Imaging incidental pulmonary nodules

The incidental nodule is an increasingly common clinical conundrum. This article outlines the characteristics that allow differentiation of benign and malignant pathologies and discusses strategies for their follow up and management.

The increased use of computed tomography in clinical practice has lead to the detection of significantly more incidental pulmonary nodules. Many of these are of uncertain clinical significance and often require further evaluation and, in many circumstances, prolonged follow up. Follow up is usually by repeated computed tomography examinations with the aim of assessing interval change in the nodule; this impacts on workload for the radiology department, adds to follow-up outpatient appointments and causes uncertainty for the patient. Despite continuing technological advances that reduce radiation doses from computed tomography examinations, there remains a significant radiation burden for the patient undergoing serial follow-up studies. In some cases further invasive tests, including radiological and surgically-guided biopsy with all the inherent associated morbidity and mortality, may be required.

This article discusses issues surrounding management of incidentally detected nodules, as well as the various computed tomography characteristics that allow differentiation of benign and malignant pathologies.

Detection and assessment

Non-calcified lung nodules are common and frequently multiple. Based on low dose screening studies of high-risk smokers from the United States their prevalence ranges from as low as 8% to as high as 51% (Wahidi et al, 2007). The overwhelming majority of incidentally detected nodules are small, with up to 96% measuring less than 10 mm – of these 72% are less than 5 mm (Diederich et al, 2002; Swensen et al, 2002).

The goal of radiographic evaluation of a pulmonary nodule is to differentiate between benign and malignant lesions as accurately as possible. The differential diagnosis of solitary pulmonary nodules is extensive and the importance of interpreting the radiographic features in the context of the clinical evaluation cannot be overstated. A brief summary of common diseases which can present as a pulmonary nodule is outlined in *Table 1*.

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Imaging features of benign nodules

Calcification

The presence and pattern of calcification can be an indicator of benignity. There are four benign patterns of calcification: central, diffuse solid, laminated and 'popcorn-like'. The first three patterns are typically seen as the result of granulomatous response to infection, in particular tuberculosis and histoplasmosis (Erasmus et al, 2000).

Popcorn-like calcification is a characteristic finding of hamartoma and virtually diagnostic of this benign tumour which accounts for 3% of all lung tumours and 6% of all benign solitary pulmonary nodules (Guo et al, 2008). The presence of fat within a lesion is also virtually pathognomic of hamartoma (Bhatia and Ellis, 2006). The presence of fat is confirmed on computed tomography by measurement of the attenuation of a nodule – values of between -40 and -120 Houndsfield units are diagnostic. Unfortunately at least a third of hamartomas contain neither fat nor calcification and overall 45% of benign nodules contain no calcification (Zerhouni et al, 1986). An example of a hamartoma is shown in *Figure 1*.

Table 1. Common causes of pulmonary nodules

Cause		Disease entity
Neoplastic	Malignant	Primary pulmonary carcinoma
		Primary pulmonary lymphoma
		Primary pulmonary carcinoid
		Solitary metastasis
	Benign	Hamartoma
		Chondroma
Inflammatory	Infectious	Granuloma (tuberculosis, fungal)
		Round pneumonia
		Abscess
	Non-infectious	Rheumatoid arthritis
		Wegener's granulomatosis
Vascular		Arteriovenous malformation
		Infarct
		Haematoma
Congenital		Bronchial atresia
		Sequestration

When present in a pulmonary nodule these specific patterns of calcification are reliable indicators of a benign cause: central, diffuse solid, laminated and popcorn-like. However, the presence of calcification per se is not necessarily an indicator of benignity. Calcification, for example, can be seen in 6–10% of cases of primary lung carcinoma and is typically punctuate, amorphous or diffuse (Mahoney et al, 1990; Grewal and Austin, 1994). Carcinoid tumours can demonstrate intralesional calcification (30% of cases) (Magid et al, 1989), and calcified metastases are typical in sarcomas but can also arise from thyroid carcinomas.

