growth over at least two years) are already excluded.

2. Many more malignant nodules occurred in women (46%) than in other large series. We postulate that the near equalization of male and female occurrence reflects the ever-increasing incidence of bronchogenic carcinoma in females.[16]

Radiographic assessment

The major challenge in assessing the solitary pulmonary nodule has been to define clinical and radiographic features that reliably identify the nodule as benign, thereby averting the need for invasive diagnostic tests. Given the frequency of bronchogenic cancer and the important survival advantage noted after resecting early stage tumors, these clinical and radiographic indicators of benignity must have the greatest possible reliability.

Many clinical and radiographic features have supposedly differentiated between benign and malignant pulmonary nodules. These features have included the patient's age; whether the patient smoked and, if so, how much; the size, shape, and sharpness of the margin of the pulmonary nodule; and the presence of calcification, the pattern of calcification, and the growth rate of the pulmonary nodule. Each of these discriminating features has received substantial attention in the literature,[5,6,17] but only two have emerged as reliable indicators of benignity: the presence of characteristic patterns of calcification[18] and the absence of growth over sufficient time.[17,19,20]

Calcification in a pulmonary nodule is usually associated with chronic inflammation and is therefore a strong indicator of benignity. Fewer than 1% of pulmonary malignancies appear cal-

Table 4. Causes of 67 solitary pulmonary nodules resected at the Cleveland Clinic (January 1—December 31, 1986)

	Number of cases	%
Malignant	46	69
Bronchogenic cancer	39	58
Adenocarcinoma	24	
Squamous	9	
Undifferentiated large cell	5	
Adenosquamous	1	
Metastasis	5	8
Breast	2	
Kidney	1	
Colon	1	
Uterus	1	
Carcinoid	2	3
Benign	21	31
Granuloma	10	
Hamartoma	6	
Fibroma	2	
Sequestration	1	
Silicotic nodule	1	
Necrobiotic nodule	1	

Table 5. How much diameter increase to double volume?

Initial diameter (cm)	Volume (cm^3)	Increase in diameter to double volume (cm)
0.5	0.07	0.14
1.0	0.52	0.24
1.5	1.8	0.40
2.0	4.2	0.52
2.5	8.2	0.64
3.0	14.1	0.78
3.5	22.4	0.90
4.0	33.4	1.04

cified on chest radiographs, though calcification in malignancies is more common in the resected specimens. O'Keefe et al[18] have shown that 14% of resected bronchogenic cancers are calcified and that 4% show a pattern of central calcification. Similarly, 10% of metastatic lesions to the lung are calcified, and 5% show central calcification. Thus, although calcification is far more common in benign than malignant lesions, it is not unique to benign lesions. On the other hand, three specific patterns of calcification—homogeneous calcification, "popcorn" calcification, and laminated calcification—have been exclusively observed in benign lesions and are therefore considered reliable evidence of benignity. Laminated calcification is the result of the serial deposition of calcium in concentric circles in the nodule and is uniquely associated with granulomas. In the data presented by O'Keefe's group, 40% of granulomas show this pattern of calcification. Popcorn calcification is considered pathognomonic of pulmonary hamartomas, although only a minority of hamartomas show this characteristic pattern (12.5% in O'Keefe's series). Homogeneous calcification is another reliable sign of benignity.

Other radiographic evidence of benignity is the absence of growth on available serial chest radiographs separated by at least 24 months, although growth over time is not a unique feature of pulmonary malignancies. For example, in a series of 156 pulmonary nodules, Good and Wilson[4] observed that 33% of pulmonary adenomas enlarged over time and that 4% of hamartomas and 6% of granulomas also enlarged.

The observation that both malignant and benign pulmonary lesions may grow has spurred investigators to examine growth rates as a means of differentiating benign from malignant pulmonary nodules. Measuring nodule growth rate is based on the concept of "doubling time," which is the time necessary for the nodule to double in volume on serial chest radiographs. The volume of a sphere is related to its radius by the equation:

$$Volume = 4/3\ \pi r^3,$$

where r is the radius of the nodule. Assuming a constant rate of growth for the pulmonary nodule, the doubling time can be calculated from measurements of the nodule radius on serial chest radiographs. Based on measurements of doubling time in a series of solitary pulmonary nodules, Nathan et al[17] have suggested that malignant pulmonary nodules can be differentiated from benign lesions. In this series of 218 nodules, malignant lesions showed doubling times between seven and 465 days, whereas benign lesions enlarged either more rapidly (in the case of inflammatory lesions) or more slowly (in the case of granulomas and hamartomas). It is troubling that one of the 177 malignant pulmonary nodules in the series reported by Nathan et al (a bronchogenic adenocarcinoma) was found to have a prolonged doubling time (well over one year). Although it is conceivable that this adenocarcinoma arose out of a benign pulmonary scar, this exception casts some doubt on the reliability of doubling times as a discriminator between benign and malignant pulmonary nodules.

