Diagnostic evaluation of the incidental pulmonary nodule

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INTRODUCTION

Pulmonary nodules may be detected on cross-sectional imaging studies performed for an unrelated reason (ie, incidental pulmonary nodule). The major question that follows detection of a pulmonary nodule is the probability of malignancy, with subsequent management varying accordingly. The approach in this topic applies to nodules found **incidentally** in patients ≥35 years old without signs or symptoms attributable to the lesion and with a baseline risk of lung cancer equivalent to that of the general population. Separate strategies and individual adjustments are needed for other populations including patients who are undergoing lung cancer screening and for those who are immunocompromised, have a history of malignancy actively under treatment or follow-up, or are presenting with pulmonary symptoms (ie, suspected lung cancer).

The approach to patients with suspected lung cancer and indications for lung cancer screening are discussed separately. (See "Overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer" and "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer" and "Screening for lung cancer".)

DEFINITIONS

A pulmonary nodule is defined on imaging as a small (≤30 mm), well defined lesion completely surrounded by pulmonary parenchyma [1-4]. Morphologically, nodules are classified as solid (image 1) or subsolid; subsolid nodules are subdivided into pure ground-glass nodules (ie, no solid component) (image 2) and part-solid nodules (ie, both ground-glass and solid components) (image 3) [1]. Lesions that measure >30 mm are considered masses, rather than nodules, harbor a much higher likelihood of being malignant, and are discussed separately. (See "Overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer".)

Multiple pulmonary nodules are, on occasion, also encountered incidentally. In this setting, the diagnostic evaluation refers to the predominant type or the most suspicious nodule (eg, largest, growing).

DIFFERENTIAL DIAGNOSIS

The causes of incidental pulmonary nodules can be categorized as benign or malignant (table 1). The estimated frequency of each etiology varies substantially among studies, reflecting differences in the population studied and the methodology used to establish a diagnosis [5-11]. Nonetheless, screening studies of smokers who are at high risk of malignancy suggest that the vast majority of nodules identified on computed tomography (CT) are benign. As an example, in the Pan-Canadian Early Detection of Lung Cancer and the British Columbia Cancer Agency studies, among

the 12,029 nodules found, only 144 (1 percent) were malignant [12]. The incidence of malignant nodules is likely much lower in patient at average or low risk for lung cancer.

Malignant etiologies — Common causes of a malignant nodule include primary lung cancer, lung metastases, and carcinoid tumors.

- Primary lung cancer – Adenocarcinoma is the histologic subtype of primary lung cancer that most commonly presents as a pulmonary nodule, followed by squamous cell carcinoma and large cell carcinoma. Both adenocarcinoma and large cell carcinoma share a tendency to originate as a peripheral lesion, whereas squamous cell carcinoma presents more frequently as a central lesion than as a peripheral nodule. In one review, most of the malignant nodules were adenocarcinoma (50 percent) and squamous cell carcinoma (20 to 25 percent); each of the other pathologic categories accounted for less than 10 percent of malignant pulmonary nodules [3]. Rarely, primary extranodal lymphomas and primary pulmonary sarcomas can present as an incidental pulmonary nodule. (See "Overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer".)

- Metastatic cancer – The most common cancers with pulmonary metastases are malignant melanoma, sarcoma, and carcinomas of the bronchus, colon, breast, kidney, and testicle [13]. In a patient with a history of extrathoracic malignancy, the probability of metastasis is approximately 25 percent when a pulmonary nodule is detected on a chest radiograph [14]. However, most metastases occur in a patient who already carries the diagnosis of the primary cancer and so would generally not be considered as an **incidental** pulmonary nodule.

- Carcinoid tumors – Although carcinoid tumors are typically endobronchial, approximately 20 percent present as a peripheral, well-circumscribed pulmonary nodule. (See "Lung neuroendocrine (carcinoid) tumors: Epidemiology, risk factors, classification, histology, diagnosis, and staging".)

Benign etiologies — Common causes of a benign pulmonary nodule include infectious granulomas and benign tumors such as a pulmonary hamartoma. Less common causes include vascular and other inflammatory lesions (table 1).

- **Infectious** – Infectious granulomas cause approximately 80 percent of benign nodules [2,9,10]. Endemic fungi (eg, histoplasmosis, coccidioidomycosis) and mycobacteria (either tuberculous or nontuberculous mycobacteria) (image 4) are the most frequently recognized causes of infectious granulomas presenting as a pulmonary nodule. While not pathognomonic, they classically appear as a well-demarcated and fully-calcified or centrally calcified nodule (image 5). However, they frequently present as non-calcified nodules and are not diagnosed until the lesion is biopsied or resected as a suspected cancer [15].

  Less commonly, infection with abscess-forming bacteria (eg, *Staphylococcus aureus*) can present as a pulmonary nodule, which may cavitate [16-19]. Rarely, dirofilariasis, a mosquito-borne disease, presents as a pulmonary nodule. Injected larvae embolize to the lungs and induce a granulomatous response, typically resulting in a noncalcified, peripheral nodule that is mistaken for cancer. (See "Miscellaneous nematodes".)

- **Benign tumors** – Pulmonary hamartomas cause approximately 10 percent of benign nodules found in the lung [2,9,10]. They typically present in middle age, grow slowly over years, and are radiologically and histologically heterogeneous. Cartilage (with scattered calcification), fat, muscle, myxomatous tissue, and fibroblastic tissue may all exist (picture 1 and picture 2A-B and image 6) [20]. The classically described and pathognomonic appearance of a hamartoma on a chest radiograph is a nodule with "popcorn" calcification, although this pattern is observed in less than 10 percent of cases (image 7). High-resolution CT of the lesion is particularly useful because it may demonstrate focal areas of fat, or calcification alternating with fat, which are virtually diagnostic of a hamartoma (image 8) [21]. Less common benign neoplasms such as fibromas, leiomyomas, hemangiomas, amyloidoma (image 9), and pneumocytoma (also called pulmonary sclerosing hemangioma) do not have characteristic features on imaging (image 10) [22].

- **Vascular** – Pulmonary arteriovenous malformations (PAVMs) are common in hereditary hemorrhagic telangiectasia but can also be idiopathic (image 11 and image 12). When a PAVM is suspected on CT (eg, a feeding artery and vein is seen) biopsy should be avoided. Rarer causes of incidental pulmonary nodules that are vascular in nature include pulmonary infarcts (image 13), pulmonary varices, and pulmonary contusion or hematoma (table 1). (See "Pulmonary arteriovenous malformations: Clinical features and diagnostic evaluation in adults".)

- **Other** – Inflammatory lesions (granulomatosis with polyangiitis, rheumatoid arthritis, sarcoidosis), amyloidoma, rounded atelectasis, perifissural pulmonary lymph nodes, and developmental lesions (bronchogenic cyst) are unusual causes of benign nodules (table 1). The presence of systemic disease elsewhere may increase the likelihood of an inflammatory nodule, but not all patients will have such a history since nodules can occasionally be the initial presenting feature of the underlying disease. Rarely are pulmonary nodules due to artifact such as pleural pseudotumor (loculated fluid in the interlobar fissure) or mucoid impaction; simple maneuvers such as diuresis and cough assistance may result in the resolution of nodules due to such entities on follow-up imaging.

  The term miliary nodules refers to innumerable, small 1 to 4 mm pulmonary nodules scattered throughout both lungs. It is classically associated with tuberculosis but can also be caused by sarcoidosis, silicosis, histoplasmosis, and rarely extrathoracic malignancy [23].

EVALUATION DURING COVID-19

A consensus statement, issued by an expert panel suggests that during the coronavirus disease 2019 (COVID-19) pandemic, the evaluation of lung nodules be modified due to risks of exposure and the need for resource reallocation [24]. However, they acknowledge that nodule care is also subject to local, regional, and patient-related factors.

INITIAL EVALUATION

The initial evaluation should use clinical and radiographic features to determine the likelihood of malignancy. The likelihood of malignancy then determines further management, usually computed tomography (CT) surveillance or biopsy.

Assessing the risk of malignancy — The probability of malignancy in an incidental pulmonary nodule should be assessed either clinically or by quantitative predictive models as the following (calculator 1) [3,25]:

- Low probability (<5 percent)
- Intermediate probability (5 to 65 percent)
- High probability (>65 percent)

Many clinicians estimate the probability of malignancy intuitively. Studies that have compared the accuracy of clinician judgment with quantitative prediction models report modest to excellent agreement in estimating the probability of malignancy, suggesting that clinical assessment and prediction models may be complementary [26-28].

Although no single quantitative predictive model is superior, they all combine clinical and imaging features to estimate the probability of malignancy [27,29-35]. They are most useful for nodules that are 8 to 30 mm to facilitate patient discussion and guide management choices [3]. Typically, lesions >30 mm that lack benign features are resected because they have such a high likelihood of malignancy that the benefit of resection outweighs the associated risk of surgery. In contrast, nodules ≤8 mm (without documented growth) are often followed with serial CT because these lesions have a low likelihood of malignancy such that the benefits of resection do not justify the risk of surgery [3,36-42]. Thus, estimating the probability of malignancy in both of these settings is unlikely to change the diagnostic strategy. However,

the risk of malignancy and diagnostic options are widely variable in nodules that are 8 to 30 mm. Thus, estimating the pretest probability of malignancy in that setting will facilitate the selection and interpretation of subsequent diagnostic tests.

Quantitative predictive models that have been validated for use include the following [12,29-31,43]:

- A full and simplified version of one model was derived using data collected from the Pan-Canadian Early Detection of Lung Cancer screening study and validated using data from the British Columbia Cancer Agency study (Brock model) [12]. Predictors of cancer were identified in 2961 patients with nodules found on first screening CT and included the following: older age, female sex, family history of lung cancer, emphysema, larger nodule size, location of the nodule in the upper lobe, part-solid nodule type, lower nodule count, and spiculation. Both full and simplified versions of the model showed excellent discrimination between benign and malignant nodules, even when applied to nodules typically difficult to characterize (nodule ≤10 mm). While the negative predictive value of this model was consistently high (99 percent), the sensitivity ranged from 60 to 86 percent when different cut-off thresholds were used. The probability of malignancy can be calculated using the calculator (calculator 1). Additional tools are available on the following site: http://www.brocku.ca/cancerpredictionresearch.

  Unlike other models, this model considers nodule attenuation (solid, subsolid, part-solid) as a variable that can affect the risk of malignancy [12]. The increased incidence of adenocarcinoma, which is more likely to present as a subsolid and part-solid nodule, gives this model a distinct advantage over the others. However, this model only estimated the probability of malignancy in a population at high risk for lung cancer (current or ex-smokers). It is not validated, and therefore could potentially overestimate the probability of cancer in low risk populations (eg, never smokers). One study suggested that this model had good discrimination and calibration when compared with other models [44].

- Another clinical predictive model (Veterans Administration Cooperative) was derived using data from CT and/or positron emission tomography (PET) in 375 veterans (current or former smokers) with nodules measuring 7 to 30 mm [30]. Independent predictors of malignant nodules included the following: smoking history (current or former) (odds ratio [OR] 7.9), older age (OR 2.2 per 10-year increment), larger nodule diameter (OR 1.1 per 1 mm increment), and time since quitting smoking (OR 0.6 per 10-year increment). This model showed excellent agreement between the predicted probability and the observed frequency of malignant nodules. While this model may be useful in high risk populations, it has not been validated in a never-smoking/low risk population. .

- Two additional older models derived data mostly from chest radiographic findings to estimate the probability of malignancy in an incidental pulmonary nodule:

  - One model (Mayo Clinic model) identified six independent predictors of malignancy: older age, smoking history, history of cancer, nodule diameter, spiculation, and upper lobe location [29]. The addition of nodule volume to the equation may increase the proportion of nodules correctly identified as malignant [43]. A tool for calculating the risk using this model is provided at the following site: http://www.chestx-ray.com/index.php/calculators/spn-calculator.

  - Another model used likelihood ratios (LRs) to estimate the probability that a nodule is malignant [31]. LRs are first determined for a number of factors including nodule size, patient age, smoking history, and overall prevalence of malignancy in the population (table 2 and table 3) [31,32]. The odds of malignancy are then calculated by multiplying the LRs. Finally, the probability of malignancy is calculated from the odds of malignancy (figure 1).

  These older models are likely to accurately reflect the estimated risk of malignancy in the general population in nodules found incidentally. However, they are based upon estimates from chest radiographic findings (not CT) and

do not include nodule attenuation as a variable.

The use of biomarkers (eg, carcinoembryonic antigen, alpha-1 antitrypsin, squamous cell carcinoma antigen) to stratify risk of malignancy in patients with incidental pulmonary nodules has been reported but is not yet validated for use [45]. Measurement of biomarkers of benign diseases (eg, fungal serologies, angiotensin converting enzyme, connective tissue disease markers) has not been tested in the general setting of incidental pulmonary nodules but can be considered on a case-by-case basis.

The Pulmonary Nodule Plasma Proteomic Classifier (PANOPTIC) trial investigated the ability of five clinical risk factors (age, smoking status, nodule diameter, shape, and location) and the expression of two plasma proteins associated with lung cancer and cancer immune response (LG3BP and C163A) to differentiate between benign and malignant pulmonary nodules. Results suggested that the integrated classifier accurately identifies benign lung nodules with good performance characteristics (high sensitivity [97 percent] and high negative predictive value [98 percent]). These findings need further validation before this index can be recommended [46].

Clinical features — Clinical features associated with an increased probability of malignancy include advanced patient age and underlying risk factors. However, younger age and the absence of risk factors do **not** preclude a diagnosis of malignancy [47].

- Patient age – The probability of malignancy rises with increasing age [6,8,29,30,47,48]. Most guidelines for incidental pulmonary nodules assume some underlying cancer risk for a patient 35 years or **older**. For example, one study stratified the percentage of nodules that were malignant according to age [8]:
  - 35 to 39 years: 3 percent
  - 40 to 49 years: 15 percent
  - 50 to 59: 43 percent
  - ≥60 years: >50 percent
- Risk factors for lung cancer – The probability of lung cancer is higher in a patient with a history of smoking, especially current smokers [36]. Other risk factors include family history, female sex, emphysema, prior malignancy, and asbestos exposure [49]. Nodules detected in high-risk patients undergoing lung cancer screening are not considered incidental and may require a modified approach [50]. (See "Cigarette smoking and other possible risk factors for lung cancer" and "Screening for lung cancer", section on 'Recommendations by expert groups' and "Clinical manifestations of lung cancer".)
- Risk factors for noncancerous lung nodules – Nodules encountered in immunocompromised patients are much more likely to represent infection than malignancy.

Imaging — Imaging assesses the size, attenuation, growth, and metabolic activity of an incidental nodule. Every effort should be made to obtain prior images that could have included the relevant area. Growing nodules are suspicious for malignancy whereas long-term stability suggests a benign etiology. (See 'Growth or stable size' below.)

Selection of modality — Imaging exams used to evaluate an incidental pulmonary nodule include chest radiography, chest CT without intravenous contrast, and fluorine-18-labelled fluorodeoxyglucose (FDG) PET with CT (PET/CT) of the whole body. Chest CT is the preferred modality for initial evaluation for malignancy risk. Thus, if a nodule has been detected on plain radiography, magnetic resonance imaging (MRI), or PET (without CT), a dedicated chest CT should be obtained with a thin-section imaging protocol tailored for pulmonary nodule evaluation. The other modalities do not offer sufficient spatial resolution for reliable size measurement, which is a key factor in nodule evaluation. (See 'Computed tomography' below.)

Computed tomography — Computed tomography (CT) of the chest without contrast using a lower than usual radiation dose technique is the preferred modality to evaluate an incidental pulmonary nodule for likelihood of malignancy. Thin-section volumetric scanning is performed to ensure diagnostic accuracy and measurement reproducibility. CT is the most reliable modality for assessing nodule size, growth, and lobar location, and also allows visualization of nodule attenuation (density) and borders.

CT imaging technique — For pulmonary nodule evaluation, CT images should be helically acquired as contiguous thin (1 mm) sections. Thin section imaging is required to optimize accuracy and to minimize variability of nodule size measurement and to evaluate for presence of calcium and fat. Maximum-intensity-projection (MIP) images are usually used to aid reader detection of nodules [51]. Coronal or sagittal reconstruction images are sometimes reviewed for nodule localization. Iodinated intravenous contrast is usually unnecessary but is sometimes administered when a vascular malformation or infarct is suspected. (See "Pulmonary arteriovenous malformations: Clinical features and diagnostic evaluation in adults", section on 'Imaging findings' and "Pulmonary arteriovenous malformations: Clinical features and diagnostic evaluation in adults", section on 'Computed tomography'.)

Average effective radiation dose of a low-dose chest CT performed for pulmonary nodule evaluation is 1.5 mSv. As some nodules need to be followed over multiple exams, imaging protocols focus on obtaining diagnostic quality images of the lungs while minimizing the radiation dose. Practice standards specify that exposure parameters be adjusted according to the patient's body habitus to achieve a volumetric dose index (CTDIvol) of no more than 3 mGy in a standard-sized patient (height, 170 cm; weight, 70 kg) CT [52]. Dose modulation and iterative reconstruction techniques are applied when available.

Nodule features — Features of an incidental pulmonary nodule to be assessed on CT are:

Size — Consistently among studies, size is an independent predictor for malignancy. Size is measured as the average of the long and short axes, rounded to the nearest millimeter. Historically, many studies report nodule size as the maximum diameter; but this method is no longer favored as it is subject to more reader variability. Data from retrospective series and prospective screening trials all confirm that the risk of malignancy rises with increasing size as follows [12,29-31,36,37,43,53-58]:

- Nodules <5 mm: <1 percent
- Nodules 5 to 9 mm: 2 to 6 percent
- Nodules 8 to 20 mm: 18 percent
- Nodules >20 mm: >50 percent

Attenuation — Nodule attenuation (density) allows classification of lesions as solid or subsolid (pure ground-glass or part-solid). Solid lesions are more common, but part-solid lesions have a higher likelihood of being malignant [12,59,60]. Quantitative density measurement of a pulmonary nodule is no longer used as part of the routine evaluation as it rarely provides added diagnostic information.

- **Solid nodules** – Solid nodules are typically dense and homogeneous on imaging. Solid nodules ≤8 mm (also known as "subcentimeter" nodules) are less likely to be malignant, are difficult to biopsy, not reliably characterized by functional imaging, and, hence, best characterized with CT surveillance. In contrast, solid nodules >8 mm have a greater likelihood of malignancy, can be more reliably characterized by functional imaging (ie, PET), and are more likely to be successfully diagnosed by biopsy.

