The contribution of conventional nuclear molecular imaging in characterizing the nature of a growing solitary pulmonary nodule. Report of a case

**Abstract**

The solitary pulmonary nodule (SPN) is a relatively common imaging finding, often representing a diagnostic challenge. Radiological appearance, growth rate calculation during follow up and probability of malignancy assessment by the Bayes’ theorem are widely used for identifying the nature of a SPN. Molecular imaging by fluoro-18 deoxy glucose positron emission tomography has revolutionised non-invasive diagnosis of lung cancer, but the low-cost, widely available conventional nuclear imaging modalities still remain valid in the field. We present a case of a growing SPN in a middle-aged male smoker. Growth rate assessment by sequential computed tomography (CT) scans, over a follow up period of five years, was suggestive of benign histology, while Bayesian analysis warranted histological confirmation of the nodule’s nature. Imaging by both labelled somatostatin analogue technetium 99m-depreotide ($^{99m}$Tc-depreotide) and thallium 201 - chloride was almost exclusive of malignancy. The nodule was excised and histology showed a pulmonary hamartoma. We briefly discuss the relative role of invasive and non-invasive methods, with emphasis in conventional radionuclide molecular imaging, for the identification of the nature of SPN.

**Introduction**

The solitary pulmonary nodule (SPN) is a relatively common imaging finding and often represents a challenging diagnostic problem. One of the most powerful discriminative criteria concerning the malignant or benign nature of a SPN is growth rate assessment by serial chest radiographs (CR) or computerised tomography (CT) scans [1]. In contrast to anatomical radiologic imaging, the diagnostic power of radionuclide methods relies upon functional characterization of tissues. Thallium 201 - chloride ($^{201}$TlCl), a well known “tumor localising” agent, indicates the presence of viable neoplastic tissue and has been widely used for the diagnosis and management of various malignancies, including lung cancer [2]. A recently introduced radionuclide technique dedicated in characterizing SPN is technetium 99m-depreotide ($^{99m}$Tc-depreotide) single photon emission tomography (SPET) imaging. Depreotide is a synthetic somatostatin analogue, which has the advantage of $^{99m}$Tc labeling, resulting in superior imaging performance and favorable dosimetry. Due to high sensitivity and negative predictive value, its diagnostic contribution lies mainly in exclusion of malignancy [3]. We describe a case of a growing SPN, imaged by both radiologic and nuclear medicine methods, which offers an example of successful application of functional imaging in non-invasive SPN characterization.

**Description of the case**

A 40-year-old male smoker with unremarkable previous medical history was hospitalised for community-acquired pneumonia. Routine CR and CT disclosed a 1.1 cm spherical SPN of the right upper lobe (Fig. 1), and the patient was advised to have regular radiological follow up. Five years (62 months) later he underwent a CT scan, in which the diameter of the SPN had increased to 1.6 cm (Fig. 2). The lesion had smooth borders, solid texture and no signs of calcification or fat. No lymphadenopathy or other pathology was detected.

Taking into account the increase in size, the history of smoking, the age of the patient and the CT findings, the probability of malignancy was calculated by Bayesian analysis, as de-
scribed by Gurney et al [4, 5]. The derived probability was 32%, an intermediate value warranting further investigation.

The time a tumour takes to double its volume, i.e. the doubling time (DT), was also calculated for our patient’s nodule from measurements of base line and follow up CT scans [6]. Measured diameters (D) from the first and second CT scan, were \(D_1 = 11\) mm and \(D_2 = 16\) mm, respectively. Given that the volume \(V\) of a sphere is: \(V = \frac{4}{3} \pi (D/2)^3\), the calculated volumes are \(V_1 = 697\) mm\(^3\) and \(V_2 = 2144\) mm\(^3\), for the first and second CT scan, respectively, which shows that the nodule has tripled its volume in five years. However, the derived doubling time was: \(DT = \frac{t \ln 2}{\ln(V_2/V_1)} = 1146\) days, a value clearly characterizing benign lesions [7, 8] \(t:\) the time between the CT scans, i.e. 62 months or 1860 days.

Before any invasive investigation, the patient underwent a \(^{99m}\)Tc-depreotide scan. Three hours after intravenous (i.v.) injection of 740 MBq of \(^{99m}\)Tc-depreotide (NeoSpect®, Amersham Health®) a SPET study of the thorax was performed. A single-head \(\gamma\)-camera (Toshiba GCA-602A/SA), equipped with a low-energy general purpose collimator, was used. Acquisition was performed in 3600 step-and-shoot circular orbit, with 60 projections of 30 sec duration each on a 64x64 pixels matrix. Raw data were processed by means of iterative reconstruction and sections at three reference planes were obtained. The study was negative for somatostatin receptor (SSTR) detection in the nodule, i.e. no focus of increased uptake of \(^{99m}\)Tc-depreotide over the surrounding parenchyma, corresponding to the investigated CT lesion, was evident (Fig. 3A). Four days later the patient underwent a two-phase \(^{201}\)TI-Cl SPET study. Twenty minutes and three hours after i.v. injection of 111 MBq of \(^{201}\)TI-chloride, a thorax SPET study with the same acquisition parameters was performed. No abnormal accumulation of the radiotracer was evident in the SPN or elsewhere within the thorax (Fig. 3B).

Despite both negative radionuclide scans, mainly because of the patient’s anxiety and, to a lesser extent, the results of Bayesian analysis, a biopsy for histological confirmation of the lesion’s nature was decided. As the location of the nodule (posterior segment of the right upper lobe) was not suitable for CT-guided fine needle aspiration (FNA), thoracotomy and surgical excision were performed. Histology showed a pulmonary hamartoma, consisting of cartilaginous and adipose tissue. Two years later the patient is well and has a negative follow up CT.

