

Evidence based imaging strategies for solitary pulmonary nodule

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Abstract: Solitary pulmonary nodule (SPN) is defined as a rounded opacity ≤ 3 cm in diameter surrounded by lung parenchyma. The majority of smokers who undergo thin-section CT have SPNs, most of which are smaller than 7 mm. In the past, multiple follow-up examinations over a two-year period, including CT follow-up at 3, 6, 12, 18, and 24 months, were recommended when such nodules are detected incidentally. This policy increases radiation burden for the affected population. Nodule features such as shape, edge characteristics, cavitation, and location have not yet been found to be accurate for distinguishing benign from malignant nodules. When SPN is considered to be indeterminate in the initial exam, the risk factor of the patients should be evaluated, which includes patients' age and smoking history. The 2005 Fleischner Society guideline stated that at least 99% of all nodules 4 mm or smaller are benign; when nodule is 5-9 mm in diameter, the best strategy is surveillance. The timing of these control examinations varies according to the nodule size (4-6, or 6-8 mm) and the type of patients, specifically at low or high risk of malignancy concerned. Noncalcified nodules larger than 8 mm diameter bear a substantial risk of malignancy, additional options such as contrast material-enhanced CT, positron emission tomography (PET), percutaneous needle biopsy, and thoracoscopic resection or videoassisted thoracoscopic resection should be considered.

Keywords: Pulmonary nodule; computerized tomography; follow-up; positron emission tomography (PET); magnetic resonance imaging; guideline; biopsy; lung cancer

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Introduction

Lung cancer is the leading cause of cancer related death throughout the world (1). Lung cancer screening programs are being investigated in the United States, Japan, and other countries with low-dose helical/multi-detector CT. Despite the controversy on its cost-effectiveness (2), evidences suggest that early detection of lung cancer allow more timely therapeutic intervention and thus a more favorable prognosis for the patient (3-5). Solitary pulmonary nodule (SPN) is defined as a rounded opacity 3 cm in diameter surrounded by lung parenchyma (6). Lesions larger than 3 cm are called masses and are often malignant (6). On CT, nodules can be solid, semisolid (mixed attenuation), or

ground-glass attenuation. Traditionally, chest radiography provides basic information about SPN. Nowadays, patients with SPN detected on radiographs are likely to undergo early CT scan (7). The majority of smokers who undergo thin-section CT have been found to have small lung nodules, most of which are smaller than 7 mm in diameter (8,9). However, the clinical importance of these small nodules differs substantially from that of larger nodules detected on chest radiographs, in that the vast majority are benign. This has been highlighted in several recent publications on CT screening for lung cancer (10-15). In the past, multiple follow-up examinations over a 2-year period, including CT follow-up at 3, 6, 12, 18, and 24 months, were recommended when such nodules are detected

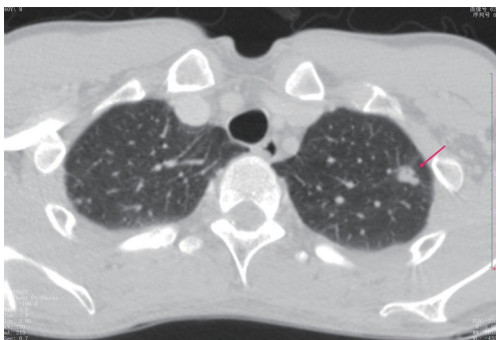


Figure 1 CT shows a case of a small hamartoma (arrow) appearing as a non-calcification solid nodule with lobulated margin, mimics a malignant nodule.

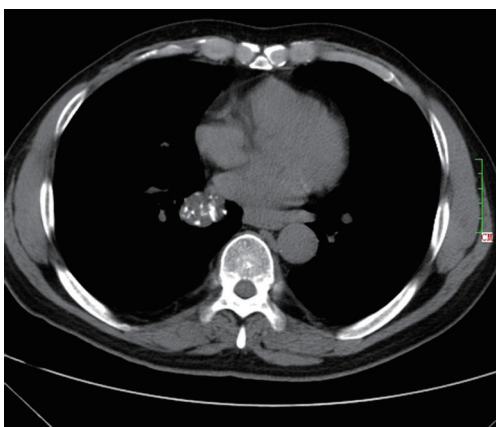


Figure 2 CT shows a case of hamartoma (size: 24 mm) with "popcorn" pattern calcification.

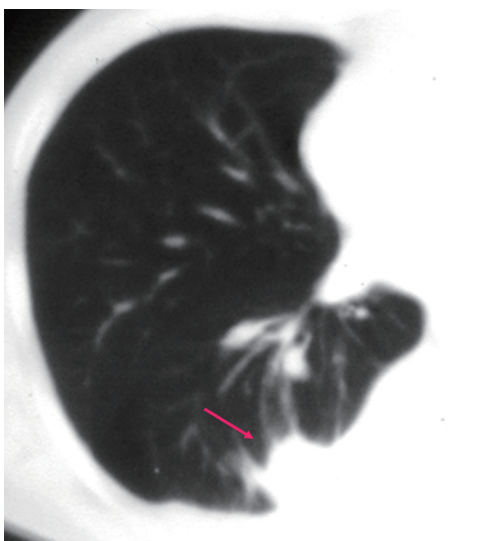


Figure 3 CT shows a case of rounded atelectasis (arrow) with morphological features of subpleural location, curved course of blood vessels into the opacity, and evidence of pleural disease.

incidentally (16,17). The policy increases radiation burden for the affected population (18-21). This editorial will present the current evidence based imaging strategies for SPN.