Shape and location

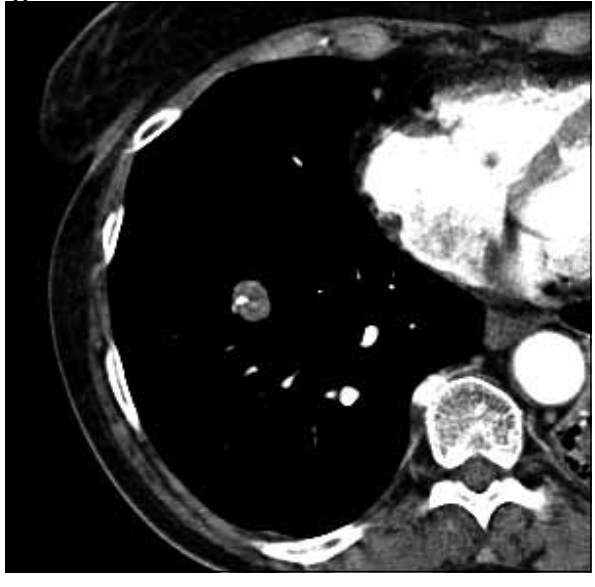
Several features of the shape of a nodule can help point towards its benign nature. In a Japanese screening population, nodules with a polygonal shape and no convex surfaces were reliably shown to be benign (Takashima et al, 2003). In the same series an ovoid, flat or tubular configuration was a strong indication of benign aetiology.

Positions of nodules relative to one another can also be a sign of benignity. Focal areas of infection manifesting as multiple nodular opacities are common and can mimic malignancy. A useful feature to suggest an infective aetiology over a malignant one is that infective nodules tend to form localized clusters, although bronchogenic tumours may have adjacent satellite nodules. Subcentimetre nodules, closely localized within 1 cm of each other, forming an isolated cluster strongly suggest benign disease (Carucci et al, 2001).

As well as the inherent shape of the nodule, the interface it makes with the surrounding lung parenchyma can be a helpful feature. A smooth border and interface between a non-lobulated lung nodule and the surrounding lung parenchyma is predictive of a benign process with a likelihood of 98–100% in one large screening series (Li et al, 2004). This relationship falls apart if there is significant local emphysema (Matsuoka et al, 2005).

In terms of location, a peripheral, subpleural location is seen more commonly in benign nodules than malignant ones and perifissural nodules seen on screening computed tomography studies have very low malignant potential (Takashima et al, 2003; Ahn et al, 2010).

Figure 1. A hamartoma – note the areas of fat and calcification typical of this lesion.



Size

Simply put, the smaller the nodule the more likely it is to be benign. Nodules <5 mm, 5–10 mm and >20 mm have malignancy rates of <1%, 6–28% and 64–82% respectively (Wahidi et al, 2007).

Intrapulmonary lymph nodes

Intrapulmonary lymph nodes (*Figure 2*) are a commonly identified cause of a pulmonary nodule and often have a stereotyped appearance that allows the radiologist to characterize them with a high degree of confidence. The majority are small, measuring between 3 and 6 mm. Their location in the lung and morphological features are largely a consequence of their relationship with the pulmonary lobule and lymphatic drainage of the lungs. Thus they tend to have a lower lobe distribution where drainage is maximal and are typically subpleural or lie within 15 mm of the pleura (the diameter of a pulmonary lobule). If nodes are subpleural they are usually triangular or half-moon shaped and if intraparenchymal they often resemble a coffee bean or a polygon. Finally the majority have a fine linear opacity connecting them to the pleural surface which corresponds to thickening of an interlobular septum (Edey and Hansell, 2009).

