Evaluation of the Pulmonary Nodule

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Disclosures
I have no relevant financial relationships or conflicts of interest to disclose.

Solitary Pulmonary Nodule (SPN)
•SPN defined as radiographic opacity $\leq$ 3 cm in diameter with at least two-thirds of margins surrounded by lung parenchyma. (excludes lymph nodes, atelectasis and postobstructive pneumonia)
•Noted on: 0.09% - 7% of all chest radiographs. 8% - 51% of CT scans with prevalence of malignancy 1.1% - 12%
•Important to establish etiology in a timely manner
•If malignant, want to resect quickly, if possible
•If benign, do not want to put pt through unnecessary surgery.
Infectious
- TB (tuberculosis)
- HIV-associated pneumonia
- Lung abscess
- Fungal: aspergillosis, blastomycosis, cryptococcosis, histoplasmosis, coccidioidomycosis
- Parasitic: strongyloidiasis, echinococcosis
- Actinomycosis
- Malaria
- Neutropenic
- Septic embolus

Neoplastic
- Benign
  - Hamartoma
  - Chondroma
  - Fibroma
  - Lipoma
  - Fibrosarcoma
  - Neurofibroma

- Malignant
  - Lung cancer
  - Primary pulmonary carcinoma
  - Solitary metastasis
  - Teratoma
  - Leiomyoma

Differential Diagnosis of Solitary Pulmonary Nodules

Vascular
- Aneurysmal subarterial
- Pulmonary embolism
- Pulmonary artery aneurysm
- Pulmonary vein aneurysm
- Infection
- Congenital
- Bronchogenic cyst
- Lung sequestration
- Bronchoalveolar carcinoma

Inflammatory
- Rheumatoid arthritis
- Granulomatous with polyglandular (Sheringer)
- Microscopic polyangitis
- Sarcoidosis

Lymphatic
- Intralobular or subepithelial lymph node
- Lymphoma
- Outside lung fields
- Skin nodule
- Nipple shadow
- Hilar lymph nodes
- Pleural thickening, mass or fluid (pseudotumor [ie, localized fluid])

Miscellaneous
- Ruptured arteriovenous malformation
- Lipoid pneumonia
- Amyloidosis
- Mucoid impaction
- Pulmonary scar
- Infected bulla

Important Clinical Risk Factors
- Age
- Smoking History
- Family History
- Female Sex
- Emphysema
- Prior Malignancy
- Asbestos Exposure
Age as a Risk Factor

• Probability of malignancy rises with increasing age

35-39 years: 3 percent
40-49 years: 15 percent
50-59 years: 43 percent
>60 years: >50 percent

Clinical Evaluation and Considerations

• Thorough Hx is important:
  older age and smoking Hx = high risk of malignancy.
  Majority of SPNs in pt with prior malignancy are malignant.
  Most malignant SPNs with prior hx of cancer are primary lung rather than metastasis (exceptions: Sarcoma, Melanoma, Testicular)

• Conditions predisposing to lung cancer:
  Idiopathic Pulmonary Fibrosis (prevalence 9%-38%), Asbestosis, Scleroderma.

• Residence or travel to an endemic area of Fungal infections may suggest benign etiology: coccidioidomycosis, cryptococcus, histoplasmosis commonly present as SPN on CT scan.

Imaging Modalities

• Chest X-ray: Can visualize nodules as small as 5-6 mm, however, there is a high false negative rate.

• CT: Higher specificity and sensitivity because it can differentiate between 2 superimposed structures. Radiograph of choice for both follow up and to confirm chest x-ray finding.

• PET: Good for oncological diagnosis, staging, and assessment of response to therapy. High sensitivity and specificity for nodules > 8-10 mm. Good when there is discordant CT and pre-test probability results.
CT SCAN

• Imaging study of choice
• Thin section, 1 mm images
• Lung and mediastinal windows
• Lung shows edges
• Mediastinal shows solid components
• Low dose milliamperes second [mAs]<80

Important Radiographic Features

• Growth Rate
• Size
• Location
• Margin/Border/Edge Characteristics
• Calcification and Attenuation
• Cavitation
• Ground Glass Nodules

Growth Rate / Volume Doubling Time

• Doubling time for solid malignant SPNs is 20-400 days
• Majority malignant SPNs <100 days
• Volume doubling time >400 days usually benign
• Volume doubling time <20 days usually infectious
• Volume sphere = 4πr³/3
• Increase diameter of 26% represents doubling of volume
• Needs to be stable for 2 years (doubling time >730 days)
Solitary pulmonary nodule (SPN) doubling time. A 4-mm nodule can double in volume over a period of time but the diameter will increase only approximately 1 mm to 5 mm, which may not be reliably detected on the CT scan. However, an increase in a bigger mass is very well appreciated by just looking at the diameter on the CT scan.

