INTRODUCTION

A solitary pulmonary nodule (SPN) is usually found on a chest radiograph or CT scan of the chest and is defined as a single round or oval increased opacity that is isolated in the pulmonary parenchyma and is not associated with lymphadenopathy, atelectasis or pneumonia [1-2] (Fig. 1a, 1b). It corresponds usually to a spherical lesion that is few millimeters and up to 3 cm in diameter. Lesions that are greater than 3 cm in diameter are considered to be masses and most likely due to a malignancy. While lesions that are less than 1 mm can be detected on today’s CT scans, noncalcified lesions that are less than 5 mm in size are not easily visualized on chest X-rays. The driving motivation in detecting, evaluating and managing a solitary pulmonary nodule is the ability to diagnose lung cancer in its early state (stage 1A) and therefore to be able to offer a chance for cure. In the United States alone, more than 150,000 patients per year are found to have a SPN on their chest radiographs [3]. Many more nodules are detected on the CT scans of the chest, most of the time found incidentally but often posing a diagnostic dilemma since they have multiple benign and malignant causes.

ETIOLOGY

Most SPNs are benign and represent a granuloma from a prior infectious disease. They are often related to prior fungal (histoplasmosis, coccidioidomycosis, blastomycosis, etc.) and bacillary (tuberculosis) disease. They are also related to sarcoidosis, granulomatous disease, and inflammatory conditions such as Wegener’s granulomatosis. 

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ABSTRACT: The solitary pulmonary nodule is a common lesion that has multiple benign and malignant causes and when detected often creates a diagnostic challenge. Such a challenge is framed on one side by the need to detect and diagnose lung cancer or other malignancies at an early manageable stage and on the other side by the need to restrain from unnecessary intervention on benign lesions. The article will review the current approach in identifying, evaluating and managing the solitary pulmonary nodule in which imaging and the radiologist play a pivotal role.

Figure 1

a. PA view of the chest on a digital chest radiograph obtained on a 43-year-old asymptomatic woman demonstrates a 9 mm nodule in the right mid lung (arrow).
b. A CT scan of the chest was obtained to further evaluate the nodule. An axial image through the lesion demonstrates a 9 mm smoothly marginated and noncalcified nodule in the posterior aspect of the right lower lobe (arrow). Based on the chest X-ray and CT appearance, the lesion is undeterminable in nature. Follow-up studies within a 2-year period showed no interval change in the size or appearance indicating a benign process (post-infectious granuloma).
as per aspergillosis, cryptococcosis), tuberculous, bacterial or parasitic infection. Noninfectious benign causes include: hematomas, sarcoidosis, Wegener’s granulomatosis, and rheumatoid arthritis or arterial venous malformations. Approximately one third of SPNs are due to a primary bronchogenic malignancy. In one fifth of the cases the lesion is due to a solitary metastasis [4-6] (Table I).

DETECTION

A solitary pulmonary nodule is detected in approximately one in 500 chest radiographs and one in 100 chest CTs. A higher number of cases are detected in endemic areas where fungal disease is prevalent (e.g. histoplasmosis in the Ohio Valley, coccidioidomycosis in southwestern U.S.). The size of the lesion, its density and its location within the lung parenchyma are among the factors that influence its detection. Lesions that are less than 5 mm or that are not solid i.e. ground glass opacities (GGOs) can be easily missed on chest radiographs. Sizeable lesions can also be missed if they are located in an area in which other thoracic structures obscure them. Such so-called hidden areas of the lungs include the apices and the regions behind the hila, the heart or diaphragm (Fig. 2a, 2b). Because of its high spatial and contrast resolution and its ability to display the lung parenchyma in a cross-sectional manner free of superimposed structures, CT imaging allows to detect many more SPNs.

Driven by the need to detect lung cancer at an early stage, most of the research efforts and technical developments in thoracic imaging have focused on improving the detection of pulmonary nodules. Dual energy subtraction (DES), tomosynthesis and computer aided detection (CAD) softwares are some of the techniques and tools being tested to help the reader to detect pulmonary nodules that are difficult to visualize and can potentially be missed.

