Is There an Ideal Diagnostic Algorithm in Solitary Pulmonary Nodules?

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A solitary pulmonary nodule (SPN) is radiologically defined as a single lesion that is <3 cm in diameter, surrounded by lung parenchyma and without associated adenopathy or atelectasis [1, 2]. The distinction between SPNs and larger nodules, called masses, is based on their higher probability of malignancy, which requires a more aggressive approach with prompt resection usually advisable.

Most SPNs are incidental findings at chest X-ray (CXR) or computed tomography (CT). Older studies showed that SPNs are evident in 1 of 500 CXRs, and the widespread use of CT and spiral CT has increased the detection rate of SPNs [2].

Although most SPNs are benign, the incidence of cancer in SPNs ranges from 10 to 70% [3]. The probability of malignancy is higher in heavy smokers with haemoptysis, higher age, larger nodule size or previous malignancy [4]. The differential diagnosis of an SPN includes neoplastic, inflammatory, vascular, traumatic and congenital lesions, and, less frequently, rheumatoid nodules, granulomas and sarcoidosis [1]. The main concern in a patient presenting with an SPN is to reach an accurate diagnosis of malignancy, since an early detection enables a better prognosis, while avoiding the morbidity and mortality associated with thoracotomy in those having a benign disease. Different diagnostic algorithms have been proposed for the SPN, but a standard clinical strategy has not been identified yet.

In some cases CXR and CT may present features that suggest a benign disease, such as the presence of calcification (central, diffuse or popcorn patterns) in the context of the nodule or a low growth rate (stability over 2 years). A malignant nature may be suggested by the 'corona radiata' sign (fine linear strands extending 4–5 mm outward from the nodule) or the presence of stippled or eccentric calcification patterns [1, 4]. Magnetic resonance imaging (MRI) has a very limited role in the evaluation of SPNs, although it can be beneficial in patients who do not tolerate intravenous contrast [2]. Overall, conventional imaging often fails to provide conclusive information regarding the nature of an SPN, as many nodules are not calcified, and often there are no previous CXRs or CT scans to review for comparison.

Positron emission tomography (PET) has become a commonly performed imaging modality in many human tumours, as the radiotracer most frequently used, [¹⁸F]fluorodeoxyglucose (¹⁸F-FDG), enters highly metabolic tumour cells revealing the sites of active disease. Since functional abnormalities may occur earlier than anatomical changes, PET imaging can contribute to a more accurate definition of areas of malignancies, even outside the thorax, therefore providing staging information on whole-body PET imaging. Moreover PET has a higher diagnostic accuracy than CT in detecting lymph nodal involvement [3]. False PET results may be due to lesion size smaller than the PET spatial resolution (about

5 mm), low FDG uptake (carcinoids, bronchoalveolar carcinoma) or a specific FDG uptake (infectious or inflammatory processes) [2]. The use of FDG-PET for evaluating SPNs is well established. A meta-analysis of pulmonary lesions studied by FDG-PET was done by Gould et al. [5] in 2001: in 1,474 cases of focal lesions of any size the FDG-PET sensitivity and specificity for malignancy were 96.7 and 77.8%, respectively. Recent papers [6, 7] reported that PET sensitivity and specificity for focal malignant lung nodules range between 79–93 and 65–77%, respectively.

Other nuclear medicine methods have been employed for the evaluation of SPN, and in particular depreotide single-photon emission CT (SPECT) has been suggested. This technique is based on a somatostatin analogue (depreotide) scintigraphy. A recent paper by Halley et al. [8] compared the value of FDG-PET and ^{99m}Tc -depreotide SPECT in the diagnosis of SPN in 28 patients. Overall FDG-PET and ^{99m}Tc -depreotide SPECT were found to be equally sensitive (92.3%) for large and equally specific (85.7%) for small SPNs. The reported higher sensitivity of FDG-PET in small-size (<1.5 cm) SNPs is partly due to the great differences in spatial resolution between PET and SPECT. Moreover the precise mechanism of depreotide uptake in tumour cells is not completely clear, and there is an ongoing debate about whether this is due to somatostatin receptors on tumour cells or to tumour-infiltrating lymphocytes [9]. The evidence of somatostatin receptors in non-small cell lung cancer cells is still controversial, while there are no data regarding their expression profile in adenocarcinomas [8] that some authors reported to be falsely negative in depreotide tests [8, 10]. A potential advantage of SPECT over PET could be the higher accuracy in detecting carcinoid tumours that may not be detectable at FDG-PET scan, but the major diagnostic problem in the evaluation of SPN concerns the identification of lesions <1 cm. Halley et al. [8] showed that FDG-PET is superior to depreotide SPECT in the detection of lesions <1.5 cm in diameter, with an accuracy of 91.7 versus 83.3% and a sensitivity of 100 versus 80%, while they presented the same specificity of 85.7%. In the detection of SPNs <1 cm in diameter, Herder et al. [6] reported a sensitivity of FDG-PET of 93% and a specificity of 77%.

In the study by Naalsund et al. [11], published in the present issue of *Respiration*, the problem of non-conclusive data regarding falsely negative SPECT scan is discussed. While falsely positive lesions are further investigated, falsely negative results may be left untreated. Although the authors report that depreotide SPECT and

FDG-PET provide overall comparable diagnostic accuracy, the number of cases in which both exams were performed is limited, not allowing to derive data for larger patient samples, especially if presenting with nodules <1 cm in diameter.

Despite the fact that the SPN still remains an open diagnostic challenge for the clinician, FDG-PET is a non-invasive imaging modality that provides good accuracy in the early detection and in the diagnosis of SPNs. FDG-PET is particularly useful and reliable in the evaluation of lesions <1 cm that are not accurately visualized by other nuclear medicine imaging modalities, including depreotide SPECT. Moreover PET provides whole-body staging information with a direct impact on clinical management. When PET results are coupled with pretest factors, the diagnostic accuracy is greatly increased [12]. If the PET scan is negative, a follow-up with high-resolution CT is warranted, while those presenting with positive lesions are candidates for surgery.

In conclusion we retain that the proposed algorithms for studying SPN, based on cost-effectiveness, are still valid [12]. Recent data regarding the usefulness of depreotide SPECT have never demonstrated better results of this approach in comparison to FDG-PET, while it is likely that depreotide SPECT is less accurate in smaller nodules. Therefore at present depreotide SPECT may only play a minor role in the diagnostic work-up of patients with indeterminate FDG-PET scanning. Of course depreotide SPECT may be important in case of a lack of PET facilities.

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