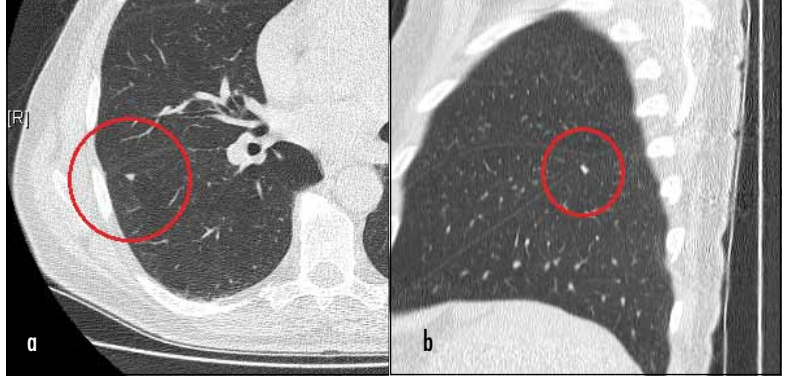
Malignant nodule imaging features

Nodule border, shape and location characteristics

Certain nodule characteristics are more commonly seen in malignant processes but unfortunately there is overlap in nodule morphology with benign lesions.

A lobulated contour (*Figure 3*) suggests uneven areas of growth within a nodule; a common outcome of disorganized malignant growth patterns. In a series by

Figure 2. a. Axial and (b) sagittal images of a triangular subpleural 6 mm nodule with a thin subpleural tag characteristic of an intrapulmonary lymph node.



Siegelman et al (1986) approximately 40% of smooth-edged lobulated nodules were malignant but lobulation can also be seen in up to 25% of benign nodules (Henschke et al, 2004). Edge irregularity and spiculate contours are likewise more commonly seen in malignant lesions with one study showing that 97% of nodules with densely spiculated margins, 93% with ragged margins, and 82% with lobulated margins were malignant (Furuya et al, 1999) and that the presence of spiculation has a positive predictive value for malignancy of approximately 90% (Winer-Muram, 2006). However, an irregular margin can also be seen in benign processes such as granulomatous disease, organizing and lipoid pneumonias, and progressive massive fibrosis.

Cavitation and air bronchograms can be seen in both benign and malignant nodules but some features can help make a distinction: irregularity of the inner wall of a cavitating nodule and increasing wall thickness are indicators of a malignancy whereas thin smooth cavities tend to be benign. The majority of cavitating nodules with a wall thickness above 16 mm are malignant (95%), while those with a wall thickness less than 4 mm (92%) are usually benign (Woodring and Fried, 1983).

Finally, air bronchograms are more common in malignant (30%) than benign (5%) lesions and bubble-like lucencies (pseudocavitation) within a nodule are present in approximately half of all adenocarcinomas with predominantly lepidic spread (previously known as bronchoalveolar cell carcinoma) (Zwirewich et al, 1991).

A nodule demonstrating cavitation and spiculated borders proven to represent a squamous cell carcinoma on surgical resection is shown in *Figure 4*.

Nodule growth

The time it takes for a nodule to double in volume, known as the volume doubling time, is a good discrimator of benign and malignant disease. The growth rate forms the basis of nodule follow-up guidelines. In a large review of screening data the median volume doubling time for 111 cancers was 98 days. For approximately half of cancers it was less than 100 days, and for three cancers (3%) it was more than 400 days (Henschke et al, 2012). In general nodules with a doubling time between 30 and 400 days are suspicious for malignancy. While volume doubling times are the best indicator of growth they require dedicated software to 'extract' and analyse the nodule; for this reason most radiologists still rely on assessment of the diameter of the nodule in its transverse plane. An example of this malignant pattern of growth is shown in *Figure 5*.

Traditionally lack of growth of a nodule over a 2-year period was considered to represent benign disease. However, this 2-year rule does not necessarily hold true in the assessment of non-solid nodules as outlined below.