- **Subsolid nodules** – Subsolid nodules have less than soft tissue attenuation (ie, density) on imaging such that normal parenchymal structures, including airways and vessels, can be visualized through them. They are further assessed for the absence (pure ground-glass nodules) or presence (part-solid) of a solid component. Compared with solid nodules, subsolid nodules are often less amenable to functional imaging and biopsy.

The incidence of subsolid nodules is increasing, likely due to the rising incidence of adenocarcinoma worldwide and the increasing use of CT. The most common histologies seen with ground-glass morphology are atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma (MIA) (picture 3) [38-41,61,62]. (See "Pathology of lung malignancies".)

The risk of malignancy in ground-glass lesions that persist beyond three months by CT ranges from 10 to 60 percent and depends upon the size and presence of a part-solid component [3,12,38-42,62]. As examples, malignancy is rare in small (≤10 mm) nodules that are pure ground-glass and more common (10 to 50 percent) in larger lesions (>10 mm). In contrast, malignancy will be identified in at least half of ground-glass lesions that have a large (>50 percent) or newly developed solid component [12]. In one study of pure ground-glass nodules, features associated with invasiveness included size (>10.5 mm or >86.5 mm^2), higher attenuation (>−632 HU), heterogeneous density, irregular shape, coarse margin, spiculation, lobulation, pleural indentation, and dilated or distorted vessels [63].

Growth or stable size — For solid nodules, growth is defined as an increase in size of >2 mm [64]. For subsolid nodules, growth can also be identified as an increased attenuation or an increase in the size of or development of a solid component. Size is measured as the average of the long and short axes, rounded to the nearest millimeter. Reliable assessment of nodule growth requires chest CT acquired as contiguous 1 mm section images for pulmonary nodule evaluation.

Differences in scanning techniques, such as use of thick sections for previous imaging, may make comparison less accurate, especially for smaller nodules. Reader variability is also a factor, especially for small nodules. One study found that, when measuring nodules 20 mm or less, the limits of intra-reader and inter-reader variability were 1.32 mm and 1.73 mm, respectively [65]. This means that a nodule can only be confidently said to have grown if its diameter has increased beyond these limits.

Traditionally, a nodule that remained stable for two years or longer on a chest radiograph was considered benign. However, retrospective studies suggest that lack of appreciable growth on a chest radiograph over a two-year duration has a poor positive predictive value (65 percent) for a benign lesion [2,66,67]. Compared with chest radiography, CT can better detect changes in diameter (0.5 mm change versus 3 to 5 mm) [2]. A solid nodule that has been stable by CT for at least two years does not need any further diagnostic evaluation [3].

Studies that assess the volume doubling time (VDT) of cancers have been helpful in predicting the probability of malignancy in a pulmonary nodule. Most malignant nodules have a VDT between 20 and 400 days, with slower VDTs (>400 days) observed in typical carcinoid and in preinvasive or low grade adenocarcinoma (eg, adenocarcinoma in situ [AIS] and minimally-invasive adenocarcinoma [MIA]) [2,5,68-71]. Thus, a nodule that has increased in size over a short period of time (<20 days) or is stable for a prolonged period of time on CT (>2 years) is likely benign. These data largely apply to solid nodules. In contrast, subsolid nodules are more likely to be seen with early or low grade adenocarcinoma, which has a slower average VDT [71,72]. One retrospective study reported median VDTs of malignant nodules according to their CT attenuation characteristics as: ground-glass (813 days), ground-glass with a solid component (457 days), and solid (149 days) [72]. Thus, purely ground-glass lesions may be less readily detected as actively growing by CT, and follow-up for five years to determine stability is probably warranted in that population [73]. It is unlikely that nodules that have been stable for five years will grow but the risk may depend upon size. One study of subsolid nodules 6 mm or greater that were stable for five years reported that 2 percent showed subsequent growth [74].

Some groups consider a <25 percent change in volume as not significant [25]. However, further evaluation and validation of VDT assessment with clear definitions for significant growth is required before it can be recommended routinely in nodule evaluation.

Calcification and fat — Calcification pattern can sometimes be used to reliably diagnose an incidental pulmonary nodule as benign. There are four benign patterns of calcification, which are central, diffuse, lamellated, and "popcorn." Central, diffuse, and lamellated are typically seen with prior infection, particularly histoplasmosis or tuberculosis. Popcorn calcification is characteristic of chondroid calcification in a hamartoma. However, lung cancers, typical and atypical pulmonary carcinoid tumors occasionally show presence of some calcification. Indeterminate patterns of calcification (eg, punctate, eccentric, and amorphous) are nonspecific and a nodule containing one of these patterns may be malignant. Metastases from chondrosarcoma or osteosarcomas, in patients who carry a diagnosis of these cancers, may demonstrate calcified nodules that resemble benign granulomas.

The presence of fat (attenuation, -40 to -120 Hounsfield units) within a smooth bordered nodule is a reliable indicator of a pulmonary hamartoma (image 14) [21,75].

Border and lobar location — While the appearance of a nodule border can suggest a diagnosis, it cannot reliably distinguish between benign and malignant nodules. Typically, benign nodules have a well-defined, smooth border, whereas malignant lesions have a spiculated or lobular border. Spiculation is attributed to growth of malignant cells along the pulmonary interstitium, and lobulation to differential growth rates within nodules. While the majority of lesions with a spiculated margin (also described as a corona radiata sign) are malignant, this can also be seen with benign lesions. Conversely, a smooth margin does not exclude malignancy with many pulmonary metastases, and up to 20 percent of lung cancers have smooth margins (image 15) [21,76,77].

Although malignant nodules can be found in any lobe of the lung, those that are located in the upper lobe have an increased probability of being malignant [12,29]. In one study of over 7000 nodules, among the 102 that were subsequently found to be malignant, almost two-thirds were located in the upper lobes [12]. In addition, among the 77 perifissural nodules observed on CT, none were reported as malignant [12].

Enhancement — With solid nodules measuring >5 mm with homogenous attenuation (ie, no fat or calcification), quantitative assessment of the enhancement with iodinated contrast can be used to noninvasively identify nodules as most likely benign. The CT acquisition protocol includes non-contrast images, and images at one, two, three, and four minutes after the onset of intravenous contrast administration. Enhancement is calculated by subtracting the precontrast attenuation of the nodule from the peak attenuation after contrast. Typically, malignant nodules enhance more than 20 Hounsfield units, whereas nodules that enhance less than 15 Hounsfield units are likely benign (sensitivity, 98 percent; specificity, 58 percent; negative predictive value, 96 percent) [78].

Chest radiography — Most nodules detected on chest radiography will require chest CT without contrast for further evaluation. CT enables better evaluation of nodule size and appearance and detection of other underlying nodules or relevant findings (eg, mediastinal lymphadenopathy). Possible exceptions to this guideline are:

- Nodule is likely a nipple shadow. Nipple shadows are apparent on up to 11 percent of frontal chest radiographs [79]. Although there are criteria to make the diagnosis [52], in cases where there is uncertainty, a repeat radiograph with nipple markers should be performed.
- Patient has symptoms of infection and pneumonia is suspected. A short term follow-up radiograph in six to eight weeks could be obtained to ensure resolution after treatment.
- Pattern of nodule calcification suggests a benign diagnosis (eg, pulmonary hamartoma). For the majority of these cases, unless this pattern is pathognomonic, CT evaluation is recommended to confirm the calcification pattern indicates a benign process.

Chest radiographs are relatively insensitive for detection of small nodules, and most nodules less than 1 cm will not be seen [52,79]. The optimum technique for chest radiography is to obtain posteroanterior (PA) and lateral views, which is

possible in most patients who can stand or sit upright. For exams performed at the bedside, only an anteroposterior (AP) view is possible. Newer techniques, including digital tomosynthesis and bone-suppressed images, are under evaluation to improve detection of pulmonary nodules.

Although the average effective radiation dose of chest radiography is 0.1 mSv, compared with 1.5mSv on CT, the radiation dose for CT evaluation of a pulmonary nodule should not preclude clinicians from obtaining further CT for evaluation when indicated.

Positron emission tomography/computed tomography — 18-FDG PET images glucose metabolism and is typically acquired as a whole body integrated PET/CT exam (concurrent PET and CT imaging in a single scanner). Pulmonary nodules can be incidentally detected on PET exams or PET is sometimes used to evaluate pulmonary nodules detected on other modalities (image 16).

- **Solid lesions** – The avidity of FDG uptake can be helpful in differentiating between benign and malignant solid nodules. Given the resolution limitations of PET, tracer avidity cannot be reliably assessed for nodules with solid components measuring <8 mm. Optimum diagnostic accuracy is achieved when PET images are interpreted with concurrent or recent diagnostic chest CT images. In patients with nodules suspected to be malignant, PET/CT is used to evaluate for metastases and to select the safest target for biopsy. (See 'Positron emission tomography' below.)

  With whole body FDG PET/CT, PET is performed in an integrated PET/CT scanner and images of the chest, abdomen and pelvis are acquired. The CT can be performed at very low dose for attenuation correction only or at higher doses for diagnostic imaging. Neither intravenous nor oral contrast is necessary for pulmonary nodule evaluation. Average effective doses are 7 mSv and 25 mSv, respectively.

  Solid nodules measuring >8 mm that are not FDG-avid are likely to be benign. On meta-analysis, PET demonstrates pooled sensitivity of 89 percent (95% CI, 86-91 percent) and specificity of 75 percent (95% CI, 71-79 percent) for detecting cancer. Sensitivity is greater for nodules >2 cm (91 percent) and specificity is greater with integrated PET/CT (76 percent) or PET interpreted with recent CT (75 percent) rather than with sole PET (70 percent) imaging. As inflammation and infection are also FDG-avid, specificity is lower by 16 percent in populations with endemic infectious lung disease [80].

- **Subsolid lesions** – In contrast to solid nodules, ground-glass nodules, or ground-glass portions of part-solid nodules, are not reliably characterized with PET (image 2). PET demonstrates a sensitivity and specificity of 10 and 20 percent, respectively, for detecting malignancy in a ground-glass nodule [81].

  FDG PET can yield false-positive and false-negative findings:

- False-positive findings occur with infectious and inflammatory conditions, in particular, pneumonia, mycobacterial disease, rheumatoid nodules, and sarcoidosis.

- False-negative results can occur with less metabolically active tumors (adenocarcinoma in situ, minimally invasive adenocarcinoma, mucinous adenocarcinoma, and carcinoid tumors) and in patients with uncontrolled hyperglycemia (high serum glucose levels retard FDG uptake). Nodules with solid components ≤8 mm and pure ground glass nodules may be also falsely negative on PET [3,82-85].

FDG-avidity is measured by the standardized uptake value (SUV). The optimal cut-off point that distinguishes benign from malignant lesions is as yet undefined. In most studies that examine diagnostic performance, an SUV >2.5 is typically used to distinguish pulmonary nodules that have a high probability of malignancy [3]. However, although SUV correlates positively with the likelihood of malignancy, even nodules with a low SUV (eg, <2.5) can be malignant [86]. One

prospective study of 344 patients demonstrated a graded range of probability for the risk of malignancy based upon FDG-avidity, such that tumors with low SUV were less likely to be malignant than those with high SUV [87].

Errors in PET/CT interpretation can arise from misregistration of the PET and CT images, as CT images are acquired during breath holding and PET images are obtained during quiet breathing. This can result in both localization errors and underestimation of the SUV. For nodules adjacent to the diaphragm and heart, volume averaging from motion can artificially decrease apparent FDG activity.

Chest tomosynthesis — Chest tomosynthesis is a radiographic technique that offers some of the tomographic benefits of CT at a lower radiation dose. The average effective dose of chest tomosynthesis is 0.15 mSv, which is about 10-fold lower than that of CT.

The technology for performing chest tomosynthesis is not widely available. The technique involves acquiring multiple angular radiographic projections of the chest using a conventional x-ray tube and detector and a special computer-controlled tube mover. Reconstruction algorithms are then applied to create the image.

For nodule detection, tomosynthesis is more sensitive than chest radiography but less sensitive than CT. Approximately one-half of nodules measuring ≥6 mm on CT are detected with tomosynthesis [88]. Thus, tomosynthesis cannot be used as the primary modality for nodule detection. However, if validated, it may be useful to longitudinally follow known nodules in combination with CT.

MANAGEMENT

Individualizing the approach — The guidelines for diagnostic evaluation of an incidental pulmonary nodule allow for individual modifications. This is because the management of a nodule needs to be individualized for the patient (table 4) [3,84,89-91]. Aggressive approaches that surgically remove nodules are more likely to result in the diagnosis of early stage lung cancer, which is potentially curable and associated with a five-year survival of 70 to 80 percent [2,42,68,92-94]. However, they also result in the unnecessary removal of benign nodules of uncertain clinical benefit. In contrast, less aggressive approaches that leave most benign nodules intact will delay evaluation of some cases of potentially curable lung cancer, which may no longer be curable after progression.

Despite the provision of guidelines, the approaches used in practice are often inconsistent with these guidelines [28,95-99]. For example, in a retrospective study of over 5000 individuals with nodules, 38 percent received guideline-concordant care, while 37 percent received a less intensive diagnostic approach and 25 percent more intensive evaluations [99]. Although adjusted analyses found no difference in the risk for more advanced (stage III or IV) disease in either the less intensive or the more intensive groups compared with guideline-concordant care, there was a modestly higher proportion of stage III and IV lung cancer diagnosed in the less intensive evaluation group. However, compared with guideline-concordant care, less intensive evaluation was associated with fewer, while more intensive evaluation was associated with more procedural complications, radiation exposure, and healthcare expenditures.

The evaluation strategy described here is intended to strike a balance between potentially life-saving benefits of detecting resectable lung cancer with possible morbidity associated with testing and interventions [3,25,84]. Our approach is based on an assumption that the risk of malignancy is that of **incidental** nodules of patients ≥35 years old without signs or symptoms attributable to the lesion and with a baseline risk of lung cancer equivalent to that of the general population [1]. Direct applicability of this approach to nodules encountered in **other clinical settings** is less clear as the risk of malignancy varies. As an example, the likelihood of benign lesions (ie, infection, inflammation, benign tumor) is higher among patients <35 years old. In contrast, the likelihood of malignancy is higher among patients who are at high risk and meet criteria for lung cancer screening. Thus, separate strategies and individual adjustments are needed for patient populations including those who are immunocompromised, with history of malignancy actively

under treatment or follow-up, or presenting with pulmonary symptoms (ie, suspected lung cancer). Nodules detected during lung cancer screening should be managed according to guidance provided by Lung-RADS (used in the United States) which differs from the approach for incidental nodules (table 5). (See 'Nodules found on lung cancer screening' below.)

Importantly, it is prudent to assess a patient's desire for an extensive work-up as well as for treatment in the eventuality that a nodule is cancer. Some individuals prefer no treatment or suboptimal therapy, especially those with life-limiting comorbid conditions. For others who are risk averse, particularly to potentially curative lobectomy, discussion of alternative noncurative therapies for lung cancer is appropriate. For patients who prefer no therapy, monitoring clinically or with computed tomography (CT) surveillance may be preferred. In contrast, surgical excision may be preferred by those who have a strong desire for diagnostic certainty, may be noncompliant with follow-up, and are willing to accept the risks associated with surgery.

Growing nodule — A pulmonary nodule that has clearly grown on serial imaging is likely to be malignant and should be evaluated pathologically. (See 'Growth or stable size' above.)

For solid nodules, growth is defined as an increase in diameter of >2 mm, rounded to the nearest millimeter [64]. For subsolid nodules, growth can also be identified as an increased attenuation or an increase in the size of or development of a solid component. Reliable assessment of nodule growth requires chest CT acquired as contiguous 1 mm section images for pulmonary nodule evaluation.

Stable nodule — A solid nodule that has been stable for ≥24 months and a subsolid nodule that is stable for ≥5 years by CT are likely to be benign, and further workup can be avoided. (See 'Growth or stable size' above.)

Nodule with fat or calcification — Fat or certain patterns of calcification of a nodule on CT enable a diagnosis of a benign hamartoma or granuloma, thereby obviating further workup. (See 'Calcification and fat' above.)

Indeterminate nodule — If a nodule cannot be characterized as benign or as requiring tissue diagnosis and has been detected on a CT which incompletely images the chest (eg, neck, abdomen, or spine CT), a dedicated chest CT without contrast should be obtained with a volumetric thin-section scanning protocol. If the chest CT demonstrates additional findings relevant to the diagnosis (eg, other nodules or mass, lymphadenopathy, consolidation), further workup should be redirected accordingly. Otherwise, clinical and CT information is used to define the subsequent approach to the diagnostic evaluation with consideration of the following [3,84,89-91]:

- Probability of malignancy – Probability of malignancy should be assessed as low (<5 percent), intermediate (5 to 65 percent), or high (>65 percent) either clinically or by quantitative predictive models. (See 'Assessing the risk of malignancy' above.)
- Nodule size and attenuation (solid or subsolid) – Solitary solid nodules >8 mm should be evaluated further for the suspicion of cancer: CT surveillance at three months if the suspicion for cancer is low, FDG PET/CT if the suspicion is intermediate, and biopsy or excision if the suspicion is high. Follow-up is not required for solitary solid or subsolid nodules measuring <6 mm in size. Solitary solid nodules measuring ≤8 mm and solitary subsolid nodules with solid components measuring ≤8 mm cannot be reliably assessed with FDG PET/CT or needle biopsy; nodules 6 to 8 mm should be followed with serial imaging or, if pathologic characterization is desired, with surgical resection. (See 'Positron emission tomography/computed tomography' above and 'Transthoracic needle biopsy' below.)
- Nodule multiplicity – Multiple nodules are more likely to represent an infectious or inflammatory process and, in general, carry a lower risk for cancer than solitary nodules. Follow-up chest CT at three to six months is usually obtained to evaluate for resolution to confirm this diagnosis. (See 'Multiple nodules, solid or subsolid' below.)

Once this information is known, a strategy is selected that is optimized to meet patient preferences (eg, for diagnosis and safety) and institutional-related expertise. (See 'Individualizing the approach' above.).