TABLE I
DIFFERENTIAL DIAGNOSIS OF SOLITARY PULMONARY NODULE

<table>
<thead>
<tr>
<th>BENIGN</th>
<th>MALIGNANT</th>
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<tr>
<td>POST-INFECTIOUS GRANULOMAS</td>
<td>Bronchogenic carcinomas</td>
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<tr>
<td>Histoplasmosis</td>
<td>Carcinoid</td>
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<tr>
<td>Tuberculosis</td>
<td>Metastasis</td>
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<td>Cryptococcosis</td>
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<td>Blastomycosis</td>
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<tr>
<td>Coccidioidomycosis</td>
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<td>Pneumocystis infection</td>
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<tr>
<td>Parasitic infection</td>
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<td>WEGENER’S GRANULOMAS</td>
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<tr>
<td>Sarcoidosis</td>
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<tr>
<td>Rheumatoid nodule</td>
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<td>Anthrosilicotic nodule</td>
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<td>Harmatomas</td>
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Chest Radiograph

In the field of imaging, the chest X-ray remains the most commonly ordered exam in any given medical institution and the SPN is often and first detected on such exam. Based on the appearance of the lesion and its density, one may reach a diagnosis without the need for further tests. A densely calcified nodule is diagnostic of a benign granuloma. A lesion with typical popcorn calcifications is highly suggestive of a hamartoma. Larger lesions with irregular/spiculated margins are highly suspicious for neoplastic

FIGURE 2

a. Chest PA of a 70-year-old smoker that presented with hemoptysis demonstrates changes of pulmonary emphysema and a vague opacity in the right apex obscured by the right clavicle and right first rib (arrow). Note the asymmetrical appearance of the apices with the right apex appearing denser than the left.
b. Concurrent CT scan of the chest demonstrates a 28 mm nodule with typical irregular and spiculated margins indicative of a neoplasm. Note the changes of centrilobular emphysema involving the apices. Biopsy of the lesion reveals a non-small cell bronchogenic carcinoma.
disease. But often the nodule shows none of these typical features and it is paramount that prior imaging studies are obtained for comparison to assess the age of the lesion, its stability or interval growth. With the advent of digital imaging, post-processing manipulation of the images can help to better visualize and analyze the SPN (Fig. 3a, 3b). Immediate access to the electronically archived comparison studies help to expedite the interpretation and management of the case allowing further testing if necessary in a timely fashion. Although not widely available, new technologies such as dual energy substraction and tomosynthesis are some of the new techniques being investigated and applied to chest radiographs in order to improve our ability to detect subtle pulmonary nodules.

By using different methods, both techniques attempt to improve the display of the pulmonary parenchyma free of superimposed rib structures that may obscure solitary pulmonary nodules. Also calcified benign nodules are more readily visualized when using DES. CAD programs are used as a second reader by bringing the attention of the reader to a region of interest that may represent a nodule or cancer (Fig. 4). When the chest radiograph and the prior comparison studies fail to help in determining the nature of the lesion, further evaluation by CT scanning will be the appropriate next step.

Chest CT
A CT scan of the chest would not only confirm the presence of an SPN and its exact location but would also allow characterization of the lesion based on its shape, contour and content [7]. It will also help in detecting other associated findings seen in both malignant and metastatic disease or confirm other benign features such as calcified lymph nodes in healed granulomatous disease. A CT scan of the chest is better suited at detecting the presence of calcium and its distribution within the pulmonary nodule. The presence of fat, necrosis or cavitation are all clues that can help in determining the nature of the lesion. While most studies are performed without the needs of intravenous contrast, post enhancement hemodynamic studies of the nodule can be useful.

**Figure 3.** a. Chest PA on a 62-year-old woman demonstrates a 1 cm round but vague opacity in the left retro-cardiac region (arrow). b. The retro-cardiac nodule is better visualized when the gray scale is inversed (arrow).

**Figure 4.** CAD program is applied on a chest radiograph of a 58-year-old woman. The circle initiated by the program is surrounding a 2.5 cm vague opacity in the right lower lung that corresponds to a lung carcinoma.
for the evaluation of lung cancer or arterial venous malformations.

**PET and PET/CT Imaging**

PET imaging using fluorodeoxyglucose (FDG) can play an important role in determining the metabolic activity of the malignant SPNs. In the cases of indeterminate nodules that are 8 mm or larger, PETor a combination of both PET and CT scan imaging offer a high degree of sensitivity (83%-97%) and specificity (69%-100%) in determining the nature of the nodule [8-9].

**MRI Imaging**

Magnetic resonance techniques are not ideal for imaging the lung parenchyma. Recently, contrast-enhanced dynamic studies of SPN have shown promises in differentiating between malignant and benign SPNs with an accuracy, specificity and sensitivity similar to that of CT [10-11].

**LOCATION**

SPNs of benign origin can be found anywhere in the lungs with no predilection for a particular location in the lungs. SPNs due to lung cancer occur most frequently in the upper lobes and more often in the right lung [12]. Adenocarcinomas are frequently located in the periphery of the lung while squamous cell carcinomas are more likely found in the central/medial aspect of the lungs [13]. The presence of pulmonary fibrosis or the type of cigarette smoking may also influence the site and development of such bronchogenic carcinomas [14].