Morphologic assessment of solitary pulmonary nodule (SPN)

The most common intrapulmonary malignant lesions are metastases and primary bronchopulmonary carcinoma. All histological types of cancer may give rise to pulmonary nodules, but adenocarcinoma is the most frequent (22). Eighty percent of benign nodules are granulomas or intrapulmonary lymph nodes, 10% are hamartomas and 10% are other rarer benign lesions (23,24). Nodule features such as shape, edge characteristics, cavitation, and location have not yet been found to be accurate for distinguishing benign from malignant nodules (*Figure 1*) (25,26). Features favoring benignity include evidence of stability for two years or more, small nodule size, smooth demarcated margins, and certain pattern of calcifications (central dense, diffuse, laminated or popcorn). Clustering of multiple nodules in a single location in the lung tend to favor an infectious process, although a dominant nodule with adjacent small satellite nodules can be seen in primary lung cancer (27,28). A laminated or central pattern is typical of a granuloma, whereas a classic "popcorn" pattern is most often seen in hamartomas (*Figure 2*) (24). In approximately half the cases of hamartoma, high-resolution CT can show a definitive pattern of fat and cartilage (29). Fat content suggests a hamartoma or occasionally a lipoid granuloma or lipoma (30). Calcification patterns that are stippled or eccentric have been associated with cancer. Another benign entity is rounded atelectasis. Diagnosis for rounded atelectasis can be made as it has specific diagnostic morphological features including subpleural location, curved course of blood vessels into the opacity, and evidence of pleural disease (*Figure 3*) (31). When nodules considered as benign no further investigation is necessary.

SPNs with irregular, spiculated margins, or lobulated contours, are typically associated with malignancy. Two patterns of the margins of a nodule are relatively specific for cancer. One is the corona radiata sign, consisting of very fine linear strands extending 4 to 5 mm outward from the nodule; they have a spiculated appearance on plain radiographs (*Figures 4,5*). A scalloped border is associated with an intermediate probability of cancer. Although most SPNs with smooth, well-defined margins are benign, these



Figure 4 CT shows a pulmonary adenocarcinoma presenting as a SPN (size: 22 mm) with spiculated margins. SPN, solitary pulmonary nodule.

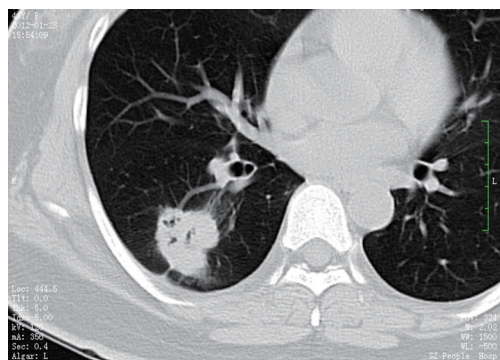


Figure 5 CT shows a pulmonary adenocarcinoma presenting as a SPN (size: 30 mm) with lobular contour, spiculated margin and plural indentation. SPN, solitary pulmonary nodule.

features are not diagnostic of benignity. A total of 21% of malignant nodules had well-defined margins (29).

For a single nodule, upper lobe location increases the likelihood of malignancy, because primary lung cancers are more common in the upper lobes (32). On the other hand, small, irregular, benign subpleural opacities, presumably due to scarring, are extremely common in the apical areas in older patients. Triangular or ovoid circumscribed nodules 3-9 mm in diameter adjacent to pleural fissures commonly

represent intrapulmonary lymph nodes (33).

In general, purely linear or sheetlike lung opacities are unlikely to represent neoplasms and do not require follow-up (34).

Approaches to indeterminate solitary pulmonary nodule (SPN)

When SPN is considered to be indeterminate in the initial exam, the risk factor of the patients should be evaluated. Increasing patient age generally correlates with increasing likelihood of malignancy. On the other hand, lung cancer is uncommon in patients younger than 40 years and is rare in those younger than 35 years (<1% of all cases) (35). The relative risk for developing lung carcinoma in male smokers was about 10 times that in nonsmokers (36). For heavy smokers, the risk was 15-35 times greater (37). Also, the cancer risk for smokers increases in proportion to the degree and duration of exposure to cigarette smoke (38). Other established risk factors include exposure to asbestos, uranium, and radon (39-41). A history of lung cancer in first-degree relatives is also a risk factor, and strong evidence for a specific lung cancer susceptibility gene has been discovered recently (42,43). A history of cancer can greatly increase the likelihood of a nodule being malignant (44). Low-risk individuals are <50 years old and have <20 pack-year smoking history. Moderate-risk group is defined as age >50 and >20 pack-year smoking history or second hand exposure, and no additional risk factor (random exposure, occupational exposure, cancer history, family history, or lung cancer).

The positive relationship of lesion size to likelihood of malignancy has been clearly demonstrated (10-15). The standard size value used is an average of the largest and smallest cross-sectional diameters of the most representative area of the nodule. In a meta-analysis of eight large screening trials, the prevalence of malignancy depended on the size of the nodules, ranging from 0% to 1% for nodules 5 mm or smaller, 6% to 28% for those between 5 and 10 mm, and 64% to 82% for nodules 20 mm or larger. Even in smokers, the percentage of all nodules smaller than 4 mm that will eventually turn into lethal cancers is very low (<1%), whereas for those in the 8-mm range the percentage is approximately 10-20%. The 2005 Fleischner Society guideline (Table 1) stated that at least 99% of all nodules 4 mm or smaller are benign and because such small opacities are common on thin-section CT scans, follow-up CT in every such case is not recommended; in selected cases with

Table 1 The 2005 Fleischner Society guideline for solitary pulmonary nodule management [reproduced with permission from (45)]

| Nodule size (mm) ^a | Low-risk patient ^b | High-risk patient ^c |
|-------------------------------|--|--|
| ≤4 | No follow-up needed ^d | Follow-up CT at 12 mo; if unchanged, no further follow-up ^e |
| >4-6 | Follow-up CT at 12 mo; if unchanged, no further follow-up ^e | Initial follow-up CT at 6-12 mo then at 18-24 mo if no change ^e |
| >6-8 | Initial follow-up CT at 6-12 mo then at 18-24 mo if no change | Initial follow-up CT at 3-6 mo then at 9-12 and 24 mo if no change |
| >8 | Follow-up CT at around 3, 9 and 24 mo, dynamic contrast-enhanced CT, PET and/or biopsy | Same as for low-risk patient |

Note: newly detected in indeterminate nodule in persons 35 years of age or older. ^a, average of length and width; ^b, minimal or absent history of smoking and of other known risk factors; ^c, history of smoking or of other known risk factors; ^d, the risk of malignancy in this category (<1%) is substantially less than that in a baseline CT scan of an asymptomatic smoker; ^e, nonsolid (ground-glass) or partly solid nodules may require longer follow-up to exclude indolent adenocarcinoma.