Solid nodule >8 mm — Patients with indeterminate solid pulmonary nodules >8 mm should be further evaluated for suspicion of cancer (algorithm 1 and table 6):

- A nodule that has a low probability (<5 percent) of being malignant is followed with serial CT examinations. Initial CT should be performed at three months:
  - If the nodule remains unchanged, continued CT surveillance is recommended at 9 to 12 and 18 to 24 months. (See 'CT surveillance' below.)
  - Nodule growth indicates a need for pathologic evaluation. (See 'Nonsurgical biopsy' below and 'Surgical biopsy' below.)
- A nodule that has an intermediate probability (5 to 65 percent) of being malignant should be evaluated usually with FDG PET/CT and/or a biopsy. (See 'Positron emission tomography/computed tomography' above.)
  - Nodules that are FDG avid should be biopsied or excised. (See 'Nonsurgical biopsy' below and 'Surgical biopsy' below.)
  - If PET/CT is unavailable, negative, or indeterminate (eg, low standardized uptake value [SUV <2.5]), the optimal diagnostic strategy is unknown. In this setting, management should be individualized for each case with a strong reliance upon clinical suspicion for malignancy and a low threshold for biopsy [3]. (See 'CT surveillance' below and 'Nonsurgical biopsy' below and 'Surgical biopsy' below.)
  - CT surveillance at three months, then at 9 to 12 and 18 to 24 months is an acceptable alternative to biopsy. In patients with early stage lung cancer, the prognosis may still be favorable even when therapy is delayed by a period as long as eight months [85,100-102].
- A nodule that has a high probability (>65 percent) of being malignant should be biopsied or excised. Although a PET/CT is not necessary in this setting for characterization of a nodule, it may be indicated as a staging modality for suspected lung cancer or to identify a non-pulmonary target that would be more amenable to biopsy. (See 'Nonsurgical biopsy' below and "Overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer", section on 'Radiographic staging'.)

Solid nodule ≤8 mm — Solid nodules 6 to 8 mm can be followed with CT; nodules <6 mm do not generally require routine follow-up (algorithm 1 and table 6). The rationale for this strategy is based upon the low prevalence of malignancy as well as the procedural difficulty and high risk of tissue biopsy in this population. Any increase in nodule size should prompt redirection of the management strategy toward biopsy or excision.

Studies that report growth for nodules found on CT suggest that the detection of growth is dependent upon the presence of risk factors in the study population. One retrospective review reported that in patients with no risk factors for lung cancer who had pulmonary nodules <5 mm, no nodules grew over a 3 to 24 month follow-up period [37]. In contrast, another study reported growth in 11 percent of nodules during a 24-month period when risk factors for malignancy or extrathoracic malignancies were present [58]. These studies provide the basis for more aggressive CT surveillance strategies in patients at risk for lung cancer compared with those at low risk. Thus, the frequency with which CT examinations should be performed is determined by the patient's risk for lung cancer as well as by the size of the nodule [3,84]. (See 'CT surveillance' below.)

Thus, we suggest the following:

- With a <6 mm solid nodule, further follow-up is not typically required; for a patient with a relevant risk factor for cancer (eg, smoking history), a CT at 12 months is optional, bearing in mind that cancer risk is considerably less than 1 percent even in patients at high risk [12,103].

- With a 6 to 8 mm solid nodule, a CT should be performed at 6 to 12 months. In a high risk patient, or if size stability of the nodule is uncertain, another CT should be performed at 18 to 24 months. For a low risk patient with a nodule that is clearly unchanged, follow-up can stop at 6 to 12 months. Modern CT surveillance protocols with contiguous thin slice (1 mm section) imaging allow for confident assessment of size stability even on a single follow-up examination.

Ground-glass nodule (subsolid) — Our approach to ground-glass nodules (ie, subsolid nodules with no solid component) is determined by size (algorithm 2 and table 7).

- With a <6 mm nodule, further follow-up is not required. Cancer risk for nodules in this size range is less than 1 percent [104].

- With a ≥6 mm nodule, CT should be performed at 6 to 12 months. If persistent but unchanged in size, surveillance CT should be performed every two years for five years (ie, one year, three years, five years) to confirm that it is benign. If the nodule resolves, no further follow-up is needed. If the nodule grows or develops a solid component, tissue diagnosis should be sought. This approach is based upon the observation that many ground-glass nodules will resolve spontaneously and are presumed to be infectious or inflammatory [105]. However, some will grow or develop a solid component (ie, changes that are worrisome for malignancy).

- The resection of pure subsolid lesions 10 to 15 mm is controversial. Many clinicians prefer to wait until the nodule is at least 15 to 20 mm before seeking a tissue diagnosis. (See 'Nonsurgical biopsy' below and 'Surgical biopsy' below.)

Part solid nodule (subsolid) — Approach to the part solid nodule is determined by the overall size and, for nodules ≥6 mm, the size of the solid component (algorithm 2 and table 7). Compared with pure ground glass nodules, those with a part-solid component have a greater likelihood of being malignant.

- With a <6 mm nodule, further follow-up is not required. Cancer risk for nodules in this size range less than 1 percent [12,103,104].

- With a ≥6 mm nodule, CT should be performed at three to six months. If the nodule is persistent but unchanged in size, the next step in the evaluation is based on the size of the solid component of the nodule.

    - If the solid component is >8 mm, FDG PET/CT with a view to biopsy or resection when PET/CT is positive is recommended since malignancy is possible. (See 'Nonsurgical biopsy' below and 'Surgical biopsy' below.)

    - If the solid component is ≤8 mm or if a nodule is not FDG-avid, surveillance CT should be performed annually for five years to confirm that it is benign. If the nodule resolves, no further follow-up is needed. If the overall nodule or the solid component of the nodule increases in size, tissue diagnosis should be sought.

Multiple nodules, solid or subsolid — The vast majority of incidental multiple nodules are benign [1,54,106-111]. Consequently, an acceptable approach is to obtain a short interval CT (eg, three to six months) follow-up to assess for resolution of a presumed subclinical infection or inflammation. This interval can be shortened if acute infection is suspected in an immunocompromised patient (see "Approach to the immunocompromised patient with fever and pulmonary infiltrates"). If nodules are persistent on short interval follow-up, subsequent management is based on the most suspicious nodule. The most suspicious nodule is defined as the one that is the largest or growing for solid nodules, the one with the largest or growing solid component for part-solid subsolid nodules, or the largest for all ground-glass subsolid nodules (algorithm 3 and table 6 and table 7).

- With solid nodules <6 mm in size, further follow-up is not required as these are likely to represent benign granulomata or intrapulmonary lymph nodes. In a patient with a high risk of malignancy, CT at 12 months is an option to document stability.

- With solid nodules ≥6 mm in size, CT should be performed at three to six months. If the nodules are persistent but are unchanged in size, another CT at 18 to 24 months should be performed routinely for patients at high or intermediate risk for malignancy and optionally for patients at low risk for malignancy. If nodules resolve, no further follow-up is needed. If any of the nodules increase in size, tissue diagnosis should be sought.

- With subsolid nodules of any size, CT should be performed at three to six months. If the nodules are persistent, subsequent management should be based on the most suspicious nodule (ie, largest solid component for part solid nodule, largest overall for ground glass nodule). (See 'Part solid nodule (subsolid)' above.)

Nodules found on lung cancer screening — Lung-RADS is a reporting system by which nodules detected during lung cancer screening with low-dose CT are classified. Each category of nodule is accompanied by an overall estimate of malignancy and guidance for the next step in management. The approach to nodules with Lung-RADS is in many ways analogous to those presented here for incidental nodules. However, there are differences that reflect the higher risk of lung cancer in the patients undergoing screening, including the continuation of annual low-dose CT scans as part of the screening protocol even if no nodules are found on the initial scan. Following the protocol for annual screening also means that patients with solid nodules <6 mm found on screening are followed annually, compared with no follow-up if the nodule were found incidentally. In addition, the pure subsolid (ground-glass) nodules found on screening are followed at one year if they are <20 mm and at six months if they are ≥20 mm; in contrast, incidental subsolid nodules are not followed if <6 mm and followed at 6 to 12 months if >6 mm. Other differences such as methods for measuring nodules and time intervals for follow-up also exist between the two management approaches (table 5).

MANAGEMENT OPTIONS

Nonsurgical biopsy — Nonsurgical biopsy can be performed by sampling the nodule through the airway (bronchoscopic techniques) or through the chest wall (transthoracic needle biopsy). Nonsurgical biopsy is preferred in patients who have a nodule at intermediate risk (5 to 65 percent) for malignancy or in patients who are at high risk (>65 percent) who are not surgical candidates or prefer a non-surgical approach. Additional indications may include patients in whom a benign diagnosis is suspected that requires therapy (eg, mycobacterial disease) or rarely, for patients at low risk of malignancy who place a high value on diagnostic certainty sooner rather than later.

The choice of sampling procedure varies according to the size and location of the nodule, the availability of the procedure, and local expertise. Typically, bronchoscopic techniques (endobronchial ultrasound [EBUS] and conventional bronchoscopy) are preferred for larger, more centrally-located lesions, and transthoracic needle biopsy techniques are preferred for smaller, more peripheral lesions. EBUS-guided sheath transbronchial biopsy may also be used in centers with expertise in sampling peripheral nodules. Navigational tools (eg, virtual bronchoscopy, electromagnetic navigation, radial ultrasound and robotic bronchoscopy) hold promise as modalities that increase the diagnostic yield of bronchoscopy for small peripheral nodules; their use depends on equipment availability and institutional expertise. (See "Image-guided bronchoscopy for biopsy of peripheral pulmonary lesions".)

Bronchoscopic techniques — The main bronchoscopic techniques that are used to obtain diagnostic material from pulmonary nodules include:

- Conventional bronchoscopic-guided transbronchial biopsy (TBB)

- Bronchoscopic-transbronchial needle aspiration (bronchoscopic-TBNA)

- Radial endobronchial ultrasound-guided transbronchial biopsy (R-EBUS-guided TBB)
- Navigation guided transbronchial biopsy

Because these modalities biopsy nodules via the airway and are most often performed under conscious sedation, they are preferred for patients who have nodules that are close to a patent airway and for those in whom the risk of complications from surgery or transthoracic needle biopsy is high. Among the bronchoscopic modalities, radial EBUS-guided TBB and navigation-guided TBB are the preferred procedures, when local expertise is available. Conventional bronchoscopic-TBNA or TBB are alternatives when radial EBUS and navigation are not available.

- R-EBUS has a diagnostic sensitivity of 73 to 85 percent for larger, centrally-located lesions, which declines for nodules <20 mm (71 percent), particularly those that are peripherally located (56 percent) [112-114]. Considerable variation exists among centers and operators. However, these data are largely extrapolated from studies of patients with lung cancer and also included patients with visible airway lesions (ie, not a true incidental pulmonary nodule). The indications and complications of EBUS and its value in the diagnosis of suspected non-small cell lung cancer (NSCLC) are discussed separately. (See "Endobronchial ultrasound: Indications, contraindications, and complications" and "Endobronchial ultrasound: Technical aspects" and "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Endobronchial ultrasound' and "Bronchoscopy: Transbronchial needle aspiration", section on 'Lung nodules or masses'.)
- Conventional bronchoscopic TBB or TBNA has a reported sensitivity for the diagnosis of lung cancer that ranges from 65 to 88 percent, with the highest sensitivity for large, central lesions and lower rates for peripheral nodules (>2 cm: 63 percent; <2 cm: 34 percent) [114,115]. Although the less invasive methods of obtaining tissue (washing, lavage, or brush) can occasionally be diagnostic of malignancy, they are unlikely to obtain enough material for immunohistochemical or genetic analysis for a benign diagnosis. The indications and complications of conventional bronchoscopy and its value in the diagnosis of suspected NSCLC are discussed separately. (See "Flexible bronchoscopy in adults: Indications and contraindications" and "Flexible bronchoscopy in adults: Overview" and "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Conventional bronchoscopy'.)
- Navigational bronchoscopy techniques have greater diagnostic sensitivity for peripheral nodules when compared with conventional bronchoscopy. The details of navigational bronchoscopy are discussed separately. (See "Image-guided bronchoscopy for biopsy of peripheral pulmonary lesions".)

R-EBUS and navigational bronchoscopy are superior to conventional bronchoscopy for the diagnosis of lung malignancies [112-114]. Their comparative performance for specific benign diagnoses is unknown but likely to also be superior to conventional bronchoscopy. However, for both procedures, high operator proficiency and multiple passes with rapid onsite cytologic evaluation (ROSE) may enhance the diagnostic accuracy [116-121].

A nondiagnostic or negative transbronchial needle aspirate does not rule out malignancy. Further evaluation of patients with these findings must weigh the benefits of diagnostic certainty against the risks of surgical resection.

Transthoracic needle biopsy — Transthoracic needle biopsy (TTNB) is performed by passing a needle percutaneously through the chest wall into the target nodule, usually under computed tomography (CT) guidance. The needle traverses pleura and lung to obtain a tissue sample of the nodule. For diagnosis of malignancy, sensitivity, specificity, and yield of TTNB are usually >90, >99, and >90 percent, respectively, even for nodules measuring <1 cm [122-126]. (See "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Transthoracic needle biopsy'.)

If TTNB yields a nonspecific or nondiagnostic result (eg, inflammation, atypical cells, insufficient specimen), then malignancy is not excluded. Additional procedures (ie, bronchoscopic biopsy, repeat TTNB, or surgical excision) to obtain a pathologic diagnosis may be warranted. If an additional procedure is not performed, continued CT imaging follow-up is necessary and, if the nodule increases in size, repeat tissue sampling or surgical removal should be performed. Approximately 15 to 30 percent of TTNB yield nonspecific or nondiagnostic results and among these up to 46 percent eventually prove to be malignant [124,127]. The rates of nondiagnostic biopsy increase for nodules measuring ≤6 mm [126].

TTNB is associated with a risk of pneumothorax and most resolve without intervention [122,123]. However, approximately 7 percent of TTNB procedures result in a pneumothorax requiring chest tube drainage. This risk is increased in patients with emphysema, greater distance between pleural surface and lesion, and when the needle crosses a fissure, and when the biopsy needle traverses greater than two pleural surfaces. Thus, TTNB is preferred for biopsy of peripheral nodules, for deeper lesions if fissures do not need to be traversed, and in patients without underlying emphysema. The risk may be reduced by dependent positioning of the biopsy site below the trachea [128].

Needle (core) **biopsy** techniques are often obtained in addition to needle **aspiration** for both benign and malignant diagnoses [69,125,129]. The decision to get both is sometimes driven by the availability of intraprocedural cytology. This preference is based upon the need for histologic architecture for benign diagnoses and the observation that although a diagnosis of malignancy can be made on cellular material, larger biopsy samples are increasingly needed for additional immunohistochemical and genomic profile sequencing.

The most common complication of TTNB is pneumothorax (10 to 17 percent). Hemoptysis occurs less commonly (1 to 9.5 percent) and hemorrhage requiring intervention is very rare [122,123,130-133]. The risk of complications appears to be greatest in smokers, older patients (>60 years), patients with chronic obstructive pulmonary disease or emphysema, and possibly in those with ground-glass nodules.

- Retrospective studies report pneumothorax rates of 10 to 17 percent [122,123,130]. However, for patients with TTNB-associated pneumothorax, catheter drainage (ie, chest tube insertion) is required in approximately half of these cases, and increases the length of hospital stay and risk for respiratory failure or mechanical ventilation [130].

- The overall incidence of hemorrhage assessed clinically (eg, hemoptysis) was reported in retrospective analyses as 1 to 7 percent [122,130,134]. Based on post-biopsy CT imaging, another study reported pulmonary hemorrhage in 41 percent of cases with 0.4 percent requiring intervention [133]. Higher rates of hemorrhage may occur in patients on antiplatelet therapy [131,134]. In a retrospective study of 1346 TTNBs, dual antiplatelet therapy (aspirin plus clopidogrel) was an independent risk factor for hemorrhage (odds ratio [OR] 10.09), along with use of cutting needles (OR 3.22), small ground-glass lesions (OR 1.94), and deeply located lesions (OR 1.17). However, use of single antiplatelet therapy (aspirin or clopidogrel) that was discontinued before the procedure (mean discontinuation time 2.6 +/- 2.3 days) was not a risk factor for hemorrhage.

Clinically apparent systemic air embolism is a rare and potentially fatal complication of TTNB, with incidence of 0.2 to 0.5 percent in single center series. While symptoms are usually transient and self-limited, cardiac or cerebral infarction requiring resuscitation and resulting in sequelae, including death, has been reported [135-139].

Surgical biopsy — Surgical excisional biopsy is the gold standard for diagnosis of a pulmonary nodule and can be curative for some malignancies. For patients who are surgical candidates, a diagnostic wedge resection by video-assisted thoracic surgery (VATS) is the preferred procedure for pulmonary nodules at high risk (>65 percent) or intermediate risk of malignancy when nonsurgical biopsy is nondiagnostic or suspicious for malignancy [140,141]. Additional indications may include patients in whom a benign diagnosis is suspected that requires therapy (eg,

mycobacterial disease), in whom nonsurgical biopsy was nondiagnostic, or rarely for patients who place a high value on diagnostic certainty.

During VATS, nodules targeted for resection are usually located by visual inspection, such that VATS is best utilized for pulmonary nodules located close to the pleural surface [140,141]. However, for deeper lesions, digital palpation or localization techniques can be performed to increase the diagnostic yield during thoracoscopy. Localization techniques include preoperative placement of a hook wire, fiducials, or microcoils and percutaneous injection of methylene blue; or intraoperative imaging with technetium-99 radioguidance, ultrasound, or fluoroscopy [142-146].

The diagnosis is typically established intraoperatively by frozen section analysis after wedge resection. When the diagnosis is consistent with non-small cell carcinoma (NSCLC), the surgery is preferably converted to a VATS lobectomy (or segmentectomy when preservation of lung function is important) with mediastinal node sampling, which is the optimal treatment for early stage NSCLC. The advantage of this approach is that for nodules that are malignant, diagnosis, staging, and therapy are performed in a single operative procedure. However, frozen section pathology is less reliable for lesions <1.1 cm and for specific pathologies, including low grade or pre-cancerous adenocarcinoma (eg, minimally invasive adenocarcinoma, adenocarcinoma in situ, atypical adenomatous hyperplasia) and carcinoid [147]. Thus, when frozen section is initially unrevealing for cancer and subsequently found by routine histology to be definitive for NSCLC, a second surgery (completion lobectomy) may be required for treatment. (See "Management of stage I and stage II non-small cell lung cancer".)

VATS is safe in experienced hands and can be performed as a day or short stay (three to five days) procedure at many centers. Although unstudied in patients with incidental pulmonary nodules, mortality varies according to the extent of the underlying lung disease; one study reported an in-hospital mortality of 1.2 percent for VATS and 2.3 percent for open biopsy when performed electively in patients with interstitial lung disease [148]. (See "Evaluation of preoperative pulmonary risk" and "Preoperative physiologic pulmonary evaluation for lung resection" and "Overview of minimally invasive thoracic surgery".)

CT surveillance — CT of the chest without contrast is the preferred exam for imaging surveillance of an incidental pulmonary nodule. Scanning protocols should be tailored for pulmonary nodule follow-up as contiguous thin (ie, 1 mm) images on a helical scanner using low radiation dose techniques. Changes in nodule size and characteristics are more readily detected with CT than chest radiography [3,84]. (See 'Growth or stable size' above.)