Non-solid nodules

Non-solid nodules range from pure 'ground glass' opacities (lesions with uniform density on computed tomography less than adjacent vessels and bronchial walls) to mixed densities with varying proportions of solid or ground glass attenuation. Non-solid nodules are important as they are a relatively common manifestation of adenocarcinoma but also have non-malignant causes. Benign causes of ground glass nodules include atypical adenomatous hyperplasia, acute infection, focal fibrosis, desquamative interstitial pneumonia and respiratory bronchiolitis interstitial lung disease (Edey and Hansell, 2009), but it is not uncommon for infection to cause mixed density lesions. *Figure 6* shows multiple ground glass opacities within the same patient. Note the normal anatomical structures visible through the areas of increased opacification typical of ground glass.

Figure 3. A subcentimetre nodule with a lobulated margin – often caused by uneven growth pattern from a malignant process.

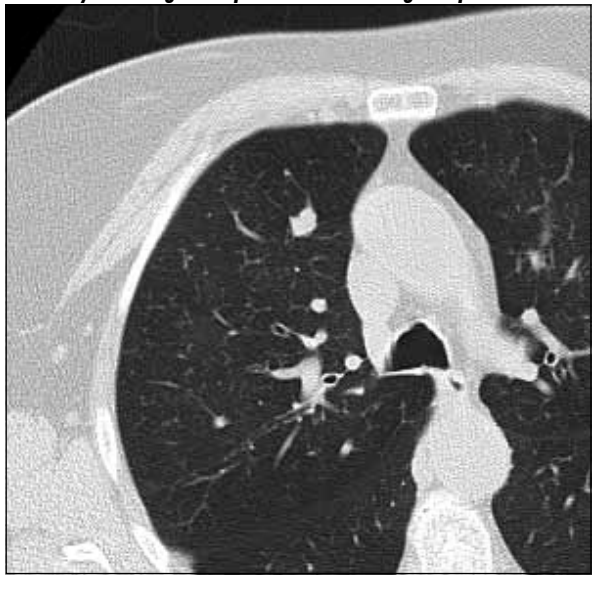
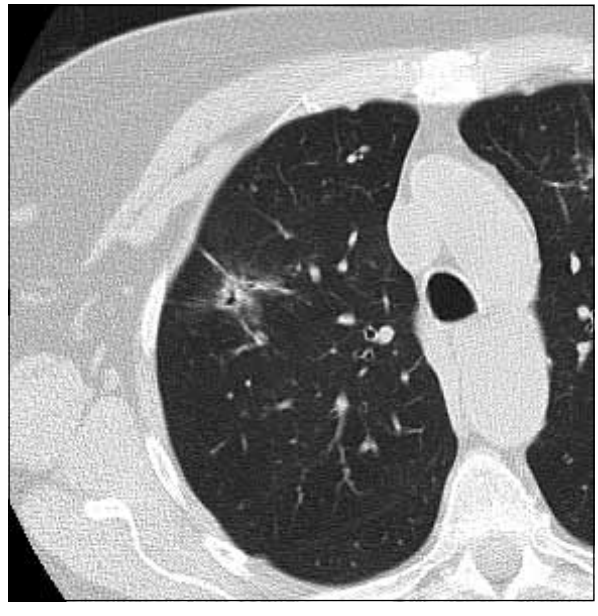


Figure 4. Squamous cell carcinoma demonstrating central cavitation and spiculated peripheral borders within the right upper lobe.