Figure 6 CT shows a case of adenocarcinoma in situ (arrow, size 6 mm) with pure ground glass opacity.



Figure 7 CT shows a case of minimally invasive adenocarcinoma, with a total size of 17 mm and solid component size of 7 mm.

suspicious morphology or in high-risk subjects, a single follow-up scan in 12 months should be considered (45). This protocol could result in a few indolent cancers being missed, the number of such instances would be extremely small relative to the reduction in the number of unnecessary studies (45).

The increased use of CT screening for lung cancer led to an increase in identification of early lesions such as adenocarcinoma in situ (AIS, histopathologically ≤30 mm, noninvasive lepidic growth, which at CT is usually nonsolid; *Figure 6*) and minimally invasive adenocarcinoma (MIA, histopathologically ≤30 mm and predominantly lepidic growth that has 5-mm or smaller invasion, which at CT is mainly nonsolid but may have a central solid component of up to approximately 5 mm; *Figure 7*) (22). These lesions should not be regarded as conventional invasive adenocarcinomas and can be observed rather than surgically resected (22).

When the nodule is 5-9 mm in diameter, approximately 6% of cases showed interval nodule growth detectable on 4-8 month follow-up scans (11). For these nodules the best strategy is surveillance. The timing of these control examinations is given in *Table 1*. This varies according to the nodule size (4-6, or 6-8 mm) and type of patients, specifically at low or high risk of malignancy concerned. Noncalcified nodules larger than 8 mm diameter can bear a substantial risk of malignancy (*Figure 8*) (46). In the case of nodules larger than 8 mm, additional options such as contrast material-enhanced CT, positron emission tomography (PET), percutaneous needle biopsy, and thoracoscopic resection or videoassisted thoracoscopic resection can be considered (13). A common aspect of invasive adenocarcinoma of the lung is metastasis to the brain (47,48). Its probability is a function of the size of the primary tumor, at least for tumors in the 20-60 mm size range. For node-negative invasive adenocarcinoma of the lung, a 20 mm primary lesion has been found to show a 14% probability of brain metastatic disease, progressing

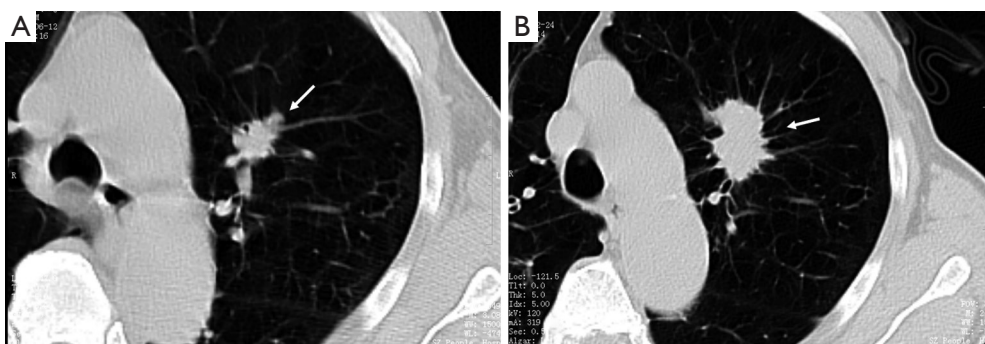


Figure 8 (A) CT shows a SPN (arrow, size =14 mm × 18 mm) in a 73 yrs male; (B) the same patient follow-up CT scan 20 month later. The size increased to 20 mm × 33 mm, with typical malignant the appearance of lobular contour and spiculated margin, and pathologically proved to be adenocarcinoma.

nearly linearly to a 60 mm primary node-negative lesion showing a 64% probability of brain metastatic disease (47).

In certain clinical settings, such as a patient presenting with neutropenic fever, the presence of a nodule may indicate active infection, and short-term imaging follow-up may be appropriate. Previous CT scans, chest radiographs, and other pertinent imaging studies should be obtained for comparison whenever possible, as they may serve to demonstrate either stability or interval growth of the nodule in question.

In a patient with known primary malignancy, lung nodules, regardless of being solitary or multiple, would be deemed suspicious for metastases. Pertinent factors will include the site, cell type, and stage of the primary tumor and whether early detection of lung metastases will affect care.

CT follow-up for solitary pulmonary nodule (SPN)

The volume doubling time (DT) for malignant bronchogenic tumors is rarely less than a month or more than a year. A nodule that was not present on a radiograph obtained less than two months before the current image is therefore not likely to be malignant. The “doubling time” (DT) of a nodule can be calculated using the following formula:

$$DT = (t \cdot \ln 2) / \ln(V_f / V_i)$$

Where V_i is the initial volume of the nodule, V_f the final volume, t the time interval between observations and \ln the logarithmic value. This formula is based on an exponential model of nodule growth (23). Note that a 5-mm nodule with a DT of 60 days will reach a diameter of 20.3 mm in 12 months, whereas a similar nodule with a DT of 240 days would reach a diameter of only 7.1 mm in the same period.