In patients undergoing follow-up imaging for an incidental pulmonary nodule detected on CT or chest radiography, the median number of additional imaging tests was 3.5 and 2.8 respectively; the mean cumulative effective dose was 24 mSv and 10 mSv respectively [149]. One of the caveats of CT surveillance is that during follow-up, approximately 10 percent of patients develop new nodules over a one-year period that will require independent assessment [53,106].

Informing the patient of the benefits and risks of CT surveillance is important when choosing this strategy. The purpose of surveillance is to avoid unnecessary invasive procedures in patients with a benign nodule. This benefit is weighed against the risk of a delayed or missed diagnosis of cancer and exposure to radiation for a potentially benign lesion. (See 'Individualizing the approach' above.)

Positron emission tomography — Integrated fluorine-18-labeled fluorodeoxyglucose positron emission tomography/CT (FDG PET/CT) can be used for nodules >8 mm to refine the probability of nodule malignancy and to identify the best target for biopsy or an alternative site for staging. FDG PET is now rarely performed alone without a concurrent CT.

- FDG-avid solid nodules or subsolid nodules with >8 mm solid component are more likely to be malignant and should be biopsied.

- FDG-nonavid solid nodules are less likely to be malignant and are sometimes triaged to CT surveillance, depending on the assessed risk of cancer.
- FDG PET/CT is not helpful in assessment of malignancy risk of pure subsolid nodules. High rates of both false-positive and false-negative occur.

In patients with nodules suspected to be malignant, the exam is also used to evaluate for metastases and to select the safest target for biopsy.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diagnosis and management of lung cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Pulmonary nodule (The Basics)")

SUMMARY AND RECOMMENDATIONS

- A pulmonary nodule is defined on imaging as a small (≤30 mm), well defined lesion completely surrounded by pulmonary parenchyma. Morphologically, nodules are classified as solid or subsolid, and the latter are subdivided into pure ground-glass (ie, no solid component) and part-solid (ie, both ground-glass and solid components). (See 'Definitions' above.)
- The majority of incidental pulmonary nodules are benign. Infectious granulomas and pulmonary hamartomas are the most common causes of benign nodules. The most common causes of malignant nodules are primary lung cancer, lung metastases, and carcinoid tumors. (See 'Differential diagnosis' above.)
- Computed tomography (CT) of the chest without contrast using low radiation dose technique is the preferred modality used to evaluate an incidental pulmonary nodule for likelihood of malignancy. CT images (initial and follow-up) should be acquired as contiguous thin (ie, 1 mm) sections on a helical scanner to ensure diagnostic accuracy and measurement reproducibility. (See 'CT imaging technique' above and 'CT surveillance' above.)
- Our approach provides guidance for nodules found **incidentally** in patients ≥35 years old without signs or symptoms attributable to the lesion and with a baseline risk of lung cancer equivalent to that of the general population. Separate strategies and individual adjustments are needed for patients who are immunocompromised,

those with history of malignancy actively under treatment or follow-up, or those presenting with pulmonary symptoms (ie, suspected lung cancer). Nodules detected during lung cancer screening should be managed according to guidance provided by Lung-RADS, which differs from the approach for incidental nodules. Individual preferences and values should also be considered. (See 'Individualizing the approach' above.)

- An incidental pulmonary nodule that has clearly grown on serial imaging or is 18-fluorodeoxyglucose (FDG)-avid on positron emission tomography (PET)/CT is likely to be malignant and should be evaluated with biopsy. For solid nodules, growth is defined as an increase in size of >2 mm. For subsolid nodules, growth can also be identified as an increased attenuation or an increase in the size of or development of a solid component. (See 'Growth or stable size' above and 'Growing nodule' above.).

- An incidental pulmonary nodule is benign if it demonstrates fat (pulmonary hamartoma) or a characteristic calcification pattern (eg, granuloma, hamartoma) or if it is stable on CT for a defined period of time (ie, >2 years for solid and >5 years for subsolid nodules). (See 'Growth or stable size' above and 'Calcification and fat' above and 'Nodule with fat or calcification' above.)

- For the remaining indeterminate nodules, the following clinical and CT information guides the diagnostic evaluation (algorithm 1 and algorithm 2 and algorithm 3). (See 'Indeterminate nodule' above.):

  - Probability of malignancy – Probability of malignancy (low [<5 percent], intermediate [5 to 65 percent], or high [>65 percent]) assessed either clinically or by quantitative predictive models. (See 'Assessing the risk of malignancy' above.)

  - Nodule size and attenuation (solid or subsolid).

    - Solid nodules >8 mm should be evaluated further for the suspicion of cancer: CT surveillance at three months if the suspicion for cancer is low, a combination of FDG PET/CT and biopsy if the suspicion is intermediate, and biopsy or excision if the suspicion is high. (See 'Solid nodule >8 mm' above.)

    - Follow-up is not required for solitary solid or subsolid nodules measuring <6 mm in size. Solid nodules measuring ≤8 mm and subsolid nodules with solid components measuring ≤8 mm cannot be reliably assessed with FDG PET/CT or needle biopsy. Nodules 6 to 8 mm should be followed with serial imaging or surgical resection. (See 'Solid nodule ≤8 mm' above and 'Ground-glass nodule (subsolid)' above and 'Part solid nodule (subsolid)' above.)

  - Nodule multiplicity – Multiple nodules are more likely to represent an infectious or inflammatory process and, in general, carry a lower risk for cancer than solitary nodules. Follow-up chest CT within three to six months is usually obtained to evaluate for resolution. (See 'Multiple nodules, solid or subsolid' above.)

- Lung-RADS is a reporting system by which nodules detected during lung cancer screening with low-dose CT are classified. Each category of nodule is accompanied by an overall estimate of malignancy and guidance for the next step in management. Approach to nodules with Lung-RADS is in many ways analogous to those presented here for incidental nodules. However, there are differences that reflect the higher risk of lung cancer in the patients undergoing screening (table 5). (See 'Nodules found on lung cancer screening' above.)

- The choice of tissue sampling procedure (nonsurgical biopsy or surgical biopsy) varies according to the probability of malignancy, size and location of the nodule, local expertise, and patient values. (See 'Nonsurgical biopsy' above and 'Surgical biopsy' above.)

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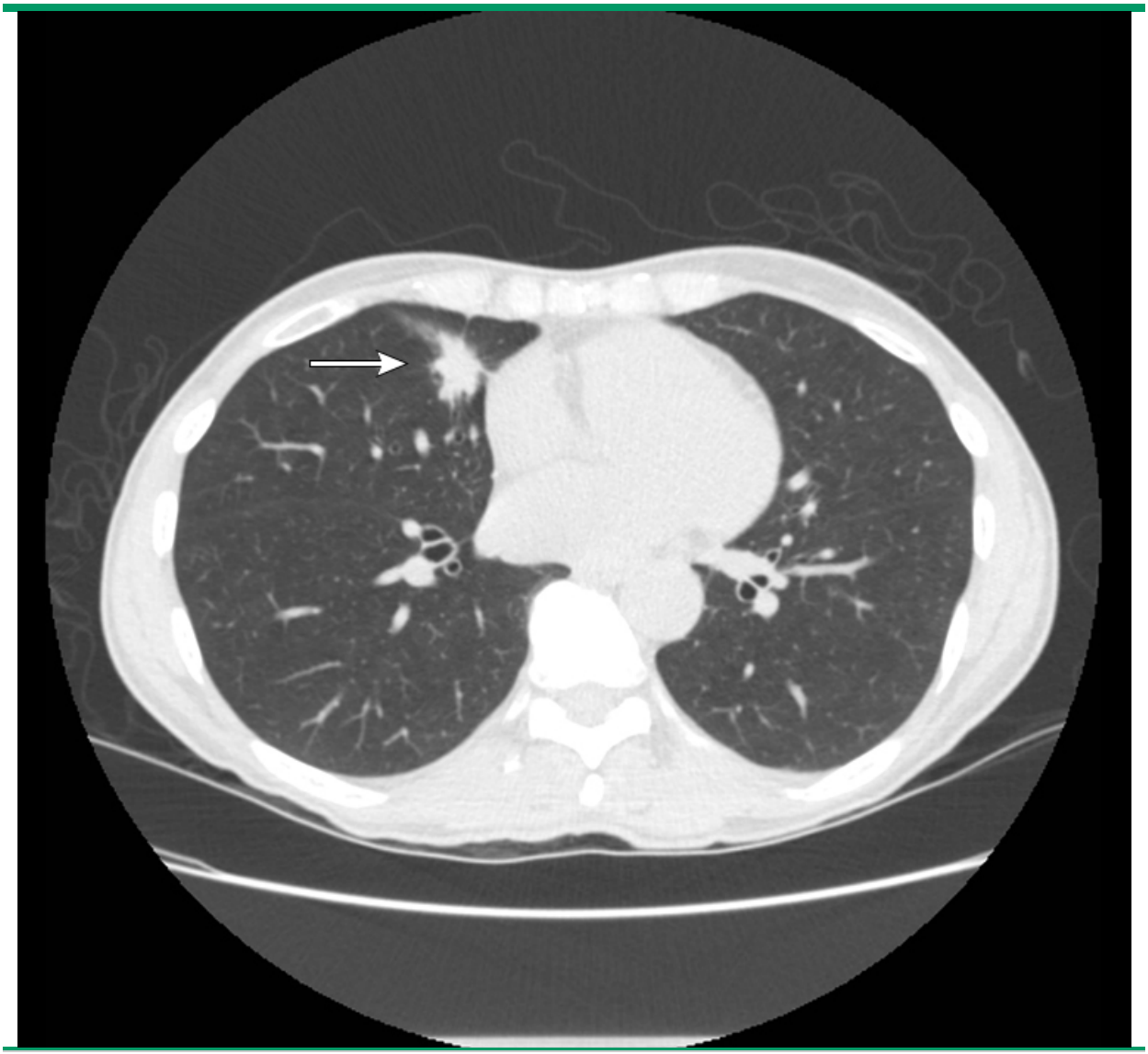
GRAPHICS

CT of a solid pulmonary nodule



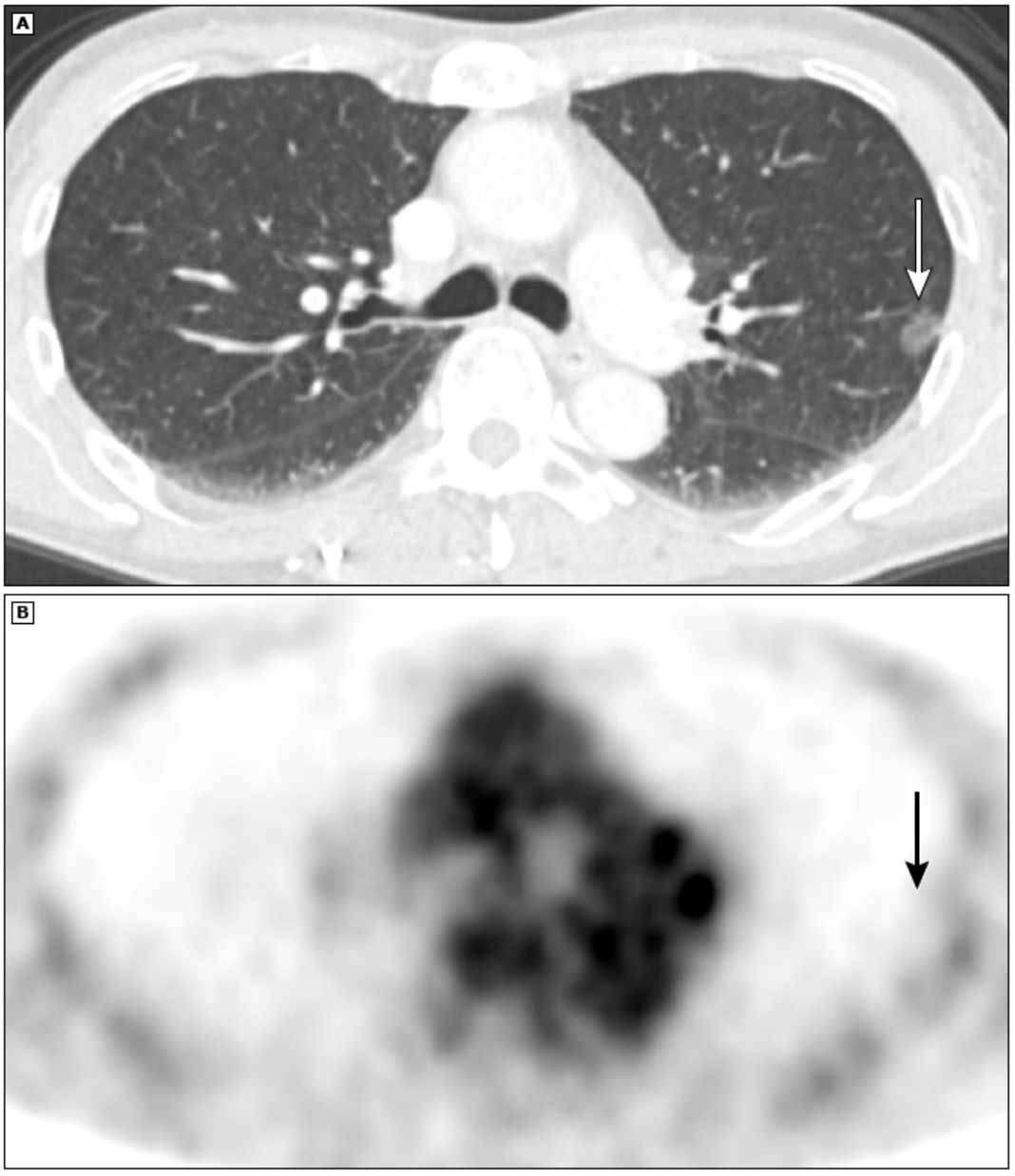
Solid pulmonary nodule. Chest CT shows a nodule (arrow) of homogeneously solid density in the right middle lobe measuring <30 mm. Pathology showed adenocarcinoma.

CT: computed tomography.

Courtesy of Shaunagh McDermott, MD.

Graphic 113384 Version 1.0

CT and FDG PET of a pure ground-glass pulmonary nodule



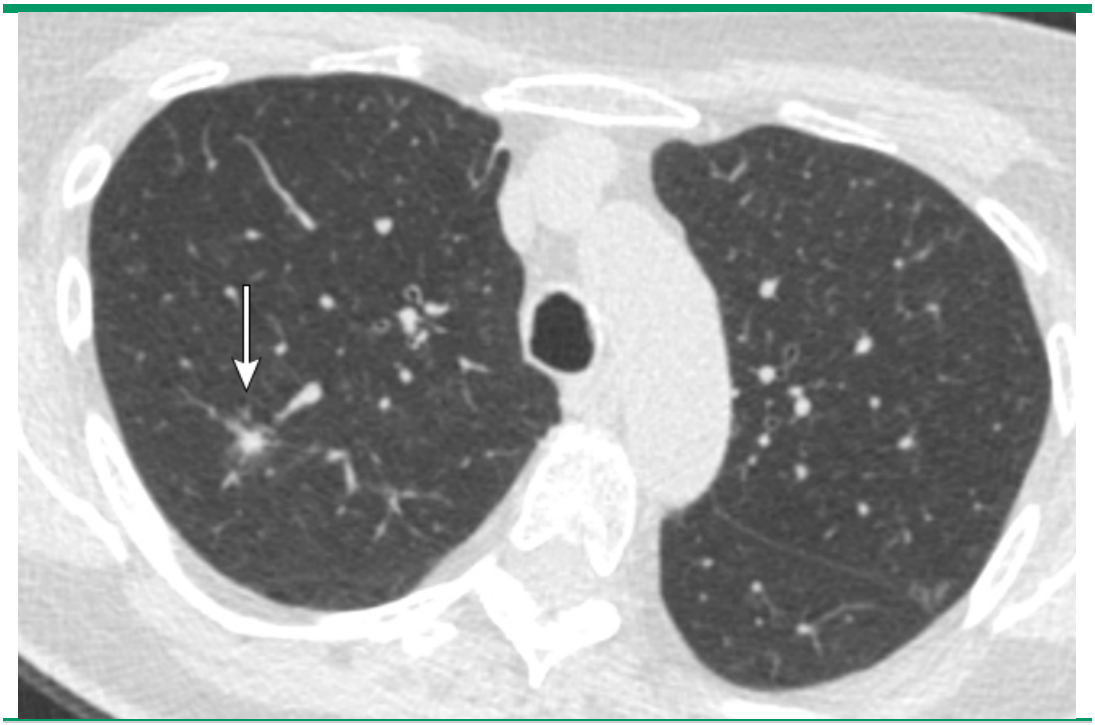
Pure ground-glass subsolid pulmonary nodule. Chest CT (A) shows a nodule (arrow) of ground-glass density measuring <30 mm in the left upper lobe that on FDG PET (B) demonstrates no tracer avidity (arrow). Pathology showed adenocarcinoma.

CT: computed tomography; FDG: fluorodeoxyglucose; PET: positron emission tomography.

Courtesy of Shaunagh McDermott, MD.

Graphic 113385 Version 1.0

CT of a part-solid pulmonary nodule



Part-solid subsolid pulmonary nodule. Chest CT shows a nodule (arrow) of both ground-glass and solid density measuring <30 mm in the right-upper lobe. Pathology showed adenocarcinoma.

CT: computed tomography.

Courtesy of Shaunagh McDermott, MD.