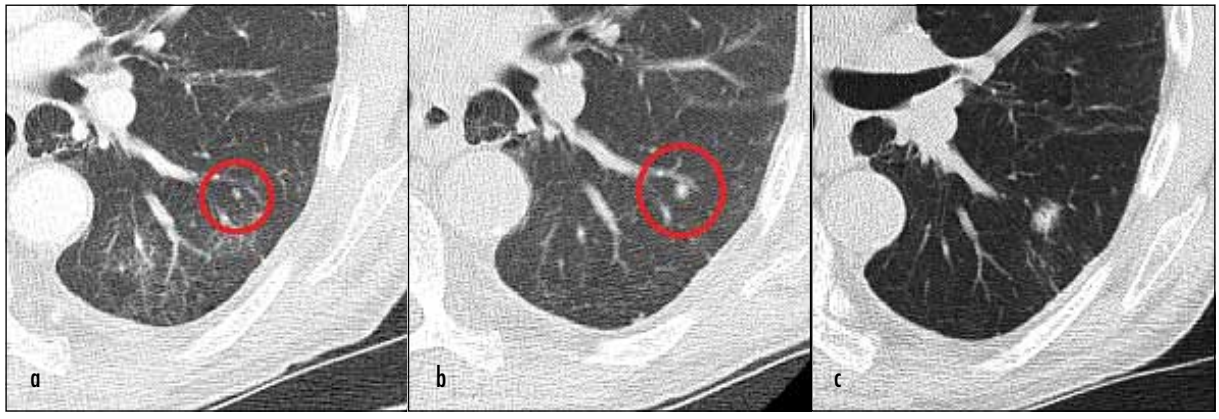


Figure 5. Example of malignant growth rate of a small nodule over the space of 5 months between (a) August 2011 through (b) October 2011 until (c) January 2012.

Godoy and Naidich (2009) have proposed guidelines for the assessment and management of ground glass pulmonary nodules:

1. Ground glass nodule <5 mm: no follow up necessary. The majority represent atypical adenomatous hyperplasia
2. Ground glass nodule 5–10 mm should have initial follow up at 3 months, with resolution at this stage implying that the lesion was inflammatory. If persistent, follow up annually for at least 3 years.
3. Ground glass nodule >10 mm. These lesions should be resected providing that the lesion persists unchanged or has increased in size at the 3-month follow up to the initial scan.

Follow up for small ground glass nodules should extend for more than the 2-year follow-up period typically used for similar sized solid nodules, because of the relatively indolent growth of adenocarcinoma with lepidic spread (Henschke et al, 2012). Follow up is recommended for a minimum of 3 years.

2-(18F)-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) has a well-established role in the diagnosis and management of lung cancer. However, FDG-PET has a lower sensitivity for small (<10 mm) and slow-growing tumours with lower glucose metabolism such as adenocarcinoma with predominantly lipidic spread which commonly manifests radiologically as a ground glass nodule. The optimum management strategy for this entity is further complicated by the relatively low diagnostic yield of adequate tissue obtained via both transbronchial and percutaneous biopsy techniques (Godoy and Naidich, 2009).

Adenocarcinomas manifesting as pure ground glass opacities can therefore be difficult to diagnose confidently because of a combination of their indolent growth pattern, requiring extended follow up, reduced metabolic activity leading to equivocal positron emission tomography findings and difficulty in obtaining adequate tissue to allow a definitive histological diagnosis. Despite the diagnostic issues they present, a large systematic review has shown that patients in whom these lesions are resected have 5-year survival approaching 100% (Travis et al, 2011).

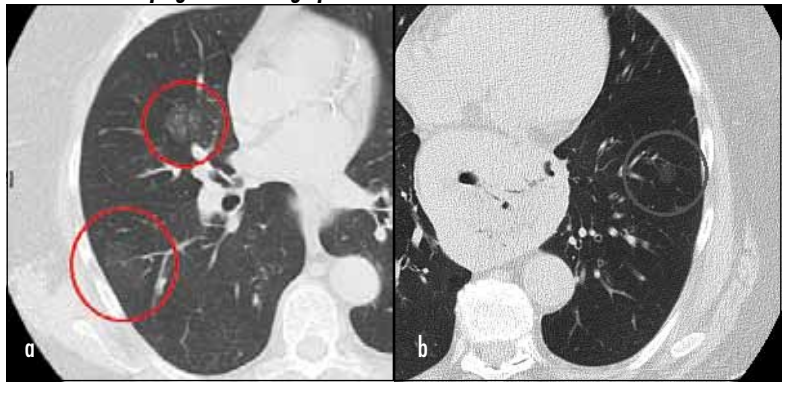
Mixed lesions with both ground glass and solid components should be followed up closely often with assessment with positron emission tomography-computed tomography and a low threshold for resection. The rate of malignancy is higher in part-solid nodules compared to pure ground glass nodule (Henschke et al, 2002). Positron emission tomography-computed tomography has a more fundamental role in the assessment of these lesions both in demonstrating metabolic activity seen in malignant lesions with higher mitotic rates and also in the evaluation of distant metastasis. *Figure 7* demonstrates a posterior peripheral area of ground glass opacification demonstrating interval growth over 10 months, confirmed as a peripheral adenocarcinoma with lipidic spread.