It has been considered that stability of nodule size for over 2 years for solid pulmonary nodules suggest benign nature. Recently, the radiologic-pathologic correlation of pure ground-glass attenuation nodules and mixed attenuation nodules with the histologic spectrum of pulmonary adenocarcinoma was described (49). Small purely ground-glass opacity (nonsolid) nodules that have malignant histopathologic features tend to grow very slowly, with a mean volume DT on the order of two years (50). Solid cancers, on the other hand, tend to grow more rapidly, with a mean volume DT on the order of 6 months. The growth rate of partly solid nodules tends to fall between these extremes, and this particular morphologic pattern is predictive of adenocarcinoma (46,51,52). Bronchoalveolar cell carcinomas and typical carcinoids occasionally appear to be stable for two or more years (53). Longer follow-up intervals are appropriate for nonsolid (ground-glass opacity) and very small opacities (50,51). Even if malignant, a nonsolid nodule that is smaller than 6 mm will probably not grow perceptibly in much less than 12 months (50,51). Currently, though the dictum that two-year stability on plain-film radiography indicates a benign process should be used with caution (54), it is still reasonable to use two-year stability on high-resolution CT as a practical guideline for predicting a benign process.

Hasegawa *et al.* (50) reported an analysis of the growth rates of small lung cancers detected during a 3-year mass screening program. They classified nodules as ground-glass opacity, as ground-glass opacity with a solid component, or as solid. Mean volume DTs were 813, 457, and 149 days, respectively. In addition, the mean volume DT for cancerous nodules in nonsmokers was significantly longer than that for cancerous

nodules in smokers. Authors of a number of other series have confirmed similar findings and have estimated the median tumor DTs, assuming a constant growth rate to be in the 160-180-day range (55,56). Authors of all of these reports, however, recognize wide variations, and in one study 22% of tumors had a volume DT of 465 days or more (56).

The use of stability as an indicator of a benign process is predicated on accurate measurement of growth and thus on the resolution of the imaging technique used. The accurate measurement of growth in subcentimeter nodules can be problematic. A doubling in volume of a sphere corresponds to an increase of only 26% of its diameter according to the formula $V=4/3\pi r^3$ where r is the radius. Therefore, it may be difficult to evaluate an increase or decrease in the axial diameter of a nodule between two successive CT examinations, or even of no value for small nodules less than or equal to 5 mm in size. In fact, a nodule of 5 mm which doubles in volume will only increase in diameter by 1.25 mm. Revel *et al.* determined that two-dimensional measurements obtained with electronic calipers were unreliable as a basis for distinguishing benign from malignant solid nodules in the 5-15-mm size range (57). Some authors compared diameter and cross-sectional area measurement with volume measurement in the assessment of lung tumour growth with serial CT. They demonstrated that growth assessment of lung tumours measuring less than 3 cm on CT serial CT scans with non-volumetric measurements frequently disagrees with growth assessment with volumetric measurements, and the three-dimensional measurements are more reliable (58-62). Volume measurement requires specific image analysis software, which allows segmentation and three-dimensional reconstruction of the nodule in order to appreciate the variations in morphology, and to automatically calculate the volume. Goodman *et al.* have raised additional caution in applying volumetric measurements, because the overall variability between scans in vivo is still substantial with wide confidence limits of $13.1\pm 26.6\%$ (63). For this reason, it is recommended to act on variations in nodule volume of 20%. A variation of <20% should not be considered as significant as it could be due to the method of measurement. Factors that affect the reproducibility of nodule volume measurement on CT include nodule size at detection, examination technique, nodule relationship to adjacent structures, underlying lung disease, and patient factors such as phase of respiration and cardiac motion (58).

For optimal CT evaluation of subsolid pulmonary nodules,

thin sections are advisable. Changes in nodule attenuation can also be assessed. For malignant subsolid nodules, measuring an increase in attenuation at serial CT examinations appears to be less subject to variability than measures of diameter or volume (64). Also, when subjective visual assessment of a nonsolid nodule at serial thin-section CT examinations suggests either possible but not definite enlargement of the nodule or possible but not definite development of a solid component, then increasing "mass" (mean volume multiplied by attenuation) may help identify early invasive growth, the increasing solid component corresponding to progression of local malignant invasion (64). For example, an increase of 100 HU in attenuation of a nonsolid nodule has been described as representing an approximately 10% increase in tumor volume (65). During surveillance of ground glass nodules, the appearance of a soft-tissue component is a highly suspicious sign of malignancy, even if the overall size of the nodule remains stable or diminishes (66).

An important aspect of adenocarcinomas of the lung is that, for small, solitary, early-stage tumors, the size of the invasive component—as measured histologically—is an independent predictor of survival (67). For part-solid lesions evaluated by using CT for tumor size, the size of the solid portion may be more predictive of prognosis than total size that includes the nonsolid dimension (67-69). A recent multicenter study in Japan has indicated that, for resected stage IA (T1N0M0) adenocarcinoma of the lung, disease-free survival correlated with solid tumor size but not with "whole tumor size" that included a nonsolid (ground-glass) component (70). For part-solid stage IA adenocarcinoma of the lung, an extensive nonsolid component is a favorable prognostic sign (22).

SPN can also appear as focal nodular areas of increased lung attenuation, including both well and poorly defined lesions, through which normal parenchymal structures, including airways and vessels, can be visualized. This appearance typically is referred to a ground-glass nodule. The term "subsidiol" nodules are used to emphasize that both pure ground-glass nodules and part-solid ground-glass nodules. It is necessary to establish lesions as true ground-glass nodule by using contiguous thin CT sections (1 mm thickness) whenever possible to avoid the pitfall of interpreting lesions as subsolid on thick sections (typically 5 mm) when they are actually solid. The 2013 Fleischner Society recommendation for the management of Subsidiol Pulmonary Nodules is shown in Table 2 (71).