**SPN CHARACTERIZATION**

**Size** (Table II)

The size of the SPN cannot be used as a predictor of benign or malignant disease [7]. The majority of the nodules smaller than 2 cm are of benign nature, but the larger the nodule the most likely it is to be malignant [15]. Retrospectively, lung cancers may be visible as early as in the millimeter stage. Sometimes benign lesions may reach a large size (Fig. 5). With a doubling time anywhere between 20 and 500 days, lung cancers will not be visible in their early life cycle (Table II). While today’s imaging methods cannot visualize three quarters of the life of the cancer, early lesions can be visualized retrospectively when they are at the millimeter stage (Fig. 6).

**TABLE III**

MORPHOLOGIC CHARACTERIZATION OF PULMONARY NODULE

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**TABLE II**

THE PROJECTED LIFE OF A CANCEROUS NODULE

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Microscopic Level</th>
<th>Gross Anatomic Level</th>
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<tbody>
<tr>
<td>0-10 days</td>
<td>CIS</td>
<td>Not visible</td>
</tr>
<tr>
<td>10-30 days</td>
<td>Inv. Ca</td>
<td>Not visible</td>
</tr>
<tr>
<td>30-90 days</td>
<td>Growth</td>
<td>Visible</td>
</tr>
<tr>
<td>90-180 days</td>
<td>Metastases</td>
<td>Visible</td>
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**TABLE III**

BENIGN

- Diffuse
- Central
- Ring-like
- Concentric
- Popcorn

SUSPICIOUS

- Stippled
- Eccentric

MALIGNANT

- Smooth-well defined
- Lobulated
- Irregular
- Spiculated

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**Figure 5.** A large left lower lobe 6 cm mass in a 70-year-old man shows typical features of a benign hamartoma with popcorn calcification (long arrow) and multiple fatty areas (short arrow).
Morphology (Table III)
The appearance of the margins is a more reliable predictor than the shape of the lesion. Benign SPNs typically have smooth and well defined margins. Irregular, lobulated or spiculated margins should raise the suspicion for malignancy [16].

Localized ground glass opacities can be due to both benign and malignant disease but the mixed high attenuation/solid nodules surrounded by a ground glass opacity are most likely due to neoplastic disease (typically adenocarcinomas with bronchoalveolar features) (Fig. 7, 8a, 9b). The presence of fat with or without the presence of calcifications is typical of a hamartoma (Fig. 10).

The presence and pattern of calcification help to differentiate between benign and malignant disease. Central, laminated and diffuse calcifications are the types...
Popcorn calcifications are typical of hamartomas (Fig. 5). Eccentric calcifications may represent a cancer engulfing a preexistent granuloma and therefore should be considered suspicious. Lung cancer may display amorphous calcifications [17-18]. Stippled or diffuse calcifications may be related to metastatic disease from a mucine secreting extra thoracic neoplasms. At the same time metastatic osteosarcomas or chondrosarcomas may have bone forming or cartilage forming pulmonary metastatic nodules which mimic calcified granulomas (Fig. 11).

Both benign and malignant SPNs may show central low attenuation areas due to necrosis. Air bronchograms and cavitations can be seen in both benign and malignant SPNs. Air bronchograms are seen in approximately half
of bronchoalveolar carcinomas [19]. While most cavitating cancers and necrosis occur in larger lesions, cavitating neoplasms such as a squamous cell carcinoma can be seen in lesions smaller than 3 cm. When a nodule displays no specific characteristics to help differentiate between a malignant or a benign cause, CT contrast-enhanced study may help differentiating between the two. While a nodule enhancement of less than 15 Hounsfield Unit (HU) has a strong positive predictive value for benign disease (90%), an enhancement of 15 HU or more is seen in 50% of the malignant nodules [20-21]. The diagnosis of an arterial venous malformation is evident when post contrast CT shows intense enhancement of the nodule often seen connected to draining and feeding prominent vessels.

An indeterminate nodule that is greater than 8 mm in diameter can be evaluated by PET imaging to demonstrate the metabolic activity of the lesion. While PET and PET/CT imaging have gained popularity for the staging and monitoring of known cancers, they can also play an important role in the initial evaluation of the indeterminate nodule (Fig. 12). With a specificity ranging from 83-97% and a sensitivity ranging from 69-100%, PET imaging not only can confirm the hypermetabolic activity of a suspected lung cancer but it can also detect unsuspected metastatic or nodal disease [9]. The limitations of PET scanning are related to its limited availability, high cost and its inability to accurately evaluate lesions less than 8 mm. False negative results are typically seen in the cases of lesions that have a low metabolic activity such as adenocarcinomas, bronchoalveolar carcinomas and carcinoid tumors while false positive results can be seen in lesions due to active inflammatory or infectious disease.

