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Pulmonary nodules: do we need a separate algorithm for non-solid lesions?

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Abstract

This article describes the aetiology, epidemiology and clinical significance of incidental non-solid pulmonary nodules. Non-solid nodules are more likely malignant. If malignant, they are mostly due to atypical adenomatous hyperplasia and bronchioloalveolar carcinoma. As these may be negative on positron emission tomography and slow growing, the diagnostic algorithms that are used for solid nodules have to be modified for non-solid nodules.

Keywords: *Ground glass opacity; solitary pulmonary nodule; incidental pulmonary nodule; part-solid nodule; non-solid nodule; lung cancer screening.*

Introduction

A pulmonary nodule is defined as a spherical well-circumscribed radiographic opacity that is surrounded completely by aerated lung. There is no associated atelectasis, hilar enlargement or pleural effusion. Lesions that are larger than 3 cm are described as lung masses. As size has been shown to be important for classification of nodules (see below) the term 'subcentimetre nodule' has been used to describe lesions smaller than 10 mm. The term 'micronodules' is usually applied to very small nodules (<7 mm, <5 mm) which are almost always multiple and diffuse. If only one pulmonary nodule is detected, it is described as a solitary pulmonary nodule (SPN). If a nodule is detected in an examination performed for other reasons than a search for pulmonary nodules, it is called an 'incidental nodule'[1,2].

Algorithms in incidental SPN

Most of the information on the aetiology and the natural course of incidentally found small pulmonary nodules is derived from studies on lung cancer screening with unenhanced low-radiation dose computed tomography (low-dose CT) in asymptomatic smokers and to a lesser extent non-smokers and workers exposed to asbestos[3–7]. In these studies, at least one non-calcified pulmonary nodule was found in up to 66% of subjects, depending on the imaging technique (e.g. multidetector-computed tomography (CT) versus single-detector CT). It was also shown that >95% of these nodules were ≤10 mm in diameter and of these >95% were benign. Therefore, in order to avoid a high rate of invasive procedures for benign lesions in small nodules, algorithms were proposed that are based on mostly non-invasive strategies and, in particular, follow-up with low-dose CT[8–10]. During follow-up changes in size (or even better volume) are recorded. Nodules that decrease in size or resolve are obviously regarded as benign and no further follow-up is required. Nodules that increase in size are likely malignant, particularly, if the growth rate is typical of malignant growth. Most malignant tumors have been shown to double their volume (i.e. increase their diameter in spherical lesions by 26%) between 30 and 400 days. If malignancy is suspected, invasive procedures are usually performed to obtain a histological diagnosis (bronchoscopic, percutaneous or thoracoscopic biopsy). In addition, positron emission tomography (PET)-CT may be useful for small nodules of intermediate size (6–10 mm), as many malignant nodules show increased uptake of [^{18}F]fluorodeoxyglucose (FDG), whereas most benign nodules do not. PET-CT, however, is often

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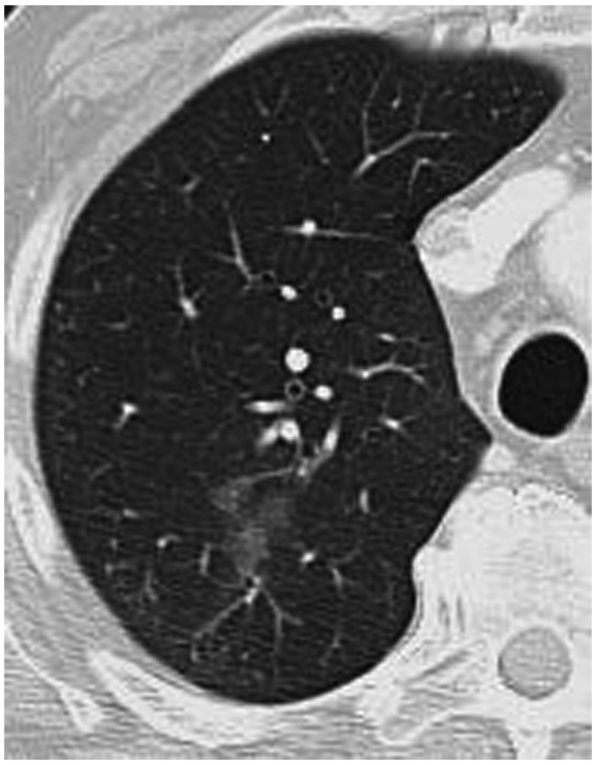

Figure 1 **Three non-solid nodules (ground glass opacities) in the posterior segment of the right upper lobe.**

negative in well-differentiated adenocarcinoma and bronchioloalveolar carcinoma (BAC) and may be positive in inflammatory nodules (e.g. sarcoid, tuberculosis).