A low-dose, thin-section, unenhanced technique should

Table 2 The 2013 Fleischner Society recommendations for the management of subsolid pulmonary nodules detected at CT [reproduced with permission from reference (71)]

| Nodule type | Management recommendations | Additional remarks |
|---|--|---|
| Solitary pure GGNs | | |
| ≤5 mm | No CT follow-up required | Obtain contiguous 1-mm-thick sections to confirm that nodule is truly a pure GGN |
| >5 mm | Initial follow-up CT at 3 months to confirm persistence then annual surveillance CT for a minimum of 3 years | FDG PET is of limited value, potentially misleading, and therefore not recommended |
| Solitary part-solid nodules | Initial follow-up CT at 3 months to confirm persistence. If persistent and solid component <5 mm, then yearly surveillance CT for a minimum of 3 years. If persistent and solid component ≥5 mm, then biopsy or surgical resection | Consider PET/CT for part-solid nodules >10 mm |
| Multiple subsolid nodules | | |
| Pure GGNs ≤5 mm | Obtain follow-up CT at 2 and 4 years | Consider alternate causes for multiple GGNs ≤5 mm |
| Pure GGNs >5 mm without a dominant lesion(s) | Initial follow-up CT at 3 months to confirm persistence and then annual surveillance CT for a minimum of 3 years | FDG PET is of limited value, potentially misleading, and therefore not recommended |
| Dominant nodule(s) with part-solid or solid component | Initial follow-up CT at 3 months to confirm persistence. If persistent, biopsy or surgical resection is recommended, especially for lesions with >5 mm solid component | Consider lung-sparing surgery for patients with dominant lesion(s) suspicious for lung cancer |
| <p>Note: these guidelines assume meticulous evaluation, optimally with contiguous thin sections (1 mm) reconstructed with narrow and/or mediastinal windows to evaluate the solid component and wide and/or lung windows to evaluate the nonsolid component of nodules, if indicated. When electronic calipers are used, bidimensional measurements of both the solid and ground-glass components of lesions should be obtained as necessary. The use of a consistent low-dose technique is recommended, especially in cases for which prolonged follow-up is recommended, particularly in younger patients. With serial scans, always compare with the original baseline study to detect subtle indolent growth.</p> | | |

be used, with limited longitudinal coverage, when follow-up of a lung nodule is the only indication for the CT examination. Malignant probability for nodules can be calculated using the software available on the website of Dr Gurney (<http://www.chestx-ray.com>).

Contrast-enhanced CT for solitary pulmonary nodule (SPN)

After administration of iodinated contrast material intravenously with power injection (300 mg/mL at 2 mL/sec), nodular enhancement of less than 15 HU is strongly predictive of benignity (*Figure 9*); whereas enhancement of more than 20 HU, reflecting presence of tumour neo-vascularisation, is indicative of malignancy (*Figure 10*). Results from a large multicenter study found that contrast-

enhanced CT has a sensitivity of 98% and a specificity of 58% when using a cutoff of 15 Hounsfield units for enhancement (72). A recent meta-analysis of ten dynamic CT studies reported pooled sensitivity of 93%, specificity of 76%, positive predictive value (PPV) of 80% and negative predictive value (NPV) of 95% for SPN characterization (73). Higher accuracy is reported for dynamic enhancement evaluation on helical CT, by analyzing combined wash-in and washout characteristics. Malignant nodules show greater washout of contrast enhancement (74). Dual-energy CT imaging has also been used in several studies to evaluate nodules with similar diagnostic accuracy (75,76). Limitations of contrast-enhanced CT relate to its false positive results for malignancy caused by inflammatory lesions; and measurement error that can occur in evaluation of small nodules. Given that measurement of the density is

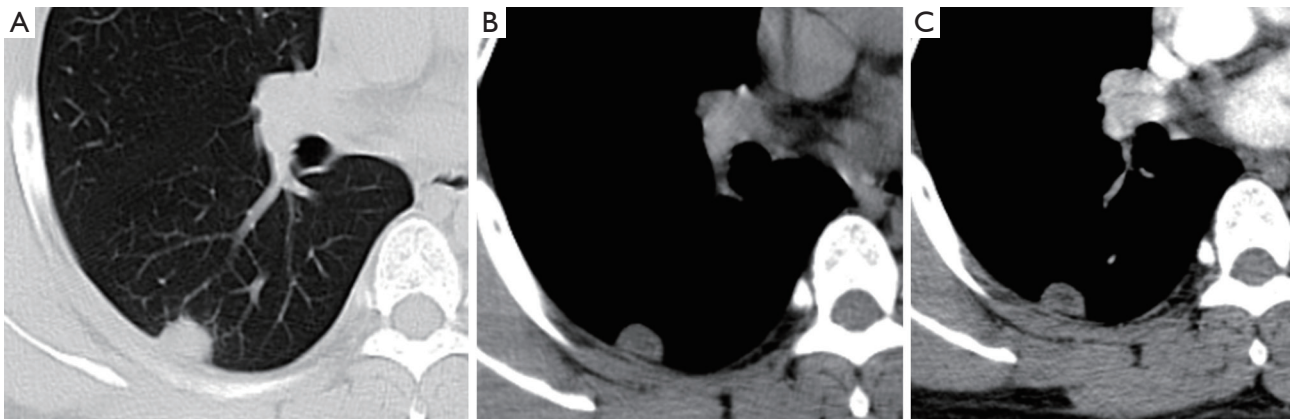


Figure 9 A small subplueral nodule (15 mm × 10 mm; arrow) with well-defined margin and enhancement of 16 Hounsfield units after CT contrast agent injection, pathologically proved to be a cryptococcal granuloma. (A,B): plain CT; contrast enhanced CT.

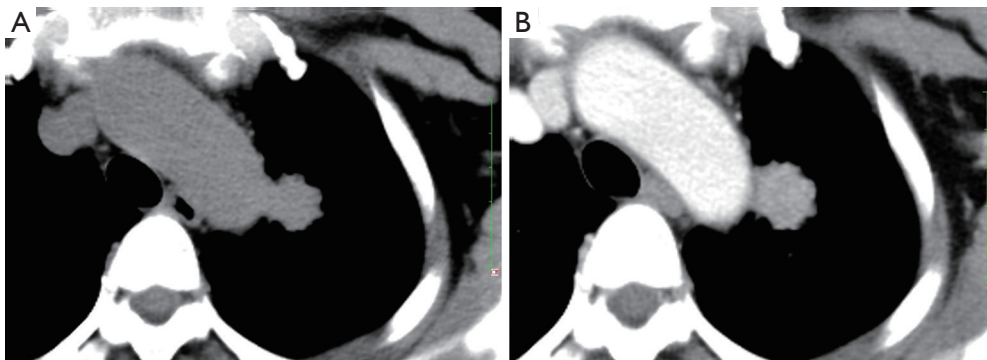


Figure 10 A pulmonary carcinoma (arrow) with enhancement of 37 Hounsfield units after CT contrast agent injection. (A) plain CT; (B) contrast enhanced CT.