Fleischner Society guidelines

These are recommended guidelines (*Table 2*), issued in 2005 for the follow up and management of small pulmonary nodules in patients over the age of 35 years with no known malignancy, which are widely used in clinical practice in the UK (MacMahon et al, 2005).

These guidelines are undoubtedly useful and based on good evidence but are limited in some aspects, for instance they do not address the common situation of

Figure 6. a and b. Multiple focal areas of ground glass opacities in the same patient. Follow-up interval computed tomography in 3 months (not shown) showed complete resolution in keeping with a benign process.



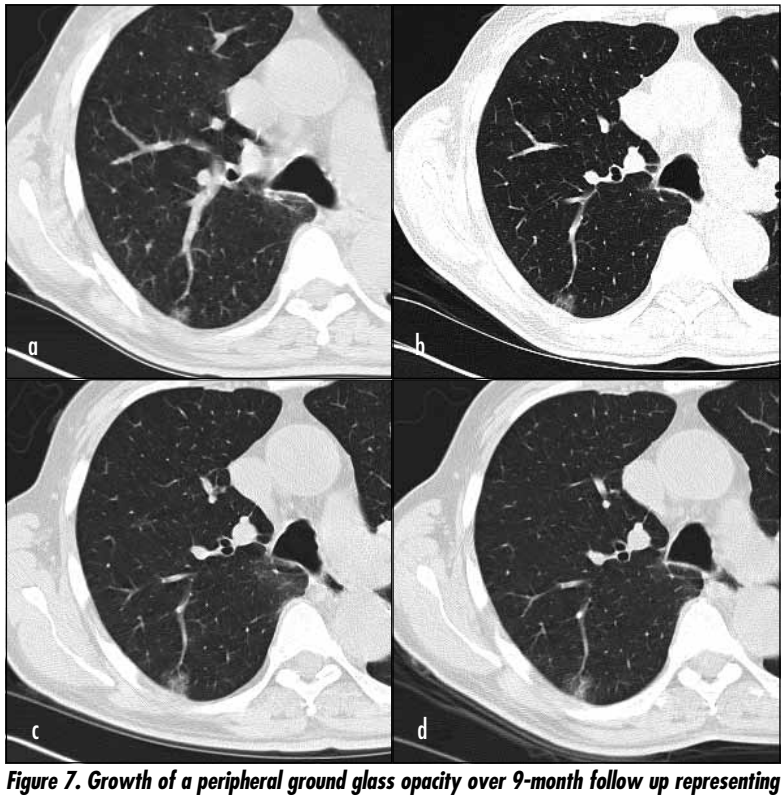


Figure 7. Growth of a peripheral ground glass opacity over 9-month follow up representing an adenocarcinoma with predominantly lepidic spread. a. Initial computed tomography with (b) 3-month follow up scan. Further scans at (c) 6 months and (d) 9 months.

multiple incidental nodules and are not suited for patients with a known malignancy. Despite this they offer an evidence-based framework for patient follow up.