Several other problems compromise the reliability of doubling time as an indicator of benignity. First, the assumption that tumor nodules grow at uniformly constant rates throughout their natural history may be incorrect. For example, in a series of 41 malignant pulmonary nodules, Garland[19] observed that growth rates tended to follow a consistent slope over time, but that rates varied from time to time in a substantial number of lesions, and that 5% of malignant nodules briefly shrank. A second problem with using doubling time measurements is that small nodules may double their volume with increases in radii that are too small to be detected on serial chest radiographs. *Table 5* shows the changes in diameter associated with volume doublings for nodules of various initial sizes. For a nodule originally 0.5 cm in diameter, a diameter increase of merely 0.14 cm (too small to be reliably detected on serial chest radiographs) will double the volume. Failure to appreciate these minute increments in diameter may cause the doubling

time to be underestimated, potentially leading to the misdiagnosis of a malignant pulmonary nodule as a slower-growing benign lesion. Finally, problems with intraobserver and interobserver variability in measurements compromise the usefulness of doubling time as a determinant of benignity. In a series in which nine observers estimated nodule sizes and doubling times for the same set of chest radiographs, Nathan et al[17] observed a 7.2% variation in estimates of doubling time. Similarly, Brenner et al[20] noted up to a 30% variation in the estimates of nodule volumes when repeat measurements were made from single chest radiographs. Overall, because of these difficulties in reliability, enthusiasm for using tumor doubling time as a criterion of benignity has waned.

The most recently proposed technique for differentiating benign from malignant pulmonary nodules is computerized-tomographic (CT) densitometry using the phantom pulmonary nodule technique. As is well known, the CT scan can quantitate the density of pulmonary nodules and assign a specific value (measured in Hounsfield units) for each degree of x-ray beam attenuation. The denser the nodule (i.e., the more calcium present within it), the higher the x-ray beam attenuation and the higher the number of Hounsfield units. Early experience with CT densitometry suggested that pulmonary nodules with densities greater than 164 Hounsfield units were uniformly benign,[21,22] but subsequent studies failed to reproduce these early data.[23] This lack of reproducibility has been ascribed to differences between different CT scanners and to changes in calibration within an individual scanner over time. In an effort to standardize CT scanners and to improve discrimination between calcified (e.g., benign) and noncalcified pulmonary nodules, Zerhouni et al[24] proposed using a phantom pulmonary nodule technique.

The phantom technique consists of scanning a mock-up of the patient's chest into which a pellet made of a calcium carbonate embedded in epoxy has been placed to simulate the intrathoracic position of the patient's pulmonary nodule. By comparing the CT attenuation of the phantom nodule to that of the actual patient's nodule, the CT scan can identify which of the two nodules is more dense. Should the patient's nodule be more dense than the known calcium carbonate pellet, it can be called calcified and, therefore, is overwhelmingly likely to be benign. On the other hand, should the patient's nodule be less dense than the phantom nodule, the patient's nodule cannot be said to be calcified, and the phantom nodule study must be classified as indeterminate. To date, two large series evaluating the diagnostic performance of the phantom nodule technique have been performed. Siegelman et al[25] evaluated 634 solitary pulmonary nodules by CT densitometry; 176 of these (27.7%) were called benign on the basis of the phantom nodule study, and the remainder (45%) were labeled indeterminate. The benignity of the 176 nodules was proved by the absence of growth on serial chest radiographs separated by at least two years. All of the indeterminate nodules underwent biopsy or were resected, and 103 were found to be benign, while 355 were malignant. Notably, no lesion labeled benign via CT densitometry was subsequently found to be malignant; that is to say, CT densitometry yielded no false-negative benign nodules. The second large available series was a multicenter trial of the phantom nodule technique and included data from 295 solitary pulmonary nodules.[26] Sixty-six of these nodules were labeled benign on the basis of the phantom nodule studies, and the remainder were considered indeterminate and were then resected or underwent biopsy. As in the series by Siegelman et al,[26] most of the indeterminate lesions (77%) were malignant, and the remainder were benign. However, unlike the other large series, one of the 66 nodules labeled benign was actually malignant. However uncommon, this experience suggests that further evaluation of the role of CT phantom nodule studies is needed. Furthermore, before CT densitometry is adopted as a routine clinical tool, its diagnostic performance should be evaluated. Such studies are currently underway at the Cleveland Clinic.