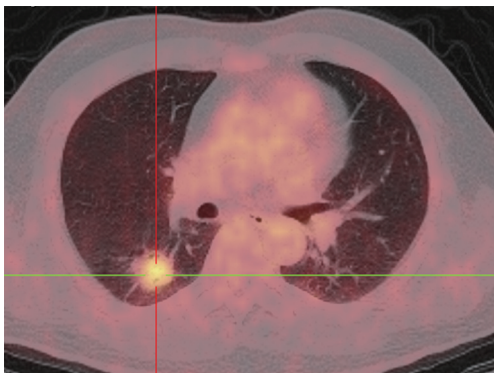


Figure 11 PET-CT shows a case of adenocarcinoma with a SUVmax of 4.14.

difficult for heterogeneous lesions and those less than 1 cm in diameter, in practice contrast-enhanced CT only yields reliable information for homogenous nodules equal to or above 8 mm in diameter.

Positron emission tomography (PET) and combined PET-CT

PET, using 18-fluorine fluoro-deoxyglucose (18F-FDG), a D-glucose analogue labeled with radio-isotope, can quantify the rate of glucose metabolism by cells, thereby detecting presence of metabolically active tissue. Malignant nodules consist of metabolically active cells that have higher uptake of glucose due to over-expression of glucose transporter protein (*Figure 11*). FDG is trapped and accumulates within these cells, as the radio-labeled glucose analogue is phosphorylated once but not metabolized further (77). A meta-analysis reported pooled sensitivity of 96.8% and specificity of 77.8% for malignant nodules for 8F-FDG PET technique alone (7). Integration of CT and PET results in an improved accuracy, with 97% sensitivity and 85% specificity, for differentiating malignant from benign SPNs (78). Kim *et al.* found that visual interpretation by experienced radiologist or nuclear medicine specialist is

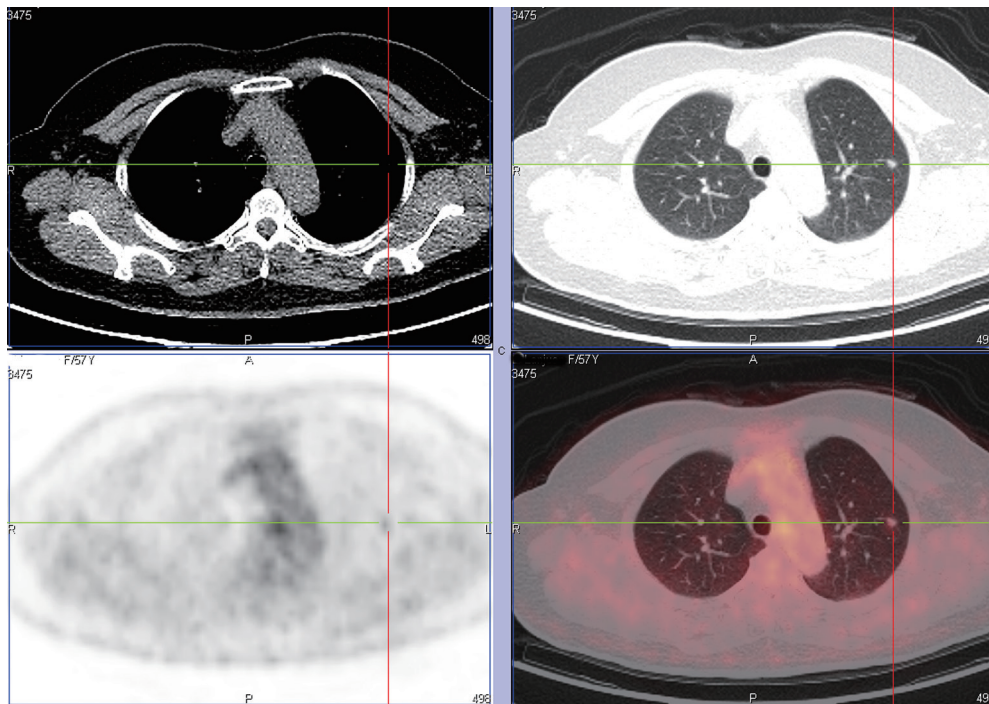


Figure 12 PET-CT shows a case of atypical adenomatous hyperplasia with a SUVmax of 1.42.

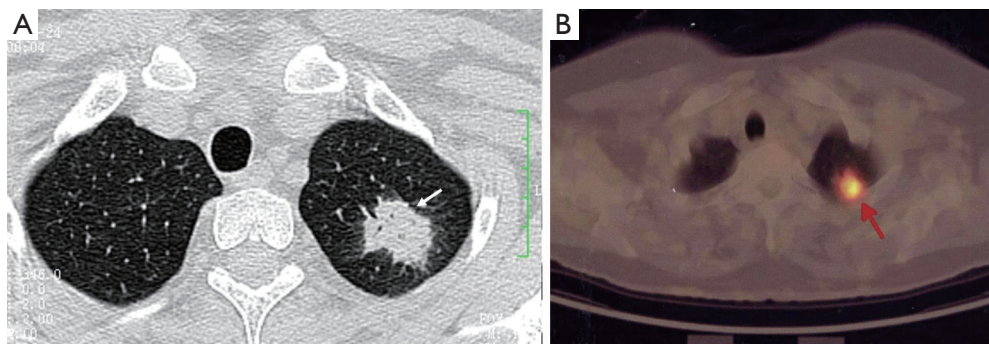


Figure 13 A case of cryptococcal granuloma (arrow) had a SUVmax of 4.5 on the FDG PET scan.

sufficient, if not superior, for characterizing SPN, and quantitative analysis (using 2.0 as cut-off SUVmax) did not improve accuracy (78). There is growing evidence that using threshold SUVmax to differentiate malignant from benign lesions is unrealistic, and SUVmax of 2.5 should not be embraced as a magic threshold.