Size as an Indicator of Malignancy

Location

- SPNs in upper lobes are more likely to be malignant
- Higher concentration of inhaled carcinogens in the upper lobes resulting from cigarette smoking
Margin Characteristics of SPNs

<table>
<thead>
<tr>
<th>Margin</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth</td>
<td>Suggests a benign lesion. However, may be malignant in up to one-third of cases.</td>
</tr>
<tr>
<td>Lobulated</td>
<td>A lobulated margin is highly predictive of malignancy, with a PPV of 80%. A few exceptions of benign SPNs that could have lobulated margins include lipoid pneumonia, focal atelectasis, tuberculosis, and progressive massive fibrosis.</td>
</tr>
<tr>
<td>Spiculated</td>
<td>A spiculated margin (the so-called corona radiata sign) is highly predictive of malignancy, with a PPV of 88% to 94%. A few exceptions of benign SPNs that could have spiculated margins include lipoid pneumonia, focal atelectasis, tuberculosis, and progressive massive fibrosis.</td>
</tr>
<tr>
<td>Ragged</td>
<td>Suggests growth pattern along the alveolar wall, lepidic pattern of adenocarcinoma.</td>
</tr>
<tr>
<td>Tentacle or polygonal</td>
<td>Seen in fibrosis, alveolar infiltration, and collapsed alveoli.</td>
</tr>
<tr>
<td>Halo</td>
<td>SPN surrounded by a “halo” of ground glass attenuation, also called the “CT halo sign.” Seen in aspergillosis, fungal infections, granulomatosis with polyangiitis (Wegener), and metastatic angiosarcoma. Other conditions that may produce a halo, due to its lepidic growth, include adenocarcinomas with overt invasion and are associated with poor prognosis.</td>
</tr>
<tr>
<td>Notches</td>
<td>SPN with notches or concavity in the margin is seen in some SPNs with tumor growth. These notches are frequently found in adenocarcinomas with overt invasion and are associated with poor prognosis.</td>
</tr>
</tbody>
</table>

SPN with a smooth border. A SPN with smooth borders may suggest benign etiology, although up to one-third of these lesions can be malignant.

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SPN with a lobulated margin suggests uneven growth and likely is malignant with a positive predictive value of 80%. Up to 25% of benign lesions such as hamartomas can have lobulated margins.

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SPN with spiculated margin (corona radiata sign). This is highly predictive of malignancy with a positive predictive value of 88% to 94%. Lipoid pneumonia, focal atelectasis, tuberculoma, and progressive massive fibrosis can have spiculated margins.

SPN with ragged margin suggests a growth pattern along the alveolar wall, as seen in adenocarcinoma with lepidic growth pattern.

SPN with polygonal margins, usually suggestive of a benign etiology. Such a pattern is seen in fibrosis, focal atelectasis, and alveolar infiltration.
SPN with surrounding halo and ground glass attenuation. This is seen in aspergillosis, Kaposi sarcoma, granulomatosis with polyangiitis (Wegener), and metastatic angiosarcoma. Adenocarcinoma can produce a halo due to lepidic growth.

Calcification and Attenuation

- Specific patterns of calcification suggest benign lesions: diffuse, central [bulls eye], laminated / concentric, popcorn
- Attenuation values >200 Hounsfield units indicates calcium in nodule
- Attenuation value between -40 and -120 Hounsfield units suggests fat (present in 60% of hamartomas)

Patterns of Calcification in SPNs

<table>
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<th>Pattern of Calcification</th>
<th>Etiology</th>
</tr>
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<tr>
<td>Laminated and concentric</td>
<td>Usually benign</td>
</tr>
<tr>
<td>Dense central core</td>
<td>Usually benign</td>
</tr>
<tr>
<td>Diffuse and solid</td>
<td>Usually benign</td>
</tr>
<tr>
<td>Popcorn</td>
<td>Hamartomas</td>
</tr>
<tr>
<td>Punctate</td>
<td>Malignant lesions: squamous, typical and atypical carcinoids, hepatic metastases, calcium, and metastases from bone, lung, breast, kidney, and desmoplastic fibroma.</td>
</tr>
<tr>
<td>Eccentric</td>
<td>Due to necrosis within the malignant nodule or engulfment of adjacent granuloma.</td>
</tr>
</tbody>
</table>
Benign Calcification Patterns

SPN with diffuse calcification as seen on (left) mediastinal windows and (right) lung windows, usually suggest benign etiology.

SPN with central calcification usually suggestive of a benign etiology. It should be noted that it is quite uncommon to come across a truly central calcified nodule.
SPN with laminated calcification, usually suggestive of a benign etiology.

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An attenuation value between −40 and −120 Hounsfield units suggests presence of fat in a SPN. Fat is present in up to 60% of hemartomas. Also seen with lipoid pneumonia, metastatic liposarcoma, and renal cell carcinoma.
Cavitation

- Seen in necrotic malignant SPNs such as squamous cell carcinoma
- Also benign lesions such as abscesses, infectious granulomas, vasculitis, Langerhans cell histiocytosis and pulmonary infarction
- Cavity wall thickness <5 mm – benign
- Cavity wall thickness > 15 mm and irregular - malignant
- Small lucencies in SPN ("bubbly lucencies") – benign or malignant

SPN with cavitation is seen in necrotic malignant SPNs such as squamous cell carcinoma. It may also be seen in benign SPNs such as abscesses, infectious granulomas, vasculitides, lymphoid interstitial pneumonia, early Langerhans-cell histiocytosis, and pulmonary infarction.