Tissue sampling techniques and their efficacy

When radiographic evaluation does not confirm that the nodule is benign, available management strategies include continued observation or biopsy for histologic diagnosis. Although recent analyses advocate "watchful waiting" when the clinical likelihood of bronchogenic cancer is small (e.g., in a young nonsmoker),[27] the possibility of lung cancer in clinically unlikely settings has led many to recommend biopsy or up-front resection for solitary pulmonary nodules that are not unequivocally considered benign.[28]

Available methods for making a histologic diagnosis of a solitary pulmonary nodule include examination of sputum cytology, biopsy by means

of fiberoptic bronchoscopy or percutaneous aspiration, and diagnostic thoracotomy.

Sputum specimens should be collected from all patients with a solitary pulmonary nodule. Exfoliative cytology will prove to be diagnostic in up to 20% of patients with malignant nodules.[29] Cytology is most likely to be positive when the tumor is centrally located, has an endobronchial communication, and is an exfoliating lesion.[29–31] These features are most commonly seen in squamous cell carcinomas. The yield of exfoliative cytology may be increased by bronchoscopic washings, brushings, and postbronchoscopy sputum specimens.

Since its introduction in 1968,[32] flexible fiberoptic bronchoscopy has become the principal technique for histologically diagnosing pulmonary nodules and masses. In addition to rendering a specific histologic diagnosis, bronchoscopy may provide details about the airways (e.g., absence of other endobronchial lesions) that may not be appreciated on the plain radiograph, but that may be important for planning therapy of malignant lesions. Estimates of the overall diagnostic yield of flexible bronchoscopy for solitary pulmonary nodules vary from 48% to 75%.[33–35] Diagnostic yield is clearly operator-dependent, but is also determined by the size of the pulmonary nodule and by its position in the chest. Specifically, Radke et al[33] have shown that the diagnostic yield is higher for lesions greater than 2 cm in diameter (64%) than for smaller nodules (28%). Also, for lesions less than 2 cm in diameter, these same investigators observed a lower yield for nodules in the peripheral third of the lung field than for more proximal lesions. This drop-off in diagnostic yield with more peripheral lesions was not seen for nodules greater than 2 cm in diameter.

Percutaneous transthoracic aspiration is an alternative and complementary diagnostic technique in which a needle is introduced through the chest wall and into the pulmonary nodule (under either fluoroscopic or CT guidance) in order to either aspirate cells from the nodule or obtain a small core of tissue. The diagnostic yield of percutaneous aspiration is also operator-dependent, and available series suggest diagnostic yields between 79% and 96.5%.[36–38] As with flexible fiberoptic bronchoscopy, the diagnostic yield is higher for larger nodules than for smaller ones.[36] In a series of 430 nodules aspirated by Berquist et al,[36] the diagnostic yield for nodules between 4 cm and 8 cm in diameter was 91% *v.* 65% for nodules less than 1 cm in diameter.

Percutaneous aspiration can usefully complement fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. Although aspiration does not provide information about the airways, some series suggest that percutaneous aspiration can succeed after bronchoscopy has been nondiagnostic. For example, Wallace and Deutsch[39] studied 133 patients with solitary pulmonary nodules, all of whom underwent flexible fiberoptic bronchoscopy. Fifty of these patients underwent needle aspiration after nondiagnostic bronchoscopy, and in 18, a specific histologic diagnosis was made. As with bronchoscopy, only in cases where percutaneous aspiration yields a specific benign or nonsurgical malignant nodule will percutaneous aspiration avert the need for a thoracotomy. Overall, the choice of fiberoptic bronchoscopy *v.* percutaneous aspiration as an initial diagnostic procedure is determined by several factors: (*a*) the importance of endobronchial inspection in planning subsequent therapy, (*b*) the size and intrapulmonary position of the nodule and, (*c*) the respective morbidities of flexible fiberoptic bronchoscopy *v.* percutaneous aspiration.

Thoracotomy with excision is the procedure of choice for all solitary pulmonary nodules that are new or growing, are without one of the benign patterns of calcification, or are not known by tissue sampling to be benign with a specific diagnosis. Conventional medical contraindications to thoracotomy and pulmonary resections apply to solitary pulmonary nodules.[40] However, with modern surgical management, complete diagnostic accuracy is obtainable with 30-day operative mortality of less than 1.4%.[41]

Overall, attention to the diagnostic strategy outlined here should limit unneeded invasive tests while preventing underdiagnosis of resectable bronchogenic cancers.

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