Higher FDG uptake in lung cancer as measured by standardized uptake value (SUV) analysis is associated with aggressive cancers and shorter survival (79,80). On the other hand, lower levels of FDG uptake often correspond to histologically and clinically less aggressive tumour behavior (*Figure 12*) (81). An added value of PET-CT is the

detection of other unexpected metabolically active lesion and/or lymphadenopathy to support probable diagnosis of SPN being a primary or secondary malignancy (82). Up to 14% of patients otherwise eligible for surgery have occult extrathoracic disease on whole body PET imaging (83). On the other hand, the sensitivity and specificity of CT scans for detecting mediastinal lymph-node involvement are 55% to 88% and 76% to 85%, respectively (84). The sensitivity and specificity of PET in the presence of abnormal lymph nodes on CT scanning are 94% and 82%, respectively. In one prospective study, the diagnostic accuracy of CT was 64%, that of PET 88%, and that of the combination of CT

and PET 96% (85).

In most studies, the sensitivity of 18F-FDG PET-CT tends to be higher than its specificity for assessment of SPN. Many benign conditions, such as granulomatous (for example histoplasmosis or tuberculosis) and inflammatory processes, can mimic malignant nodules and produce false-positive results (*Figure 13*) (86). On the other hand, false negative results for SPN characterization on PET-CT can occur in three main settings: small lesion size, low tumor metabolic activity, and hyperglycemia. Small lesions (<1 cm) are challenging due to limited spatial resolution of PET, which is approximately 7 mm for modern scanners (7). Some highly differentiated malignant tumors have relatively little metabolic activity and low rate of proliferation, resulting in false-negative PET-CT. FDG PET is falsely negative in around 50% of patients with bronchioloalveolar carcinoma (87), or adenocarcinoma in situ (88-90). In addition, metastasis from certain primary malignancy, such as renal cell carcinoma, testicular or prostate cancer, may show little FDG tracer accumulation and may even be undetectable on PET-CT (91). False negative FDG PET-CT scans may also occur in patients with hyperglycemia (77). Some authors have proposed dual time point FDG-PET imaging, using the change in SUVmax between early and delayed scans to help differentiate benign and malignant SPNs (92). However, the role of dual time point PET imaging (DTPI) has been disputed by some authors (93). A meta-analysis on diagnostic performance of dual time point FDG-PET imaging in assessing lung nodules reported similar sensitivity and specificity to single time point FDG-PET (94). Further studies are needed to clarify this point.

The major obstacles to widespread use of PET-CT are limited availability and high costs. In the United States, with increasing availability of PET scanners and the reimbursement for SPN evaluation and lung cancer staging with PET scans being supported by Medicare, PET-CT has become much more common. In the United Kingdom, the National Institute for Clinical Excellence (NICE) currently recommends 18F-FDG PET for investigation of SPNs in cases where a biopsy is not possible or has failed, depending on nodule size, position and CT characterization (95).

Magnetic resonance imaging (MRI)

Use of MRI in the evaluation of pulmonary nodules has so far been limited. Faster imaging sequences and techniques to mitigate artefacts have allowed for detection of smaller

nodules (6 to 10 mm) with a sensitivity of almost 95% (96). For nodules >1 cm, contrast-enhanced dynamic MRI has been shown to be comparable to CT for distinguishing benign from malignant nodules (97-99). A meta-analysis of six dynamic contrast-enhanced MR studies reported pooled sensitivity of 94%, which is comparable to dynamic contrast enhanced CT, but with higher pooled specificity of 79% (73). Mori *et al.* found diffusion weighted imaging (DWI) was more specific for SPNs than FDG PET, due to fewer false positives for active inflammation, which does not affect diffusion of water molecules (100). An obvious advantage of MRI is this technique does not involve radiation. Further development in sequencing, scanners and coils, adaptation of parallel and sparse MR imaging will speed up the scan time (101,102), making MRI a realistic tool for the imaging of lung, particularly for lung cancer screen.

Computer-aided detection and diagnosis

Modern CT generates a large number of images that must be read by radiologists/physicians. This may lead to “information overload” for the radiologists/physicians. They may miss some cancers during their interpretation of CT images (52,103). Therefore, a computer-aided diagnosis (CAD) scheme for detection of lung nodules in CT images has been investigated as a tool for lung cancer detection. CAD is often categorized into two major groups: computer-aided detection (CADE) and computer-aided diagnosis (CADx). CADE focuses on a detection task, i.e., detection (or localization) of lesions in medical images. CADx focuses on a diagnosis (characterization) task, e.g., distinction between benign and malignant lesions, and classification among different lesion types (103,104). The use of CADE systems improves the performance of radiologists in the detection process of pulmonary nodules (105-107). It has been reported that CADE systems improved the sensitivity of radiologists in detecting small nodules on CT scans higher than that with conventional double reading (108). It has been also shown that observer’s nodule detection remained imperfect, and that a maximum-intensity-projection processing technique reduced the number of overlooked small nodules, particularly in the central lung (109).

Various approaches have been proposed for CADE schemes for lung nodules in CT. Sensitivities for detection of lung nodules in CT range from 70% to 95%, with from a few to 70 false positives (FP) per case. *Figure 14* illustrates CADE outputs on a CT image of the lungs (110,111). Major sources of FPs are various-sized lung vessels. Major sources

of false negatives are ground glass nodules, nodules attached to vessels, and nodules attached to the lung wall (i.e., juxtapleural nodules). Ground glass nodules are difficult to detect, because they are subtle, of low-contrast, and have ill-defined boundaries.