**GROWTH**

Growth or the lack of it is one of the most important factors that can determine the malignant or benign nature of the indeterminate SPN. It is well accepted that a nodule that is stable in size for a period of two years is considered to be of benign nature [22]. In the absence of prior imaging studies, it is proposed that serial imaging at 3, 6, 12 and 24-month time periods is a reliable way in assessing stability or interval growth. Slowly growing lesions with a low doubling rate or ground glass opacity due to slow growing bronchoalveolar carcinomas need longer follow-up studies. There are limitations in determining accurate growth rate in nodules that are smaller than one cm. Measurement of volume and volume changes is a more reliable mean than diameter measurement in assessing the
doubling rate of a lesion. With the advent of CT scanning, new software programs are now allowing for more precise automated volumetric measurement [23-24].

**RISK FACTORS**

The probability of malignancy in a particular patient can be determined by computing a series of clinical and radiological features (Bayesian analysis). They include the patient’s age, smoking history, symptoms such as hemoptysis and history of prior malignancies. Radiographic features include: size of the lesion, margin features and content characteristics [15]. Such consideration do not however include newer technologies such as PET imaging and dynamic CT techniques.

**MANAGEMENT OF THE SPN**

There is not a single or simple approach in the management of the SPN. The size and appearance of the lesion, the risk factors of the patient and the variety of the different diagnostic tools and techniques of variable accuracy are all factors that will influence the proper approach. There is a high probability of a benign SPN when the lesion has a benign pattern of calcification or shows no growth for at least two years. At the same time, there is a high probability of malignancy when the SPN displays irregular/spiculated contours or measurable growth. Such lesions can be further evaluated by transbronchial or transthoracic biopsy for tissue sampling and diagnosis confirmation (Fig. 13). With the advent of CT scanning and its increasing use for the purpose of screening, a large number of nodular lesions are now being detected. Most often the lesions are too small to characterize creating a diagnostic dilemma since they cannot be sampled and interval growth cannot be precisely evaluated. A recent statement from the Fleischner Society offers a guideline in managing such lesions. Such approach takes into consideration the patients risk factors and the recent developments in imaging techniques. Such guidelines apply for incidental nodules in patients that are 35 years old or more and without a history of infection, fever of unknown origin or suspected metastatic disease. Such guidelines do not apply to ground glass opacities since such lesions may have a very slow growth rate (Table IV).

**SUMMARY OF THE KEY POINTS**

When confronted with the discovery of a solitary pulmonary nodule, few key points need to be remembered.
- The majority or approximately two thirds of the lesions are benign granulomas.
- The presence of calcium or fat and/or the lack of growth within two years usually indicate benign disease.
- Lesions with spiculated or irregular contours indicate malignancy.
- Almost one third of the lesions are due to lung cancer and the likelihood of a single metastasis increases with a history of thoracic or extra thoracic malignancies.
- Lung cancer rarely occurs before the age of 40 but its likelihood increases with increasing age.
- Likelihood of lung cancer increases with the history of smoking, asbestosis and radon exposure, prior radiation treatment to the chest, pulmonary fibrosis, HIV and immunocompromised status.
- The majority of the SPNs that are 2 cm or less are benign but the likelihood of malignancy increases with size.
- A 5 mm spiculated SPN in a smoker is more likely a lung cancer than a 2 cm indeterminate SPN in a low risk patient.
- Nonenhancing lesions on dynamic CT indicate benign disease while hyper metabolic activity in PET scanning points to malignancy.

**ACKNOWLEDGEMENTS**

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**REFERENCES**

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TABLE IV
FLEISCHNER SOCIETY GUIDELINES

<table>
<thead>
<tr>
<th>MANAGEMENT/ FOLLOW UP</th>
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<tr>
<td><strong>LOW RISK PATIENTS</strong></td>
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<tr>
<td><strong>HIGH RISK PATIENTS</strong></td>
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<tr>
<td>Ø : No Change</td>
</tr>
<tr>
<td>☐ : No Further work up/follow up needed</td>
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**Consider: Dependent CT, PET &/or Ex**

**Guidelines apply for patients 35 years of age and older (< 35 yo = No FU)**

**Guidelines apply for incidental nodules (< 8 mm = No FU)**

**The site of the nodule is the average of its length and width**

**The risk (low vs. high) is based on hx of smoking and other risk factors**

**Ground glass nodules may require longer follow up to exclude incidental adenocarcinoma**

solitary pulmonary nodule. Chest Jan 2003 ; 123 : 89S-96S.