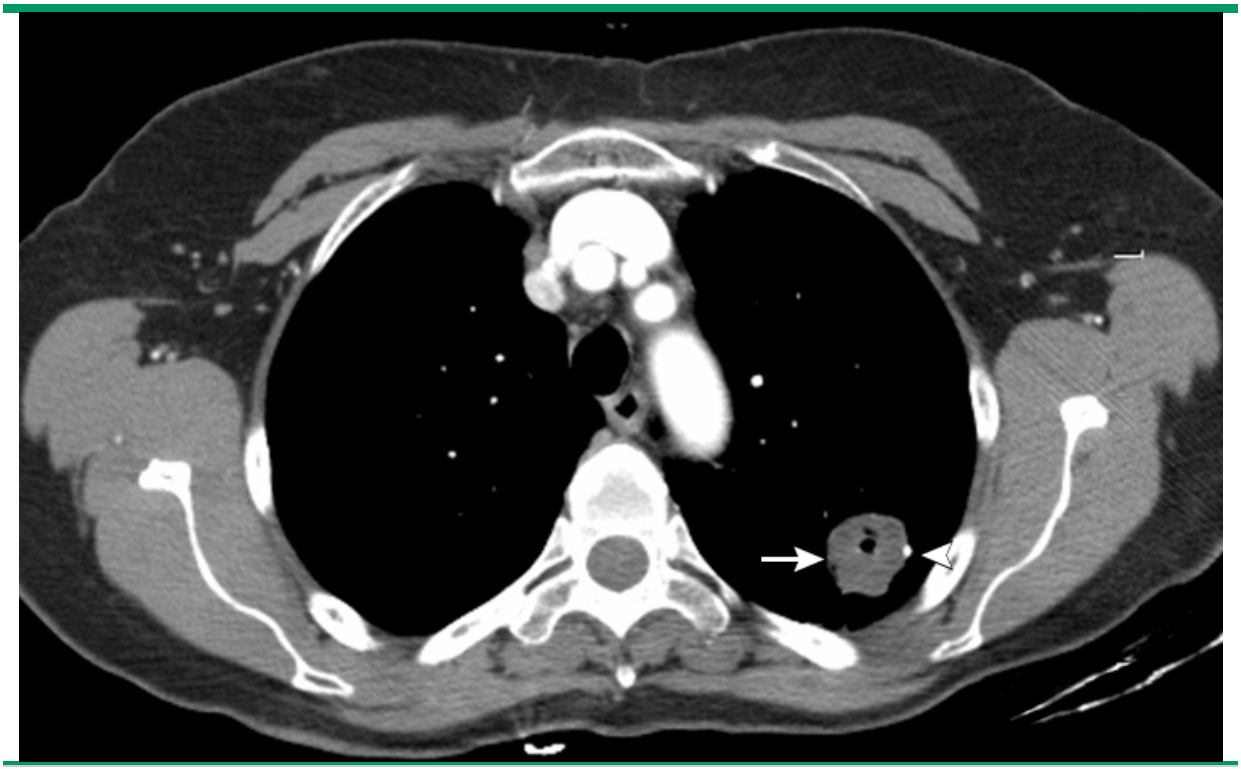
Graphic 113386 Version 1.0

Causes of solitary pulmonary nodules

Malignant	Benign
Bronchogenic carcinoma	**Infectious granuloma**
Adenocarcinoma	Histoplasmosis
Squamous cell carcinoma	Coccidioidomycosis
Large cell carcinoma	Tuberculosis
Small cell carcinoma	Atypical mycobacteria
Metastatic lesions	Cryptococcosis
Breast	Blastomycosis
Head and neck	**Other infections**
Melanoma	Bacterial abscess
Colon	Dirofilaria immitis
Kidney	Echinococcus cyst
Sarcoma	Ascariasis
Germ cell tumor	Pneumocystis jirovecii
Others	Aspergillus
Pulmonary carcinoid	**Benign neoplasms**
Extranodal lymphoma	Hamartoma
Miscellaneous	Lipoma
Plasmacytoma	Fibroma
Schwannoma	Neurofibroma
	Leiomyoma
	Angioma
	Vascular
	Arteriovenous malformation
	Pulmonary varix
	Hematoma
	Pulmonary infarct
	Developmental
	Bronchogenic cyst
	Inflammatory
	Granulomatosis with polyangiitis (Wegener's)
	Rheumatoid nodule
	Sarcoidosis
	Other
	Amyloidoma
	Rounded atelectasis
	Intrapulmonary lymph nodes
	Pseudotumor (loculated fluid)
	Mucoid impaction

Graphic 62644 Version 5.0

CT of a cavitating atypical mycobacterium pulmonary nodule

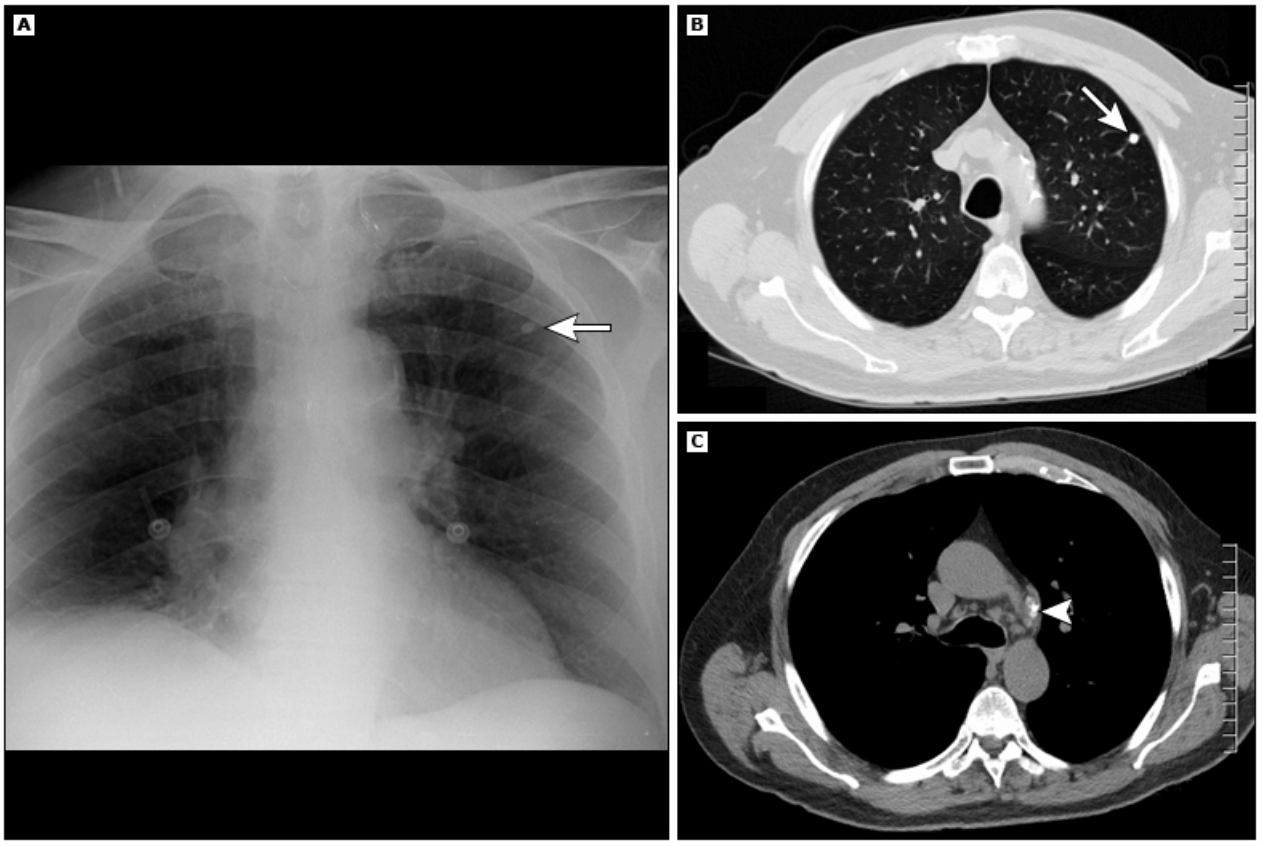


Atypical mycobacterium. Chest CT with contrast shows a 2.8 cm nodule (arrow) and punctate calcification (arrowhead). Central lucency within the nodule indicates cavitation.

CT: computed tomography.

Graphic 99561 Version 2.0

Radiography and CT of calcified pulmonary granuloma



Pulmonary granuloma. Chest radiograph AP view shows a well-circumscribed calcified nodule in the left upper lobe (arrow). Images from a chest CT without contrast viewed in lung (B) and soft tissue (C) windows shows the calcified granuloma (arrow) and ipsilateral calcified aortopulmonary lymph nodes (arrowhead).

CT: computed tomography; AP: anteroposterior.

Graphic 99558 Version 2.0

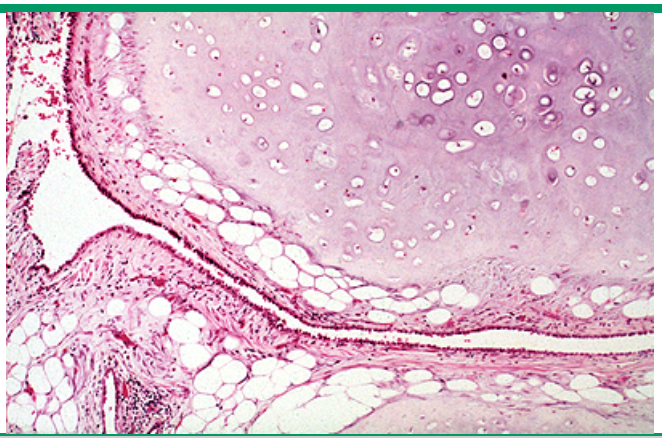
Pulmonary hamartoma

Photograph of a pulmonary hamartoma shows a well circumscribed mass with a variegated yellow and white appearance, which corresponds to fat and cartilage respectively.

From Colby, TV, Koss, MN, Travis, WD. Tumors of the Lower Respiratory Tract. Armed Forces Institute of Pathology, Washington, DC.

Graphic 61914 Version 1.0

Pulmonary hamartoma

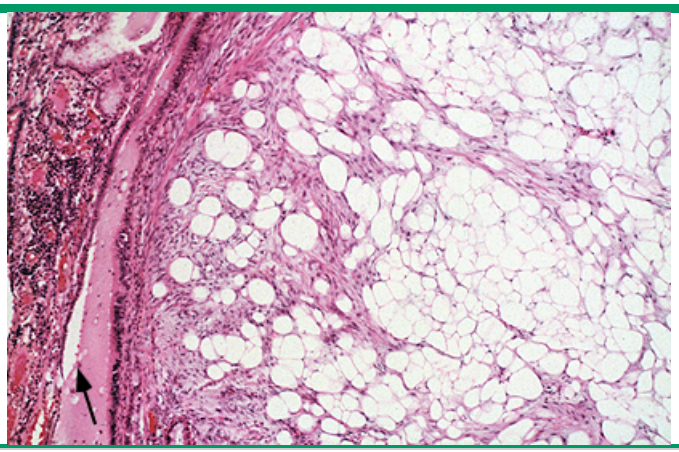


Low power photomicrograph shows a predominance of cartilagenous tissue. The cleft-like space on the left of the image is lined with cuboidal respiratory epithelium.

From Colby, TV, Koss, MN, Travis, WD. Tumors of the Lower Respiratory Tract. Armed Forces Institute of Pathology, Washington, DC.

Graphic 62271 Version 1.0

Pulmonary hamartoma

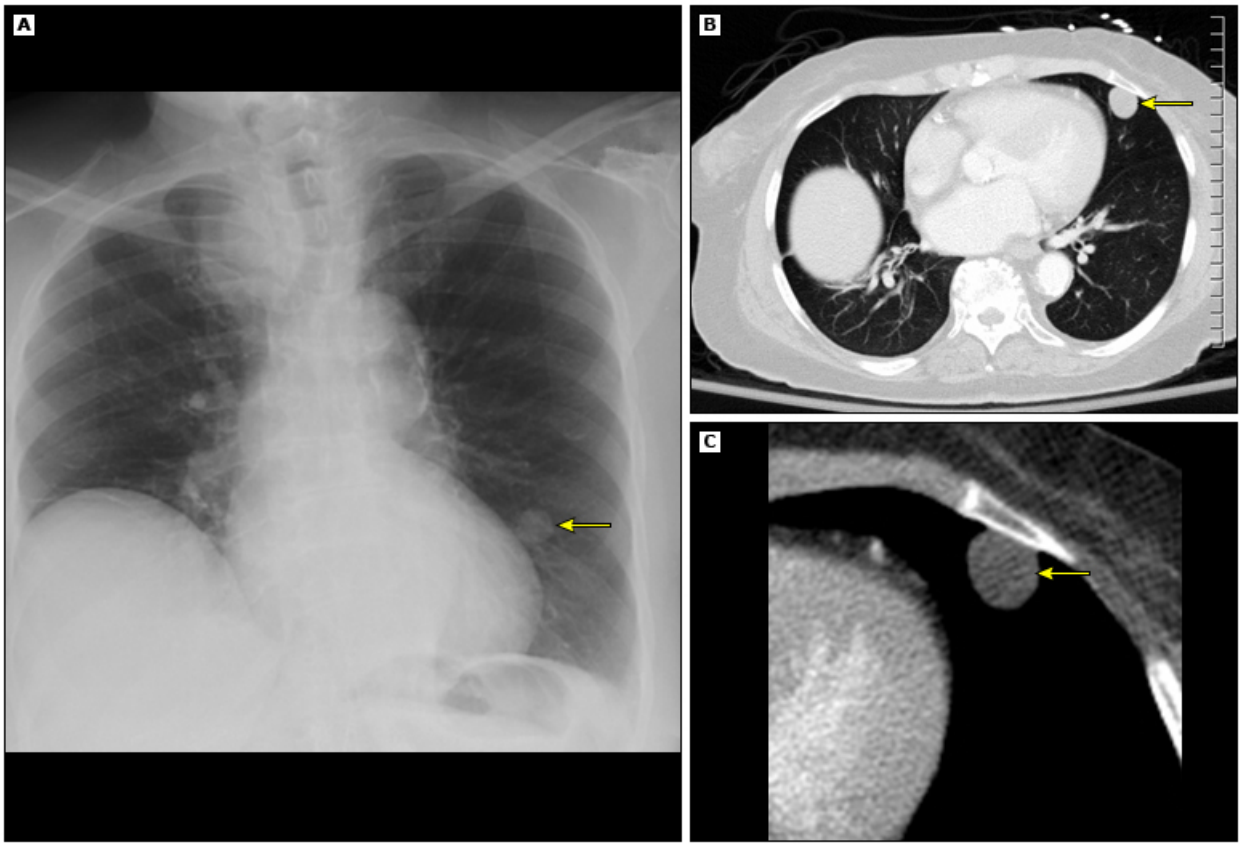


Low power photomicrograph shows a pulmonary hamartoma composed largely of fat. An elongated cleft lined by respiratory epithelium (arrow) is visible at the left.

From Colby, TV, Koss, MN, Travis, WD. Tumors of the Lower Respiratory Tract. Armed Forces Institute of Pathology, Washington, DC.

Graphic 72996 Version 1.0

Radiography and CT of a fat-containing benign pulmonary nodule

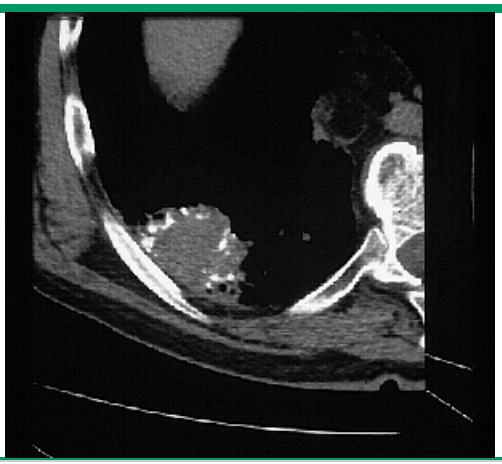


Benign pulmonary nodule. PA chest radiograph (A) shows a solid nodule (arrow) in the lingula (arrow). Images from a chest CT with contrast viewed in lung (C) and soft tissue (C) windows shows a solid nodule (arrow) measuring -30 HU, consistent with fat. The nodule was stable over two years.

PA: posteroanterior; CT: computed tomography; HU: Hounsfield units.

Graphic 99567 Version 2.0

CT of a pulmonary hamartoma

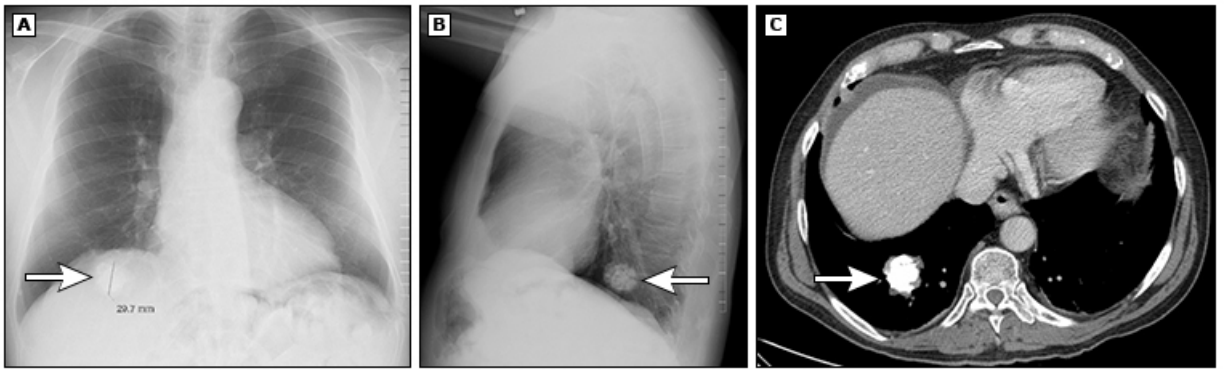


Pulmonary hamartoma. CT of the chest without contrast shows a solid pulmonary nodule with characteristic popcorn calcifications.

Courtesy of Paul Stark, MD.

Graphic 80219 Version 3.0

Radiography and CT of a pulmonary hamartoma

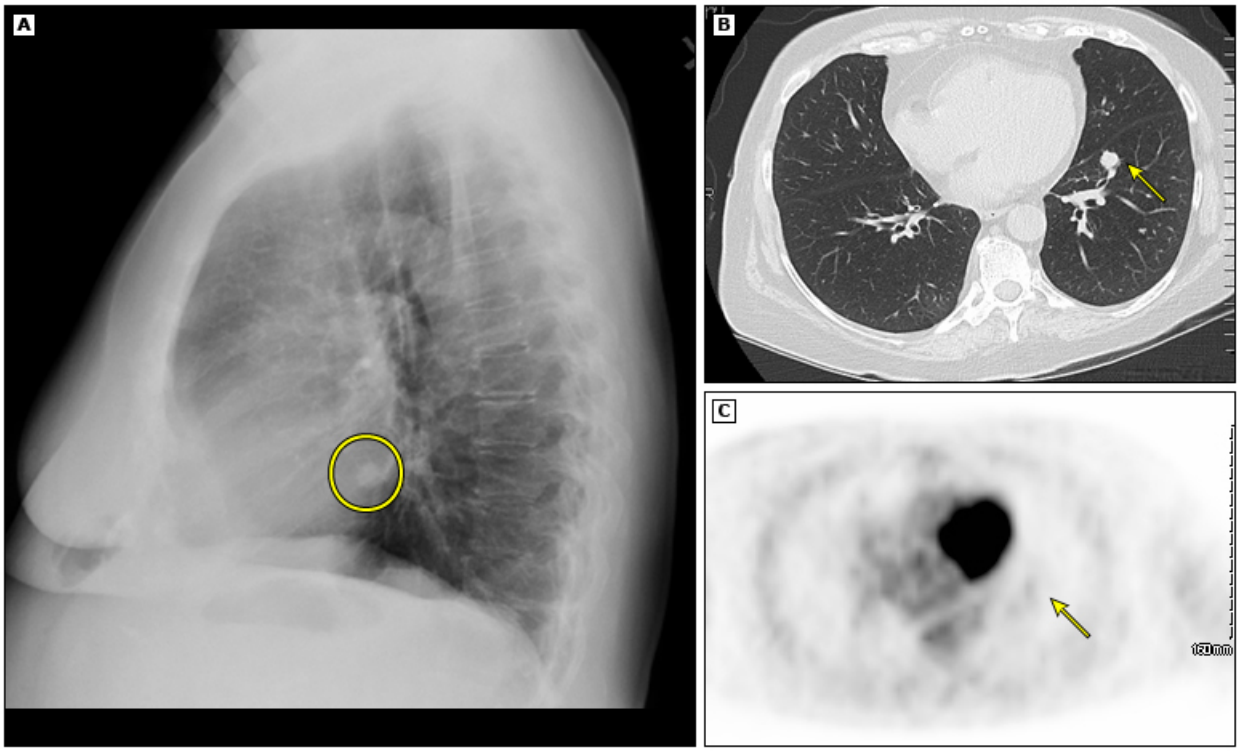


Pulmonary hamartoma. A chest radiograph PA (A) and lateral (B) projections shows a 3 cm nodule with popcorn calcification (arrow) in the right lower lobe. Chest CT with contrast (C) performed two years later shows the nodule (arrow) unchanged in size and appearance.