A number of researchers developed CADx schemes distinguishing malignant nodules from benign nodules on CT images automatically and/or determining the likelihood of malignancy for the detected nodules. *Figure 15* illustrates CADx outputs on malignant and benign lung nodules on high-resolution CT images (112,113). The performance of CADx schemes ranges from area under the receiver-operating-characteristic curve (AUC) values of 0.85 to 0.95 (107). Overall, the sensitivities of CADe schemes are relatively high, but the number of FPs is high compared to



Figure 14 CADe outputs (indicated by circles) on an axial CT slice of the lungs. A lung nodule (indicated by an arrow) was detected correctly by a CADe scheme with one false positive detection [branch of lung vessel; reproduced from (107) with permission].

radiologists' performance (107). Further improvement in specificity is necessary in future research.

Transthoracic fine-needle aspiration biopsy

Transthoracic fine-needle aspiration biopsy may be optimised by the presence of an onsite cytopathologist at the time of biopsy, allowing repeated sampling if insufficient cells are obtained. For those teams not have an onsite cytopathologist, coaxial cutting needles are recommended which yield more voluminous biopsy samples. This technique improves the accuracy of diagnosis without significant increase in the complication rate. CT may be useful in biopsy planning by specifying lesion depth and the point of the needle in order to aid the approach, and to avoid the needle path traversing a bulla or fissure. Although the minimum size varies according to the expertise of the radiologist, a diameter of at least 7 mm is usually required. For malignant lesions, transthoracic fine-needle aspiration biopsy offer the sensitivity of 80% to 95% and the specificity is 50% to 88%. For lesions that are less than 2 cm in diameter, transthoracic fine-needle aspiration biopsy has a sensitivity of more than 60 percent for detecting a malignant process (114). However, the false negative rate is 3% to 29% (115).

The Achilles heel of needle biopsy is negative biopsy result for malignancy without specific benign lesion diagnosis does not exclude malignancy. In addition, the technique has limited ability in producing specific diagnosis of benign lesions. SPN with high clinical suspicion of malignancy that is operable, the best approach is surgical

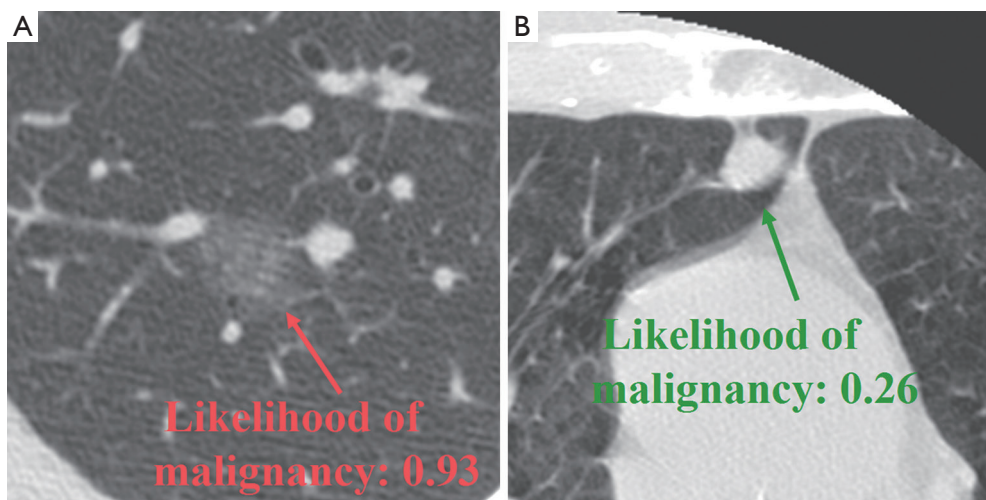


Figure 15 CADx scheme accurately determined the likelihood of malignancy for a malignant nodule (A) and a benign nodule (B).

resection as needle biopsy does not influence management (positive result confirms the high clinical suspicion and will be followed by resection, negative result does not exclude malignancy and the lesion has to be removed surgically because of the high clinical suspicion) so the result whether positive or negative does not alter the patient's management. For inoperable SPN, needle biopsy is justified to confirm the histology. Complication rates of needle biopsy are higher than those for bronchoscopy. Pneumothorax and haemorrhage are seen in 5-30% of cases, although in most cases, treatment is not required.

Bronchoscopy

If the nodule is linked to a narrowed or obstructed bronchus, a bronchus is visible within the nodule or an endobronchial lesion is detected on CT, then "bronchoscopy targeting" to the appropriate level is recommended. In such a case, the CT examination can optimize the approach to biopsy, and guide direct transbronchial biopsy. The sensitivity of bronchoscopy for detecting a malignant process in a SPN ranges from 20% to 80%, depending on the size of the nodule, its proximity to the bronchial tree, and the prevalence of cancer in the study population (116). For nodules that are less than 1.5 cm in diameter, the sensitivity is 10%, and for those that are 2.0 to 3.0 cm in diameter, it is 40% to 60% (116,117). When CT reveals a bronchus leading to the lesion, bronchoscopy may have a 70% sensitivity (118).

Conclusions

This paper highlights the importance of avoiding excessive patient irradiation caused by unnecessary follow-up CTs (45). The radiation dosage for a chest varies between 1-10 mSv, while that of whole body FDG-PET/CT is 10-30 mSv. More details on medical X-ray radiation risk can be found at <http://www.xrayrisk.com/>. After the publication of the Fleischner Society guideline in 2005, it was reported more frequent CT follow-ups than necessary are still being performed (119,120). The policy of low-dose, thin-section, with limited longitudinal coverage for follow-up CTs is not always carried out (119,120).

Information from the morphologic appearance of the nodule can be combined with clinical risk information to produce an overall probability for malignancy. If this probability can be set sufficiently low, strategies that include observing nodules for interval change can be advocated. The patient's age and the presence of comorbid conditions

influence management recommendations. The patient's preference is also a very important factor, especially if the potential difference among strategies is small. It is also highly practical that management approaches differ from institution to institution because of the varying prevalence of lung disease in different parts of the world, varying skill levels of operators, and varying availability of equipments.

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