Non-solid nodules

Most pulmonary nodules present as solid lesions (i.e. soft tissue density). These lesions exhibit the same density as pulmonary vessels. If the density of a nodule is lower than soft tissue attenuation, it does not obscure adjacent or transgressing vessels. These lesions are also known as ground glass opacities (GGOs). Part-solid nodules are characterised by a mixture of ground glass attenuation and solid components. Benign non-solid nodules are due to inflammation (eosinophilic pneumonia, cryptogenic organizing pneumonia), focal haemorrhage (pulmonary endometriosis, pulmonary trauma, post biopsy), and focal interstitial fibrosis[11]. Most benign non-solid lesions resolve during follow-up. Persistent non-solid lesions, in contrast, mostly represent neoplasms, predominantly malignant ones. In a study by Nakata *et al*.[12] 54% of persistent GGOs represented bronchioloalveolar carcinoma, 26% adenocarcinoma with mixed bronchioloalveolar carcinoma components and 21% atypical adenomatous hyperplasia.

The proportion of malignant lesions differs between solid, part-solid and non-solid lesions. In a study by Henschke *et al*.[13] 7% of solid, 63% of part-solid and 18% of non-solid lesions were malignant. The majority

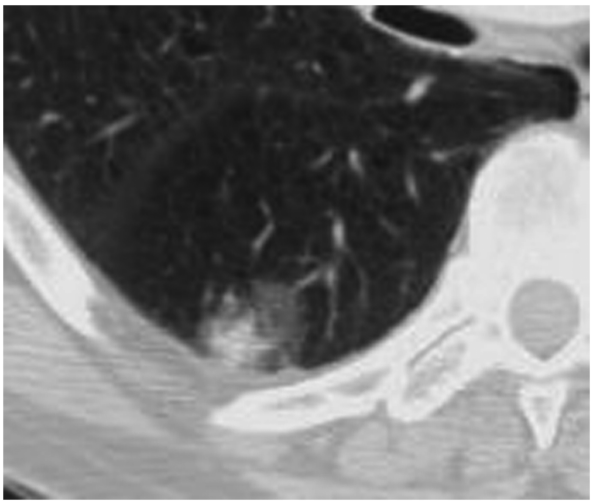

Figure 2 **Part-solid nodule in the apical segment of the right lower lobe. Peripheral ill-defined lesion with mixed density; the more peripheral component exhibits ground glass attenuation, whereas the more central part exhibits soft tissue (solid) attenuation.**

of part-solid and non-solid malignant lesions were bronchioloalveolar carcinomas and adenocarcinomas with bronchioloalveolar features. Noguchi *et al*.[14] have described a classification of adenocarcinomas based on their histology which is reflected by their prognosis and this is also reflected by their thin-section CT morphology. Types A and B represent bronchioloalveolar carcinomas, are characterised by a 100% 5-year survival rate and appear as non-solid lesions at thin-section CT, whereas types C, D, E and F represent more aggressive BACs or adenocarcinomas, exhibit part-solid or solid appearances with a less favourable prognosis[14].

Another non-solid lesion which was just recently defined is atypical adenomatous hyperplasia (AAH). This lesion is recognized as a separate entity which in itself is not malignant but may be a precursor of adenocarcinoma[11]. It is characterised by proliferation of atypical cuboidal or columnar epithelial cells along the alveoli and respiratory bronchioles without invasion of the stroma or adjacent structures. At CT, AAH usually appears as small pure ground glass opacity.

Algorithms in non-solid nodules

Most of the recommendations for the management of solid nodules[8,10] also apply to non-solid and part-solid lesions. For example, the risk of malignancy should be estimated, previous imaging should be reviewed, and if growth is detected biopsy should be performed. There are, however, some recommendations unique to non-solid or part-solid nodules:

– If such a nodule is malignant the underlying lesion is likely to be bronchioloalveolar carcinoma

or adenocarcinoma with bronchioloalveolar features.

- These may grow more slowly than other malignant tumors. Therefore, the recommendation of follow-up after 3, 6, 12 and 24 months and no further follow-up when no growth is demonstrated in 2 years should not be applied to non-solid and part-solid lesions. These require longer follow-up to exclude growth for several years. Because of the cumulative radiation exposure, dose levels during follow-up should be as low as possible[8].
- As bronchioloalveolar carcinoma and adenocarcinoma with bronchioloalveolar features may be negative at PET, examination with PET-CT should not be performed routinely as a negative result does not exclude malignancy.

Conclusions

Non-solid pulmonary nodules are more likely malignant than solid nodules. If malignant they are usually due to atypical adenomatous hyperplasia and bronchioloalveolar carcinoma. These lesions tend to grow more slowly than other malignant pulmonary lesions and are often not hypermetabolic at FDG-PET. Therefore, follow-up to exclude growth in non-solid nodules needs to be longer than in solid lesions and PET-CT is not appropriate to rule out malignancy in non-solid nodules.

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