CT: computed tomography; PA: posteroanterior.

Graphic 99563 Version 2.0

Radiography, CT and FDG PET of a pulmonary amyloid nodule

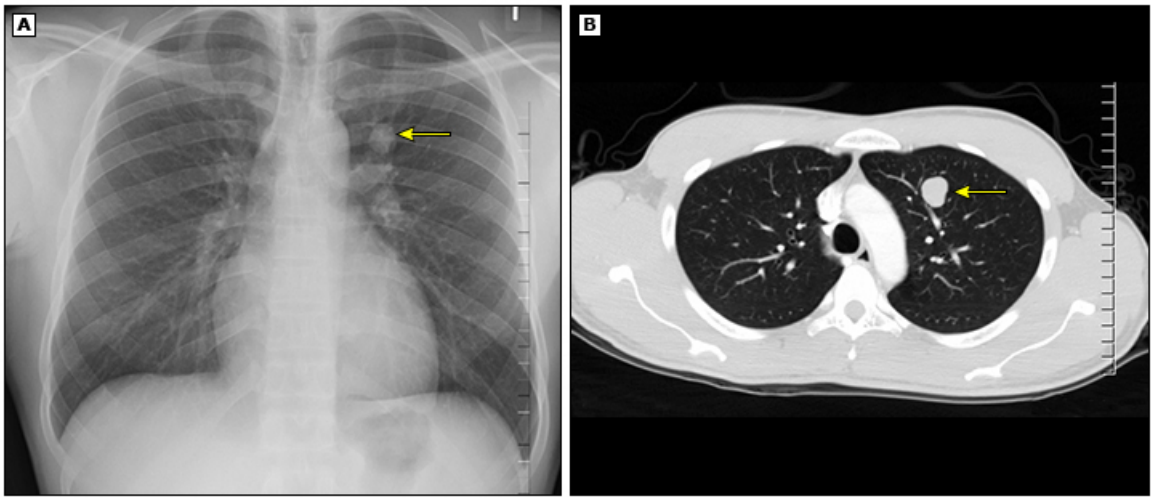


Pulmonary amyloid. Chest radiograph lateral view (A) shows a nodule (circle) in the retrocardiac region. CT (B) and FDG PET (C) images of the chest shows a 12 mm non-FDG avid nodule (arrow) in the left lower lobe confirmed to be amyloid on pathology.

CT: computed tomography; FDG: fluorodeoxyglucose; PET: positron emission tomography.

Graphic 99733 Version 2.0

Radiography and CT of a benign pulmonary nodule

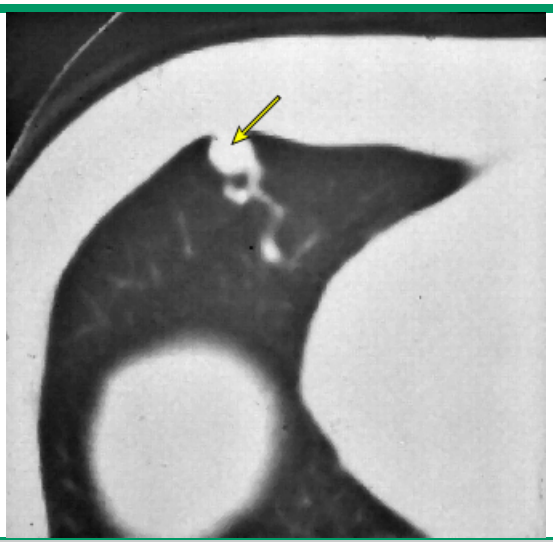


Benign pulmonary nodule. Chest radiograph PA view (A) and CT (B) shows a 30mm nodule in the left upper lobe (arrow) that was unchanged in size and appearance for over two years.

CT: computed tomography; PA: posteroanterior.

Graphic 99566 Version 3.0

CT of a pulmonary arteriovenous malformation (AVM)



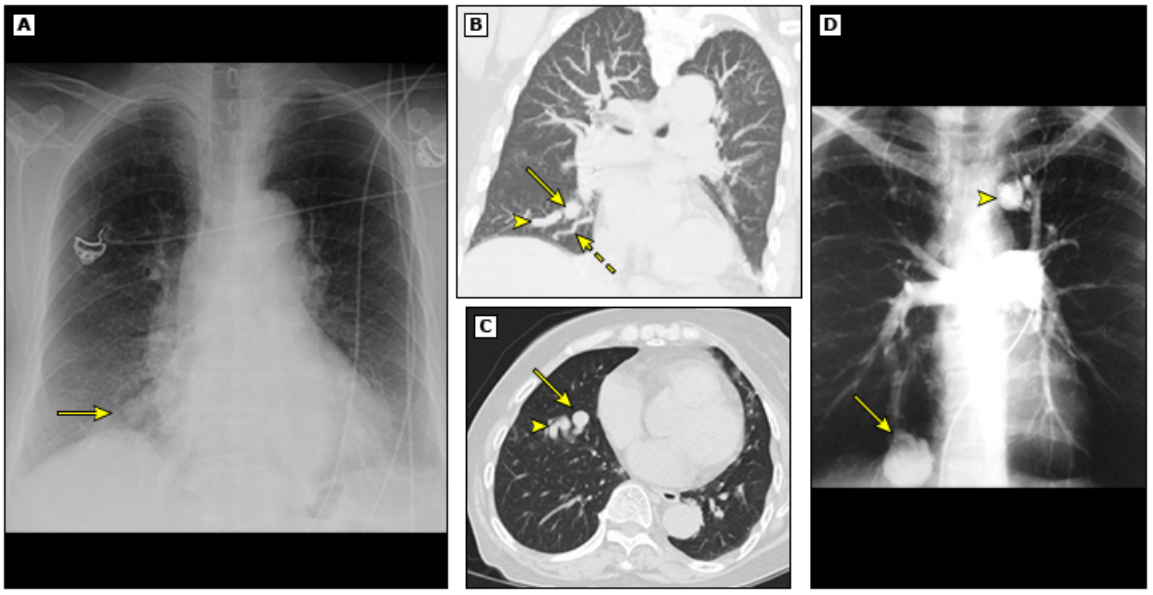
Pulmonary arteriovenous malformation presenting as a solitary pulmonary nodule. Chest CT shows a nodule in the periphery of the right middle lobe (arrow) with a proximal tail-like extension corresponding to the supplying artery and the draining vein.

CT: computed tomography; AVM: arteriovenous malformation.

Courtesy of Paul Stark, MD.

Graphic 56072 Version 5.0

Radiography, CT and angiography of an arteriovenous malformation



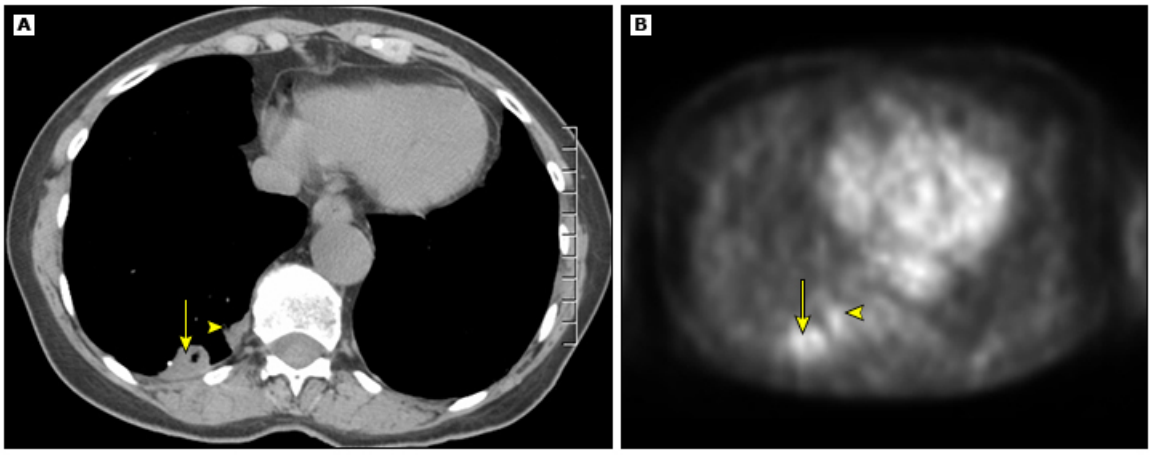
Pulmonary arteriovenous malformation. Chest radiograph AP view (A) shows a right lung nodule (arrow). Chest CT coronal reconstruction (B) and axial (C) images shows the nodule (arrow) with a feeding artery (dashed arrow) and large draining vein (arrowhead). A pulmonary angiogram of another patient in the arterial phase (D) shows arteriovenous malformations of the right lower (arrow) and left upper (arrowhead) lobes.

CT: computed tomography; AP: anteroposterior.

Images A, B, and C courtesy of Scott Sequerra, MD.

Graphic 99565 Version 3.0

CT and FDG PET of a pulmonary infarct from embolism



Chest CT without contrast (A) and FDG PET images (B) show a cavitating nodule (arrow) and subsegmental air space opacity (arrowhead) in the right lower lobe. Both are mildly FDG-avid with an indeterminate SUV of 2.1. Pathology of the nodule showed subacute infarction resulting from pulmonary embolism. The subsegmental air space opacity could represent another infarct or inflammation.

CT: computed tomography; FDG: fluorodeoxyglucose (18F); PET: positron emission tomography; SUV: standardized uptake value.

Graphic 99736 Version 2.0

Likelihood ratios for malignancy in solitary pulmonary nodules in men

Finding	Probability of this finding among men with:		Likelihood ratio for malignancy*
	Malignant nodules	Benign nodules	
Diameter of nodule, cm			
<1.5	0.026	0.232	0.1
1.5-2.2	0.255	0.501	0.5
2.3-3.2	0.343	0.203	1.7
3.3-4.2	0.193	0.045	4.3
4.3-5.2	0.118	0.018	6.6
5.3-6.0	0.065	0.002	29.4
Patient's age, yr			
≤35	0.011	0.155	0.1
36-44	0.111	0.329	0.3
45-49	0.096	0.136	0.7
50-59	0.2	0.138	1.5
60-69	0.454	0.22	2.1
70-83	0.129	0.023	5.7
Smoking history			
Never smoked	0.03	0.21	0.15
Pipe or cigar only	0.05	0.15	0.3
Ever smoked cigarettes	0.92	0.63	1.5
Current smoker or quit within past 9 yr			
Average number of cigarettes per day:			
1-9	0.03	0.1	0.3
10-20	0.27	0.27	1
21-40	0.38	0.19	2
≥41	0.24	0.06	3.9
Quit smoking, yr			
≤3	0.07	0.05	1.4
4-6	0.04	0.04	1
7-12	0.04	0.07	0.5
≥13	0.02	0.19	0.1
Overall prevalence			
Clinical settings	(0.4)		0.7•
Community surveys	(0.1)		0.1

* These likelihood ratios represent the numerator of odds that have the number 1 as the denominator (eg, 0.25:1). For simplicity, we have omitted the 1 denominator from the table.

¶ Defined as: Prevalence of malignancy/(1-Prevalence of malignancy).

Redrawn from Cummings, SR, Lillington, GA, Richard, RJ, Am Rev Respir Dis 1986; 134:449.

Graphic 69674 Version 2.0

Likelihood ratios for malignancy in solitary pulmonary nodules

Characteristic	Characteristic probability		Number of patients	Likelihood ratio for malignancy*
	Malignant nodules	Benign nodules		
Size				
0-1 cm	–¶	–¶	1063	0.52
1.1-2 cm	–¶	–¶		0.74
2.1-3 cm	–¶	–¶		3.67
>3 cm	–¶	–¶		5.23
Edge (chest radiography)				
Ill defined	0.71	0.28	152	2.51
Well defined, lobular	0.89	0.7		1.27
Well defined, smooth	0.11	0.3		0.36
Tomographic appearance				
Malignant	0.44	0.01	238	37.2
Indeterminate	0.56	0.76		0.73
Benign	0	0.23		0
Edge (CT)				
Smooth	–¶	–¶	903	0.3
Lobulated	–¶	–¶		0.74
Irregular/spicular	–¶	–¶		5.54
Calcification at tomography				
Calcified	0	0.34	323	0
Noncalcified	1	0.66		1.5
Calcification at CT				
in phantom (benign)	–¶	–¶	1041	0.01Δ
in phantom	–¶	–¶		2.2
Growth rate				
<7 d	0	0.24	217	0
7-465 d	0.99	0.29		3.4
>465 d	0.01	0.46		0.01
Location				
Upper/middle lobe	0.74	0.61	179	1.22
Lower lobe	0.26	0.39		0.66
Maximal cavity wall thickness				
≤4 mm	0.03	0.47	123	0.07
5-15 mm	0.37	0.52		0.72
≥16 mm	0.59	0.02		37.97
Age				
20-29 y	–¶	–¶	529	0.05
30-39 y	–¶	–¶		0.24
40-49 y	–¶	–¶		0.94
50-59 y	–¶	–¶		1.9
60-69 y	–¶	–¶		2.64
≥70 y	–¶	–¶		4.16
Smoking history				
Never smoked	0.06	0.33	9036	0.19
Current cigarette smoker	0.58	0.26		2.27
Pipe/cigar smoker	0.08	0.08		1
Ex-cigarette smoker	0.24	0.26		0.92
Ex-pipe/cigar smoker	0.04	0.08		0.55
Hemoptysis	0.09	0.02	215	5.08

Previous malignancy	0.15	0.03	845	4.95

* The denominator of the likelihood ratio is omitted from the table for simplicity (eg, 0.52:1).
¶ A weighted likelihood ratio was estimated by combining results of studies.
Δ The standardization of the reference nodule has changed; 0.07 may be a better estimate for the likelihood ratio.

Redrawn from Gurney, JW, Radiology 1993; 186:405.

Graphic 54379 Version 2.0

Estimating the probability of cancer (PCa) in a solitary pulmonary nodule

Step 1: Find the appropriate values of likelihood ratios for overall prevalence of malignancy (LRprev), diameter of the nodule (LRsize), patient's age (LRage), and smoking history (LRsmoke) from figure 3.

Step 2: Multiply all of these likelihood ratios together:

$$\text{Odds of malignancy (OddsCa)} = \text{LRprev} \times \text{LRsize} \times \text{LRage} \times \text{LRsmoke}$$

Step 3: Convert these odds into a probability of cancer:

$$\text{Probability of cancer (PCa)} = \frac{\text{OddsCa}}{(1 + \text{OddsCa})}$$

(Multiply PCa by 100 to express PCa as a percentage)

Example: 55 year old man, 1.5 pack (30 cigarettes) per day smoker with a 2.5 cm nodule:

1. LRprev = 0.7:1; LRsize = 1.7:1; LRage = 1.5:1; LRsmoke = 2.0:1

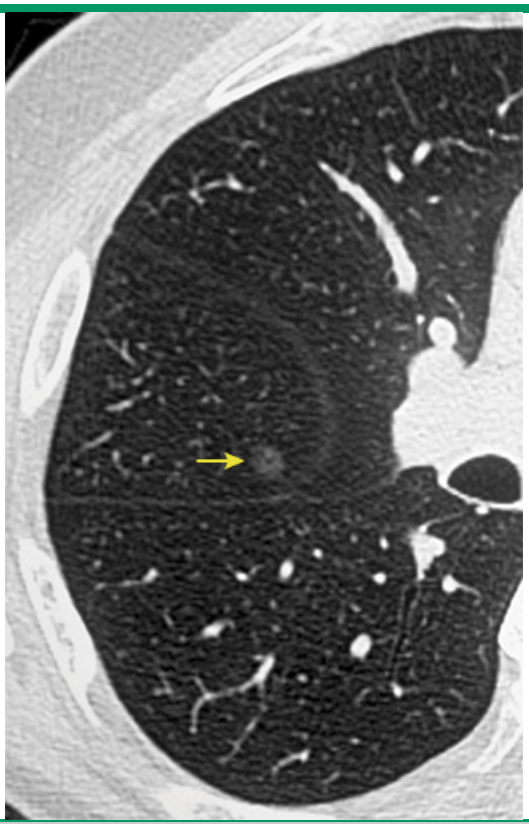
2. $\text{OddsCa} = \frac{0.7 \times 1.7 \times 1.5 \times 2.0}{1} = 3.57{:}1$

3. $\text{PCa (as percent)} = \frac{3.57}{1 + 3.57} \times 100 = 78 \text{ percent}$

Adapted from: Cummings, SR, Lillington, GA, Richard, RJ, Am Rev Respir Dis 1986; 134:449.