SPN with bubbly lucencies. Bubbly lucencies can be seen in adenocarcinoma in situ (previously known as bronchoalveolar carcinoma), pulmonary lymphoma, sarcoidosis, round pneumonia, and organizing pneumonia.
CT-PET scanning

- Glucose analog tagged with a positron-emitting isotope of fluorine (FDG) is introduced into the body and taken up by biologically active tissues.
- 3D images are then constructed of the body to see areas that take up tracer.
- Malignant cells are more metabolically active and take up more glucose than other tissues.
- Metabolic activity is quantified using the standard uptake value (SUV).
- Mean SUV > 2.5 is cutoff.

FDG-PET Advantages

- Accurate noninvasive evaluation for SPN.
- Sensitivity 87%, Specificity 83%.
- Assesses hilum and mediastinum.
- Whole-body image detects extrapulmonary tumors.
- Ability to stage known lung cancer.

Combined PET-CT scan showing $^{18}$F-2-deoxy-2-fluoro-D-glucose-avid SPN. Malignant cells are more metabolically active and import glucose more avidly than other tissues.

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PET limitations

• PET is only recommended for nodules > 8-10 mm because the sensitivity decreases for smaller nodules. This means a malignant nodule could potentially be missed on PET scan if too small.

• Adenocarcinoma can be missed on PET because it can have low metabolic activity

• With subsolid nodules, PET can not reliably differentiate between inflammatory and malignant nodules because inflammatory nodules paradoxically can uptake more tracer resulting in a higher SUV.

Factors Taken Into Consideration to Determine the Probability of Malignancy

Gurney et al
Bayesian analysis
www.chestx-ray.com

1. Age
2. Smoking (ever vs never, moderate vs heavy)
3. Hemoptysis
4. History of prior malignancy
5. Nodule diameter
6. Location
7. Subsolid characteristic
8. Growth rate
9. Cavity wall thickness
10. Calcification
11. Contrast enhancement on CT scan > 15 HU
12. PET scan

Swensen et al
Mayo Clinic Model

1. Age
2. Smoking history (ever vs never)
3. History of previous malignancy > 5 y ago
4. Presence of spiculation
5. Upper lobe location

Gould et al
VA Model

1. Age
2. Smoking history (ever vs never)
3. Nodule diameter
4. Time since quitting smoking

Determining pre-test probability

Swensen et al, Mayo Clinic Model

Probability of Malignancy = \( e^x / (1+e^x) \)

\[ x = -6.8272 + (0.0391 \times \text{age}) + (0.7917 \times \text{smoke}) + (1.3388 \times \text{cancer}) + (0.1274 \times \text{diameter}) + (1.0407 \times \text{spiculation}) + (0.7838 \times \text{location}) \]

*Note: Natural log. If smoker = 1, if spiculations = 1, if upper lobe = 1, diameter in millimeters, and age. If none then 0.*
**Pulmonary Nodules**

- **Solid**
  - completely obscure lung parenchyma
- **Subsolid**
  - Pure Ground Glass
  - Partly Solid Ground Glass
  - focal nodular areas of increased lung attenuation through which normal parenchymal structures such as airways, vessels, and interlobular septa are visible

**Nodule Types**

- **Solid**
- **Subsolid**
  - Pure Ground Glass
  - Part-Solid

**Ground Glass Nodules**

- Frequently represent spectrums of adenocarcinomas
- Atypical adenomatous hyperplasia, adenocarcinoma in situ, minimally invasive adenocarcinomas, lepidic predominant adenocarcinomas
- Slower growth rate (VDT 567±168 days)
- Still significant possibility of cancer even after 2 years of stability
- PET scan fails to demonstrate activity
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Figure 2

Figure 3

Figure 4
United States Preventative Services Task Force (USPSTF) for Lung Cancer Prevention

- Low dose CT Chest Yearly
- Age 55-80
- 30 pack year history of tobacco
- Currently smoke or quit within last 15 years
- Stop if not smoked 15 years
- Stop if develop health problem with limited life expectancy or inability to have curative lung surgery
- Screening was associated with significant reductions in lung cancer (20%) and all-cause (6.7%) mortality

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Endobronchial Ultrasound (EBUS)

Virtual Navigational Bronchoscopy (VNB)

Electromagnetic Navigational Bronchoscopy (ENB)
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Diagnostic Techniques

Video Assisted Thoracoscopy / VATS

Conclusion

• There are many factors to consider when working up a pulmonary nodule including but not limited to medical Hx, risk factors, radiographic characteristics, and overall clinical presentation.

• Consideration of these factors helps to stratify the pt into likely malignant vs. likely benign and will help with choosing the best diagnostic options for that patient.

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