**Discussion**

The SPN, defined as a nodule smaller than 3 cm surrounded by healthy lung parenchyma, without evidence of lymphadenopathy, is a relatively common imaging finding (1 in 500 unselected CR) [9]. SPN, if malignant, corresponds mainly to stage I lung carcinoma and surgical treatment at this early stage is associated with relatively good prognosis and a survival rate of 60%-70% at 5 years [10]. Therefore, early and accurate discrimination between malignant and benign SPN is crucial.

For the differential diagnosis of SPN a number of morphological criteria have been adopted in CR and CT imaging, based on size, shape (borders and cavitations), composition (presence and pattern of calcification and presence of fat) and rate of growth (stability for 2 years is considered evidence of benign histology) [10-12]. However, these criteria are often inadequate for the excluding malignancy, frequently necessitating invasive procedures [13]. The main reason for this drawback is that anatomical imaging methods like CR and CT, primarily describe morphological features, which may not closely correspond to the biological status of a pulmonary nodule.

The contribution of nuclear medicine in the diagnostic work-up of SPN is based on functional imaging of specific
PET) and comparison with impact of lung cancer [15]. However, despite the overwhelming imaging test in the diagnosis and management of patients with lung cancer [15]. However, despite the overwhelming impact of $^{18}$F-FDG PET in clinical oncology, head-to-head comparison with $^{99m}$Tc-depreotide and $^{201}$TlCl revealed a similar diagnostic performance regarding the characterisation of SPN [16-19]. Besides, conventional $\gamma$-camera systems and radiopharmaceuticals are of lower cost and wider available in comparison to $^{18}$F-FDG PET.

Invasive diagnostic procedures are reliable in experienced hands, but they are not always diagnostic and they do not lack complications. Bronchoscopic biopsy may be non-diagnostic in as much as 25% [20]. Transthoracic CT guided biopsy has been reported as non-diagnostic in 10%-15% of patients, with a frequency of pneumothorax ranging from 5%-61%, necessitating hospitalization in 1.6%-17% of the cases [21]. Thoracoscopy is very accurate but with a complication rate of 14% and mortality rate rising up to 4.5% [22]. When a definite diagnosis cannot be reached despite the combined use of the above mentioned techniques, thoracotomy and excision biopsy is mandatory. Although thoracotomy has a therapeutic potential, it shares the morbidity and mortality of a major surgical procedure.

Pulmonary hamartomas are developmental malformations representing the most common benign tumor of the lung and comprising 5.7% of SPN [23]. They most often present as peripheral SPN in CR or CT of asymptomatic adults. Histologically, they usually contain cartilage, fat, fibrous tissue and epithelial components. Calcification is observed in up to 30% of cases, often with a characteristic “popcorn” appearance. The presence of fat and calcification on a CT scan are almost pathognomonic for hamartomas and allows for a safe diagnosis to be made. On serial scans, hamartomas may show some degree of enlargement but they never undergo malignant transformation [24].

In our patient, failure of CT scan to demonstrate calcification and fat, despite their histologically proven presence, combined with the results of Bayesian analysis, raised the suspicion of malignancy. Actually, about 50% of nodules >8 mm are malignant and it has been proposed that they should undergo CT-guided fine needle aspiration (FNA) biopsy or PET scan with $^{18}$F-FDG, if available [13].

Calculation of the doubling time or the growth rate of the nodule by serial CT scans is substantial for the diagnostic work-up of an enlarging SPN [6]. It has been shown though, that three-dimensional tumor growth can be asymmetric and may not always be accurately represented by two-dimensional measurements [7]. The nodule of our patient had an almost spherical configuration and probably a spatially uniform growth pattern, so that volume calculation as a function of the maximum measured diameter might be valid. The calculated DT of 1146 days is a definitely benign figure, as cut-off values between 395 and 465 days have been reported [7, 8].

Negative $^{99m}$Tc-depreotide and $^{201}$TlCl scans are ‘straight-forward’ in their interpretation in tissue characterization. The presence of SSTR has been confirmed in numerous malignancies and the surrounding tissues [25], but also in many benign conditions such as granulomas and inflammatory lesions [26]. Accordingly, $^{99m}$Tc-depreotide scan is very sensitive for the presence of SSTR, leading to a very high (>97%) negative predictive value but only to a moderate specificity for malignancy [3]. The negative $^{201}$TlCl scan was also consistent with the non-malignant nature of the nodule [2]. The low uptake of $^{201}$TCl might also reflect the limited cellularity of fat and cartilaginous tissue, present in our patient’s SPN, a condition observed in other types of cartilage-containing tumours as well [27].

As both scans were negative, no quantitative approach of the data was used (tumour to background ratio), that could further help in scan interpretation, in case of positivity. According to our experience, as well as the experience of other researchers [2, 28], quantitative analysis of the images increases specificity by eliminating false positive results, thus enhancing diagnostic accuracy of the tests. In our patient, despite the smoking history and the moderate enlargement of the lesion, the radionuclide scans were negative and almost excluded malignancy, as was confirmed by histology.

In conclusion, our case offers a histologically documented example of successful application of conventional nuclear molecular imaging in non-invasive SPN characterization. It is the authors’ belief that, although $^{18}$F-FDG PET has much improved oncological imaging in the field of lung cancer, functional pulmonary tumor characterization may also be achieved by means of conventional, low-cost, widely available $\gamma$-camera imaging systems and radiopharmaceuticals. A formal comparison might further define the cost-effectiveness aspect of PET versus conventional $\gamma$-camera imaging, in SPN characterization.

Bibliography
Case Report