Graphic 81528 Version 6.0

Ground-glass solitary pulmonary nodule

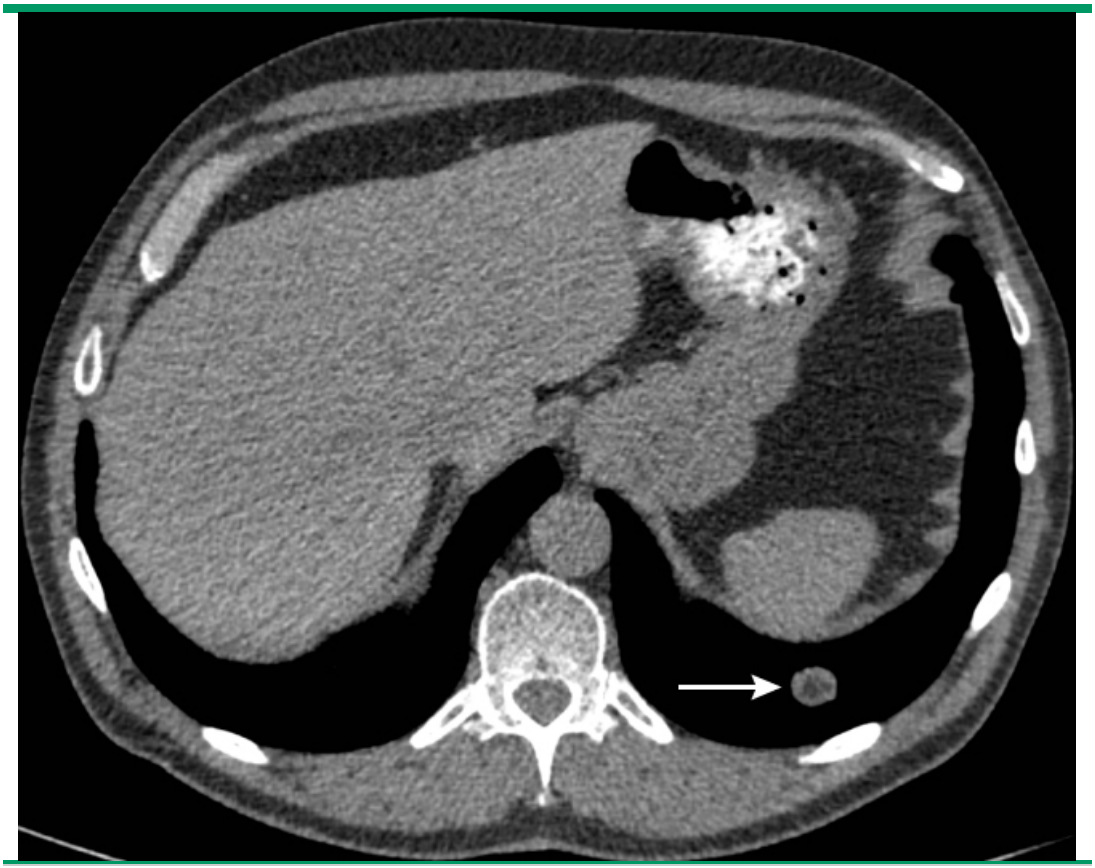


A ground-glass solitary pulmonary nodule in the right middle lobe (arrow), most likely representing a focus of atypical alveolar hyperplasia.

Courtesy of Paul Stark, MD.

Graphic 83407 Version 1.0

CT of a pulmonary hamartoma with fat



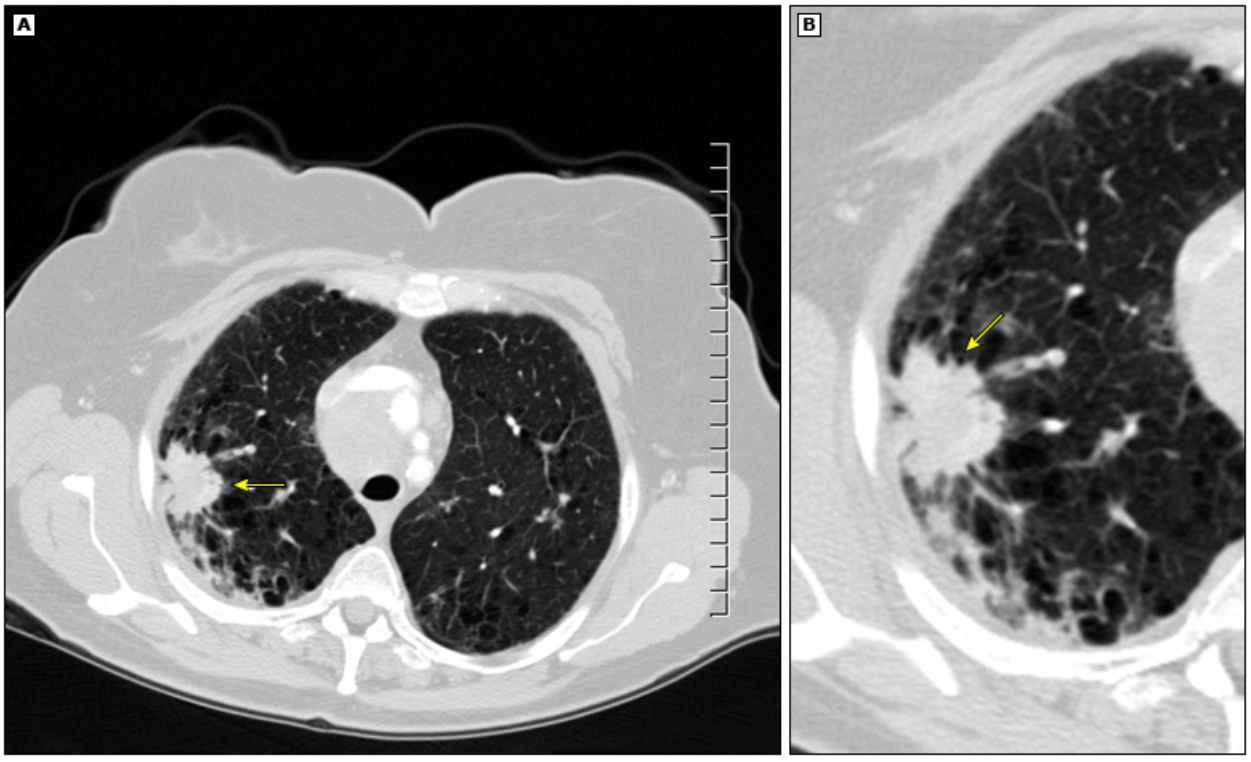
Pulmonary hamartoma. Chest CT shows a left lung nodule (arrow) containing fat density diagnostic of a hamartoma.

CT: computed tomography.

Courtesy of Shaunagh McDermott, MD.

Graphic 113387 Version 1.0

CT of a pulmonary nodule with spiculated margins

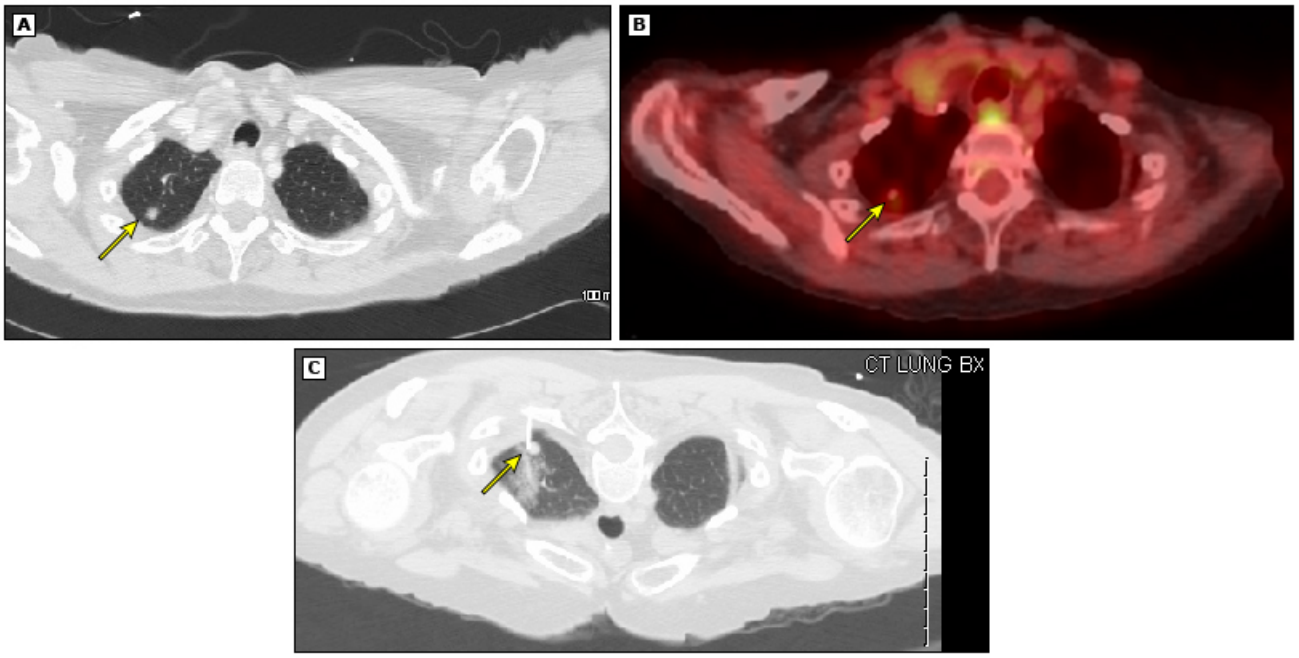


Pulmonary nodule with spiculated margins. Chest CT images (A & B) show a 27 mm right lung nodule (arrow) with spiculated margins, a finding usually associated with malignancy.

CT: computed tomography.

Graphic 99732 Version 2.0

FDG PET/CT pulmonary neuroendocrine tumor



Images of the chest from CT (A) and fusion PET/CT (B) show a nodule in lung apex measuring 12 mm and with an SUV of 1.7 (arrow). CT-guided needle biopsy (C) revealed neuroendocrine tumor from a gastric primary malignancy.

FDG: fluorodeoxyglucose (18F); PET: positron emission tomography; CT: computed tomography; SUV: standardized uptake value.

Graphic 99735 Version 3.0

Factors that influence the management of nodules 8 to 30 mm in size

Factor	Level	CT scan surveillance	PET imaging	Nonsurgical biopsy	VATS wedge resection
Clinical probability of lung cancer	Very low (<5%)	++++	–	–	–
	Low-moderate	+	+++	++	+
	High (<65%)	–	(± staging)	++	++++
Surgical risk	Low	++	++	++	+++
	High	++	+++	++	–
Biopsy risk	Low	–	++	+++	+++
	High	++	+++	–	+
High suspicion of active infection or inflammation		–	–	++++	++
Values and preferences	Desires certainty	–	+	+++	++++
	Risk averse to procedure-related complications	++++	+++	++	–
Poor adherence with follow-up		–	–	+++	++++

Selection of modality (surveillance or biopsy) will depend on patient values and preferences; please refer to the UpToDate topic on diagnostic evaluation and management of the solitary pulmonary nodule for more details. Nonsurgical biopsy usually refers to image-guided or endoscopic biopsy.

CT: computed tomography; PET: positron emission tomography; VATS: video-assisted thorascopic surgery.

Graphic 93548 Version 3.0

Lung-RADS assessment categories for lung cancer screening

Category descriptor	Lung-RADS score	Findings	Management	Risk of malignancy (%)	Estimated population prevalence (%)
Incomplete	0	Prior chest CT examination(s) being located for comparison Part or all of lungs cannot be evaluated	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed.	NA	1
Negative No nodules and definitely benign nodules	1	No lung nodules Nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules	Continue annual screening with LDCT in 12 months.	<1	90
Benign appearance or behavior Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	Perifissural nodule(s): (refer to important note 11) ▪ <10 mm (<523.6 mm^3) Solid nodule(s): ▪ <6 mm (<113.1 mm^3) ▪ New <4 mm (<33.5 mm^3) Part solid nodule(s): ▪ <6 mm total diameter (<113.1 mm^3) on baseline screening Non solid nodule(s) (GGN): ▪ <30 mm (<14137.2 mm^3) **OR** ▪ ≥30 mm (≥14137.2 mm^3) and unchanged or slowly growing Category 3 or 4 nodules unchanged for ≥3 months	Continue annual screening with LDCT in 12 months.	<1	90
Probably benign Probably benign finding(s) – short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	Solid nodule(s): ▪ ≥6 to <8 mm (≥113.1 to <268.1 mm^3) at baseline **OR** ▪ New 4 mm to <6 mm (33.5 to <113.1 mm^3) Part solid nodule(s): ▪ ≥6 mm total diameter (≥113.1 mm^3) with solid component <6 mm (<113.1 mm^3) **OR** ▪ New <6 mm total diameter (<113.1 mm^3) Non solid nodule(s) (GGN): ▪ ≥30 mm (≥14137.2 mm^3) on baseline CT or new	6 month LDCT.	1 to 2	5
Suspicious Findings for which additional diagnostic testing is recommended	4A	Solid nodule(s): ▪ ≥8 to <15 mm (≥268.1 to <1767.1 mm^3) at baseline **OR** ▪ Growing <8 mm (<268.1 mm^3) **OR** ▪ New 6 to <8 mm (113.1 to <268.1 mm^3) Part solid nodule(s): ▪ ≥6 mm (≥113.1 mm^3) with solid component ≥6 mm to <8 mm (≥113.1 to <268.1 mm^3) **OR** ▪ With a new or growing <4 mm (<33.5 mm^3) solid component Endobronchial nodule	3 month LDCT; PET/CT may be used when there is a ≥8 mm (≥268.1 mm^3) solid component.	5 to 15	2
Very suspicious	4B	Solid nodule(s):	Chest CT with or without contrast,	>15	2

Findings for which additional diagnostic testing and/or tissue sampling is recommended		▪ ≥15 mm (≥1767.1 mm^3) **OR** ▪ New or growing, and ≥8 mm (≥268.1 mm^3)	PET/CT and/or tissue sampling depending on the probability of malignancy and comorbidities*. PET/CT may be used when there is a ≥8 mm (≥268.1 mm^3) solid component. *For new large nodules that develop on an annual repeat screening CT, a 1 month LDCT may be recommended to address potentially infectious or inflammatory conditions.*		
		Part solid nodule(s) with: ▪ A solid component ≥8 mm (≥268.1 mm^3) **OR** ▪ A new or growing ≥4 mm (≥33.5 mm^3) solid component			
	4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy			
Other Clinically significant or potentially clinically significant findings (non lung cancer)	S	Modifier – may add on to category 0 to 4 coding	As appropriate to the specific finding.	NA	10

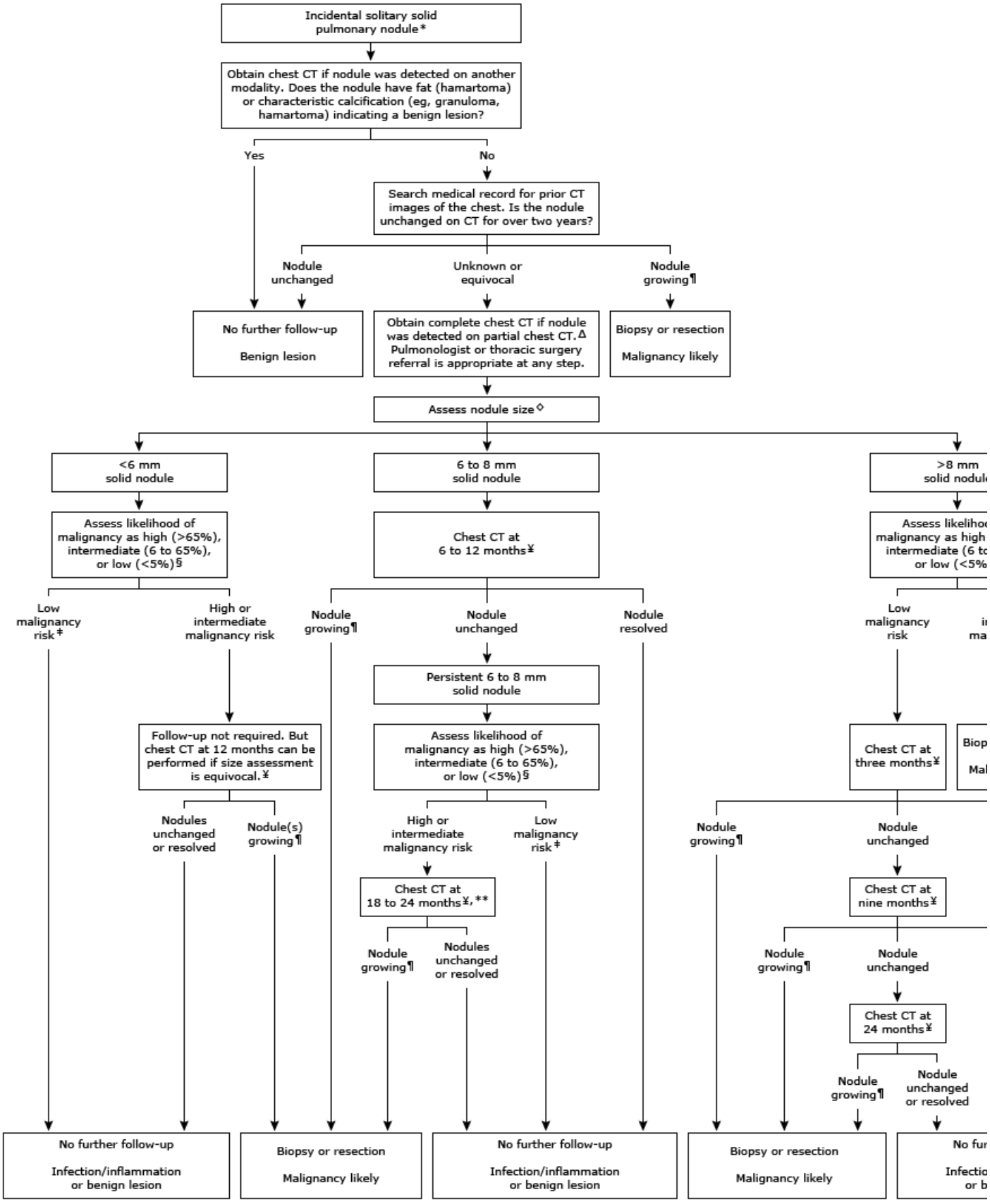
IMPORTANT NOTES FOR USE:

1. Negative screen: does not mean that an individual does not have lung cancer.
2. Size: to calculate nodule mean diameter, measure both the long and short axis to one decimal point, and report nodule mean diameter to one decimal point.
3. Size thresholds: apply to nodules at first detection, and that grow and reach a higher size category.
4. Growth: an increase in size of >1.5 mm (>1.8 mm^3).
5. Exam category: each exam should be coded 0 to 4 based on the nodule(s) with the highest degree of suspicion.
6. Exam modifiers: S modifier may be added to the 0 to 4 category.
7. Lung cancer diagnosis: once a patient is diagnosed with lung cancer, further management (including additional imaging such as PET/CT) may be performed for purposes of lung cancer staging; this is no longer screening.
8. Practice audit definitions: a negative screen is defined as categories 1 and 2; a positive screen is defined as categories 3 and 4.
9. Category 4B management: this is predicated on the probability of malignancy based on patient evaluation, patient preference and risk of malignancy; radiologists are encouraged to use the McWilliams et al assessment tool when making recommendations.
10. Category 4X: nodules with additional imaging findings that increase the suspicion of lung cancer, such as speculation, GGN that doubles in size in 1 year, enlarged lymph nodes, etc.
11. Solid nodules with smooth margins, an oval, lentiform or triangular shape, and maximum diameter <10 mm or 523.6 mm^3 (perifissural nodules) should be classified as category 2.
12. Category 3 and 4A nodules that are unchanged on interval CT should be coded as category 2, and individuals returned to screening in 12 months.