Fluoro-2-deoxyglucose positron emission tomography

The emergence of FDG-PET has proved a valuable tool in the non-invasive characterization of pulmonary pathology, although its inherently low spatial resolution reduces its usefulness in the interrogation of nodules measuring less than 1 cm. Despite this FDG-PET may have a role in segregating equivocal lesions within the 8–10 mm size bracket into a lower category of risk for malignancy if FDG negative and demonstrating benign characteristics outlined above. Conversely an FDG-avid nodule may predicate further invasive diagnostic tests (Edey and Hansell, 2009). The other important role of positron emission tomography is exclusion of sites of malignancy elsewhere in the body before resection of nodules suspicious for malignancy.

Invasive diagnostic tests

Invasive testing may be necessary for the definitive characterization of an equivocal pulmonary nodule. The decision to proceed to invasive tests should be undertaken on a case by case basis with appropriate consideration of the risk–benefit rationale for the individual patient, and should be made within the context of the local lung multidisciplinary team.

Options for histological sampling include radiological techniques such as percutaneous computed tomography-guided fine needle aspiration or co-axial core biopsy and surgical techniques including video-assisted thoracoscopic surgery and open mini-thoracotomy.

Conclusions

Incidentally detected pulmonary nodules remain a diagnostic and management challenge. Imaging features suggestive of benignity or malignancy should be carefully scrutinized by the reporting radiologist. Management guidelines published by the Fleischner Society have gone some way to provide an evidence-based framework for their follow up but have their shortcomings. If the nodule remains equivocal then the risks of further invasive testing should be carefully weighed against the wishes and circumstances of the individual patient within the context of a multidisciplinary lung team. BJHM

Conflict of interest: none.

Ahn M, Gleeson T, Chan I et al (2010) Perifissural nodules seen at CT Screening for lung cancer. *Radiology* **254**(3): 949–56
Bhatia K, Ellis S (2006) Unusual lung tumours: an illustrated review of CT features suggestive of this diagnosis. *Cancer Imaging* **6**(1): 72–82
Carucci L, Maki D, Miller W (2001) Clustered pulmonary nodules: highly suggestive of benign disease. *J Thorac Imaging* **16**(2): 103–5
Diederich S, Wormanns D, Semik M et al (2002) Screening for early lung cancer with low-dose spiral CT: prevalence in 817

Table 2. Guidelines for management of small pulmonary nodules detected on computed tomography scans

Pre-test risk			Low risk			High risk		
Nodule size	<4 mm ↓	4–6 mm ↓	6–8 mm ↓	>8 mm ↓	<4 mm ↓	4–6 mm ↓	6–8 mm ↓	>8 mm ↓
Initial follow up	No follow up	12 months ↓	6–12 months ↓	3 months ↓	12 months ↓	6–12 months ↓	3–6 months ↓	3 months ↓
Subsequent follow up		Stop if no growth	18–24 months	9 months and 24 months ↓	Stop if no growth	18–24 months, stop if no growth	9 months and 24 months	9 months and 24 months ↓
Additional tests				Biopsy, PET-CT, contrast-enhanced CT				Biopsy, PET-CT contrast-enhanced CT

Low risk = no smoking or other risk factors; high risk = smoker or other risk factors. CT = computed tomography; PET = positron emission tomography. From MacMahon et al (2005)