Lung-RADS: lung imaging reporting and data system; CT: computed tomography; NA: not applicable; LDCT: low-dose computed tomography; GGN: ground-glass density nodule; PET: positron emission tomography.

* Link to Lung-RADS calculator: https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/.

Incidental solitary solid pulmonary nodule evaluation



Algorithm applies to asymptomatic, immunocompetent adults, age >35 years without malignancy that is actively under treatment or follow-up. It is not designed for in those undergoing lung cancer screening. The clinician is expected to use his or her independent medical judgment in the context of individual circumstances and p make adjustments, as necessary. Chest CT should be performed without contrast as contiguous thin (ie, 1 mm) images on a helical scanner using low radiation dose t

CT: computed tomography; FDG: fluorodeoxyglucose; PET: positron emission tomography.
* Nodule is a well-defined opacity completely surrounded by lung parenchyma measuring <30 mm in longest dimension.
¶ Growth is defined as >2 mm increase in overall size.
Δ If the chest CT reveals findings relevant to nodule diagnosis (eg, other nodules or masses, mediastinal lymphadenopathy, or findings of pulmonary inflammation or infection), be based on these findings.
◊ Nodule size is defined as the average of long and short axes in axial cross-section.
§ Likelihood of malignancy assessed either clinically or by quantitative predictive models.
¥ Timing of chest CT is relative to the date of the initial nodule detection.
‡ Another chest CT at 18 to 24 months is an option if stability of nodules is equivocal.
† FDG PET/CT is an option in patients at intermediate cancer risk or those considered high medical risk for biopsy. FDG-avid nodules proceed to tissue sampling. FDG-nonavid no CT surveillance.
** Follow-up interval should be the same or longer than the preceding one that showed no nodule growth. In addition, longer interval is needed to demonstrate unequivocal gr

Graphic 113777 Version 4.0

Evaluation of the incidental solid pulmonary nodule in adults

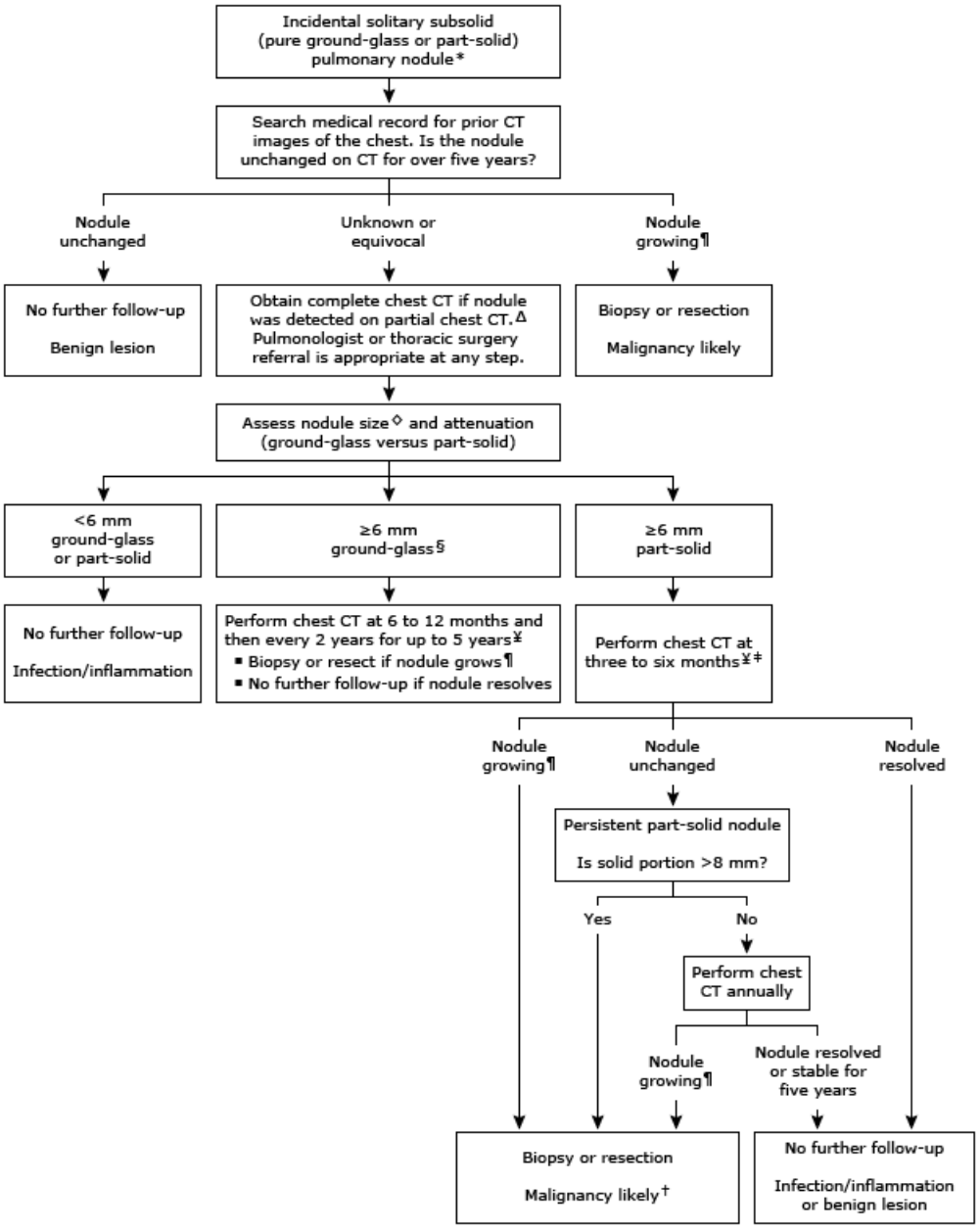
Nodule size (mm)	Low (<5%) cancer risk	High (>65%) or moderate (5 to 65%) cancer risk
Solitary		
<6	No routine follow-up	Optional CT at 12 months
6 to 8	CT at 6 to 12 months, then consider CT at 18 to 24 months	CT at 6 to 12 months, then CT at 18 to 24 months
>8	CT at 3 months, then at 9 and 24 months	FDG PET/CT, biopsy or resection
Multiple (evaluation based on largest nodule)		
<6	No routine follow-up	Optional CT at 12 months
≥6	CT at 3 to 6 months, then consider CT at 18 to 24 months	CT at 3 to 6 months, then CT at 18 to 24 months

1. Not applicable to patients age <35 years, in lung cancer screening, with immunosuppression, known pulmonary disease or symptoms or active primary cancer.
2. Chest CT performed without contrast as contiguous 1 mm sections using low dose technique.
3. Growing or FDG-avid nodules should undergo biopsy or resection. Growth is defined as >1.5 mm increase.
4. Nodules unchanged for >2 years are benign.

CT: computed tomography; FDG: 18-fluorodeoxyglucose; PET: positron emission tomography.

Graphic 113379 Version 1.0

Incidental solitary subsolid pulmonary nodule evaluation



Algorithm applies to asymptomatic, immunocompetent adults, age >35 years without malignancy that is actively under treatment or follow-up. It is not designed for use in other populations or in those undergoing lung cancer screening. The clinician is expected to use his or her independent medical judgment in the context of individual circumstances and patient preferences to make adjustments, as necessary. Chest CT should be performed without contrast as contiguous thin (ie, 1 mm) images on a helical scanner using low radiation dose techniques.

CT: computed tomography.

* Nodule is a well-defined opacity completely surrounded by lung parenchyma measuring <30 mm in longest dimension.

¶ Growth is defined as >2 mm increase in overall size, increase in attenuation or appearance or enlargement of a solid component.

Δ If the chest CT reveals findings relevant to nodule diagnosis (eg, other nodules or masses, mediastinal lymphadenopathy, or findings of pulmonary inflammation or infection), subsequent workup should be based on these findings.

◊ Nodule size is defined as the average of long and short axes in axial cross-section.

§ Ground glass nodules >20 mm are managed with resection in some cases.

¥ Timing of chest CT is relative to the date of the initial nodule detection.

‡ If solid portion of nodule is >8 mm and if clinical suspicion for malignancy is high, this CT can be deferred and the clinician may proceed to the next step with the assumption of a persistent non-enlarging, part-solid nodule.

† If nodule is persistent but not growing and the solid portion is >8 mm, FDG PET/CT is an option. FDG-avid nodules proceed to tissue sampling. FDG non-avid nodules are triaged to annual CT surveillance.

Graphic 113778 Version 2.0

Evaluation of the incidental subsolid pulmonary nodule in adults

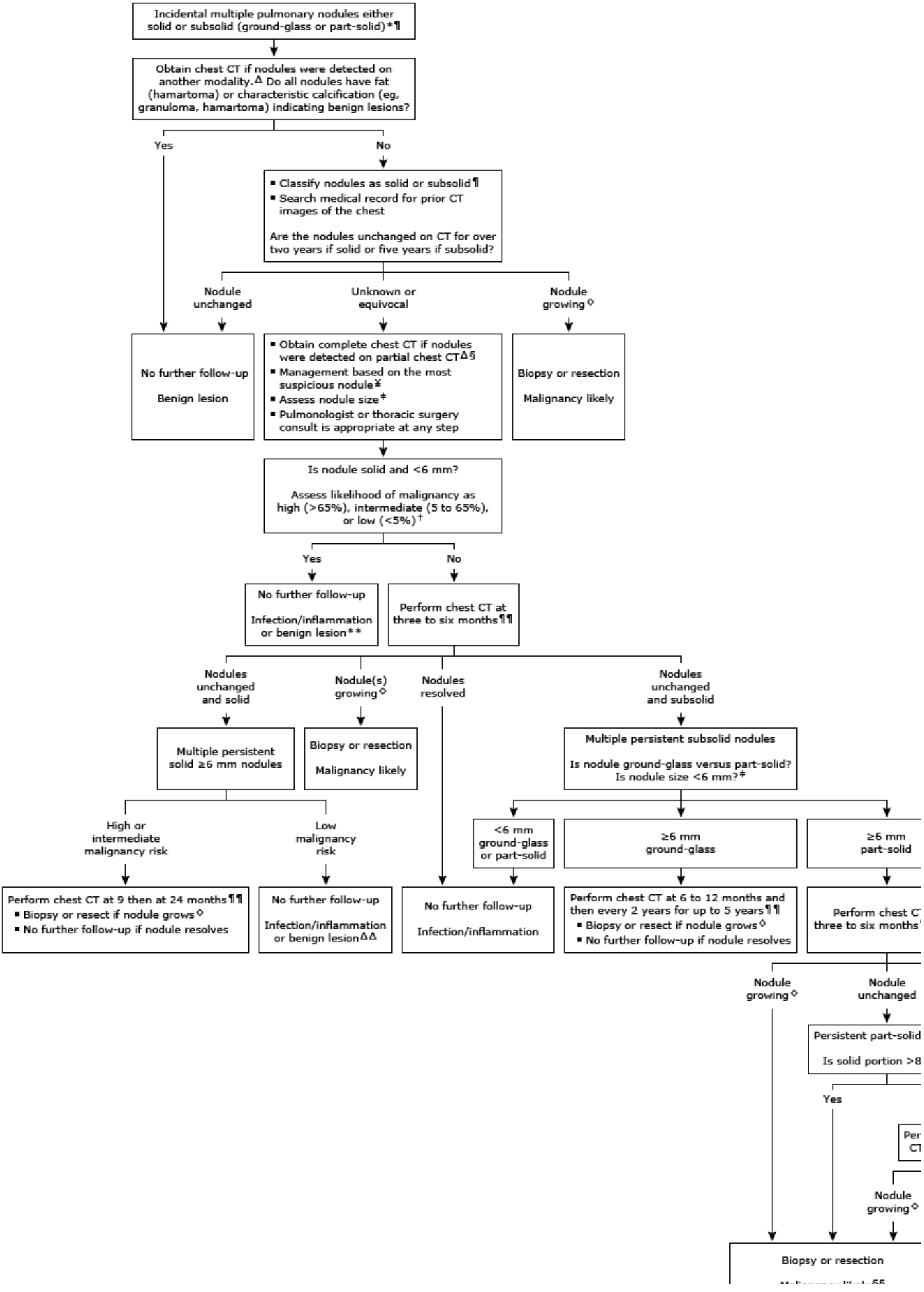
Nodule type and size (mm)	Recommendation	Comments
Solitary pure ground-glass		
<6	No routine follow-up.	Consider CT at two and four years if patient is considered high risk for cancer.
≥6	CT at 6 to 12 months to confirm persistence. If unchanged, then CT every two years until five years. Growing nodules should undergo histologic sampling.*	Histologic sampling requires resection as ground glass nodules are not amenable to needle biopsy.
Solitary part-solid		
<6	No routine follow-up.	In practice, part-solid nodules <6 mm cannot be defined as such until ≥6 mm. Consequently, these should be managed as a pure ground-glass nodule.
≥6	CT at three to six months to confirm persistence. If unchanged and solid component remains <6 mm, annual CT should be performed for five years. Nodules with solid component >8 mm or growing nodules should undergo histologic sampling.*	For nodules with solid component ≤8 mm, histologic sampling requires resection as they are not amenable to needle biopsy.
Multiple		
<6	CT at three to six months. If stable, no routine follow-up.	Consider CT at two and four years if patient is considered high risk for cancer.
≥6	CT at three to six months. If stable, subsequent evaluation is based on the most suspicious nodule (largest nodule for pure ground-glass and largest solid component for part-solid).	

1. Not applicable to patients age <35 years, in lung cancer screening, with immunosuppression, known pulmonary disease or symptoms or active primary cancer.
2. Chest CT performed without contrast as contiguous 1 mm sections using low dose technique.
3. Nodules unchanged for >5 years are benign.

CT: computed tomography.
* Growth is defined as >2 mm increase in overall size, increase in attenuation or appearance or enlargement of a solid component.

Graphic 113380 Version 2.0

Incidental multiple pulmonary nodules evaluation


Incidental multiple pulmonary nodules either solid or subsolid (ground-glass or part-solid)*¶
Obtain chest CT if nodules were detected on another modality.Δ Do all nodules have fat (hamartoma) or characteristic calcification (eg, granuloma, hamartoma) indicating benign lesions?
Yes
No
Classify nodules as solid or subsolid¶
Search medical record for prior CT images of the chest
Are the nodules unchanged on CT for over two years if solid or five years if subsolid?
Nodule unchanged
Unknown or equivocal
Nodule growing◇
No further follow-up
Benign lesion
Obtain complete chest CT if nodules were detected on partial chest CTΔ§
Management based on the most suspicious nodule¥
Assess nodule size‡
Pulmonologist or thoracic surgery consult is appropriate at any step
Biopsy or resection
Malignancy likely
Is nodule solid and <6 mm?
Assess likelihood of malignancy as high (>65%), intermediate (5 to 65%), or low (<5%)†
Yes
No
No further follow-up
Infection/inflammation or benign lesion**
Perform chest CT at three to six months¶¶
Nodules unchanged and solid
Nodule(s) growing◇
Nodules resolved
Nodules unchanged and subsolid
Multiple persistent solid ≥6 mm nodules
Biopsy or resection
Malignancy likely
Multiple persistent subsolid nodules
Is nodule ground-glass versus part-solid?
Is nodule size <6 mm?‡
High or intermediate malignancy risk
Low malignancy risk
<6 mm ground-glass or part-solid
≥6 mm ground-glass
≥6 mm part-solid
Perform chest CT at 9 then at 24 months¶¶
Biopsy or resect if nodule grows◇
No further follow-up if nodule resolves
No further follow-up
Infection/inflammation or benign lesionΔΔ
No further follow-up
Infection/inflammation
Perform chest CT at 6 to 12 months and then every 2 years for up to 5 years¶¶
Biopsy or resect if nodule grows◇
No further follow-up if nodule resolves
Perform chest CT
three to six months
Nodule growing◇
Nodule unchanged
Persistent part-solid
Is solid portion >8
Yes
Per
CT
Nodule growing◇
Biopsy or resection

Malignancy likely§§

Algorithm applies to asymptomatic, immunocompetent adults, age >35 years without malignancy that is actively under treatment or follow-up. It is not designed for those undergoing lung cancer screening. The clinician is expected to use his or her independent medical judgment in the context of individual circumstances and pat adjustments, as necessary. Chest CT should be performed without contrast as contiguous thin (ie, 1 mm) images on a helical scanner using low radiation dose techni

CT: computed tomography.

* Nodule is a well-defined opacity completely surrounded by lung parenchyma measuring <30 mm in longest dimension.

¶ For multiple nodules, choice of solid versus subsolid is based on the largest or the predominant pattern.

Δ Chest CT should be performed without contrast as contiguous thin (ie, 1 mm) images on a helical scanner using low radiation dose techniques.

◊ Growth is defined as >2 mm increase in overall size. For subsolid nodules, growth can also be an increase in attenuation or appearance or enlargement of a solid component.

§ If the chest CT reveals findings relevant to nodule diagnosis (eg, other nodules or masses, mediastinal lymphadenopathy, or findings of pulmonary inflammation or infection), on these findings.

¥ Suspicious nodule is the one with the largest or, for part solid nodules, the one with the most solid component.

‡ Nodule size is defined as the average of long and short axes in axial cross-section.

† Likelihood of malignancy assessed either clinically or by quantitative predictive models.

** Chest CT follow-up at 12 months is optional in patients who are high or intermediate risk for malignancy.

¶¶ Timing of chest CT is relative to the date of the initial nodule detection.

ΔΔ Optional chest CT at 18 to 24 months if stability of nodules is equivocal.

◊◊ If solid portion of nodule is >8 mm and if clinical suspicion for malignancy is high, this CT can be deferred and the clinician may proceed to the next step with the assumption c solid nodule.

§§ If nodule is persistent but not growing and the solid portion is >8 mm, FDG PET/CT is an option. FDG-avid nodules proceed to tissue sampling. FDG non-avid nodules are triag

Graphic 113779 Version 3.0

Contributor Disclosures

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