asymptomatic smokers. *Radiology* **222**: 773–81
Edey A, Hansell D (2009) Incidentally detected pulmonary nodules on CT. *Clin Radiol* **64**: 872–84
Erasmus JJ, Connolly JE, McAdams HP, Roggli VL (2000) Solitary pulmonary nodules: part I. Morphologic evaluation for differentiation of benign and malignant lesions. *RadioGraphics* **20**: 43–58
Furuya K, Murayama S, Soeda H et al (1999) New classification of small pulmonary nodules by margin characteristics on high-resolution CT. *Acta Radiol* **40**: 496–504
Godoy M, Naidich D (2009) Subsolid pulmonary nodules and the spectrum of peripheral adenocarcinomas of the lung: recommended interim guidelines for assessment and management. *Radiology* **253**: 606–22
Grewal RG, Austin JH (1994) CT demonstration of calcification in carcinoma of the lung. *J Comput Assist Tomogr* **18**: 867–71
Guo W, Zhao YP, Jiang YG, Wang RW, Ma Z (2008) Surgical treatment and outcome of pulmonary hamartoma: a retrospective study of 20-year experience. *J Exp Clin Cancer Res* **27**: 8
Henschke C, Yankelevitz D, Mirtcheva R, McGuinness G, McCauley D, Miettinen OS (2002) CT screening for lung cancer: frequency and significance of part-solid and non-solid nodules. *Am J Roentgenol* **178**(5): 1053–7
Henschke CI, Yankelevitz DF, Naidich DP et al (2004) CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. *Radiology* **231**: 164–8
Henschke C, Yankelevitz D, Yip R et al (2012) Lung cancers diagnosed at annual CT screening: volume doubling times. *Radiology* (epub before print) March 27 doi:10.1148/radiol.12102489
Li F, Sone S, Abe H, MacMahon H, Doi K (2004) Malignant versus benign nodules at CT screening for lung cancer: Comparison of thin-section CT findings. *Radiology* **233**: 793–8
MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP (2005) Guidelines for Management of Small Pulmonary Nodules Detected on CT Scans: A Statement from the Fleischner Society. *Radiology* **237**(2): 395–400
Mahoney MC, Shipley RT, Corcoran HL, Dickson BA (1990) CT demonstration of calcification in carcinoma of the lung. *AJR Am J Roentgenol* **154**: 255–8
Magid D, Siegelman SS, Eggleston JC, Fishman EK, Zerhouni EA (1989) Pulmonary carcinoid tumors: CT assessment. *J Comput Assist Tomogr* **13**: 244–7
Matsuoka S, Kurihara Y, Yagihashi K, Niimi H, Nakajima Y (2005) Peripheral solitary pulmonary nodule: CT findings in patients with pulmonary emphysema. *Radiology* **235**: 266–73
Siegelman SS, Khouri NF, Leo FP, Fishman EK, Braverman RM, Zerhouni EA (1986) Solitary pulmonary nodules: CT assessment. *Radiology* **160**(2): 307–12
Swensen SJ, Jett JR, Sloan JA et al (2002) Screening for lung cancer with low-dose spiral computed tomography. *Am J Respir Crit Care Med* **165**: 508–13
Takashima S, Sone S, Li F et al (2003) Small solitary pulmonary nodules (< or = 1 cm) detected at population-based CT screening for lung cancer: reliable high-resolution CT features of benign lesions. *AJR Am J Roentgenol* **180**: 955–64
Travis W, Brambilla E, Noguchi M et al (2011) International Association For the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* **6**(2): 244–85
Wahidi MM, Govert JA, Goudar RK, Gould MK, McCrory DC (2007) Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* **132**(3 Suppl): 94S–107S
Winer-Muram H (2006) The solitary pulmonary nodule. *Radiology* **239**(1): 34–49
Woodring JH, Fried AM (1983) Significance of wall thickness in solitary cavities of the lung: a follow-up study. *Am J Roentgenol* **140**: 473–4
Zerhouni EA, Stitik FP, Siegelman SS et al (1986) CT of the pulmonary nodule: a cooperative study. *Radiology* **160**(2): 319–327
Zwirewich CV, Vedal S, Miller RR et al (1991) Solitary pulmonary nodule: high-resolution CT and radiologic - pathologic correlation. *Radiology* **179**: 469–76

KEY POINTS

- Patterns of benign nodule calcification are either central, diffuse solid, laminated or popcorn-like.
- Benign nodule features are calcification (central, diffuse solid, laminated, popcorn-like), fat, size <5 mm, shape (polygonal, ovoid, flat, tubular), and position (subpleural or perifissural).
- Malignant nodule features are cavitation, pseudocavitation, air bronchograms, spiculation and non-solid components.
- Incidental lung nodules should be followed up according to Fleishner Society guidelines with discussion of the management of equivocal lesions undertaken in the context of the local multidisciplinary lung team.