The Solitary Pulmonary Nodule Revisited

Eric Bensadoun MD
Division of Pulmonary, Critical Care, and Sleep Medicine
Multidisciplinary Lung Cancer Clinic
University of Kentucky

Definitions

- **Solitary Pulmonary Nodule (SPN)**
  - A discrete, more or less rounded opacity < 3 cm in diameter, completely surrounded by lung parenchyma without associated adenopathy, atelectasis or pneumonia

- **Lung Mass**
  - A discrete more or less rounded opacity > 3 cm in diameter
**Common Causes of SPNs**

<table>
<thead>
<tr>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary lung carcinoma</td>
<td>Infectious Granulomas</td>
</tr>
<tr>
<td>Solitary metastasis</td>
<td>Hamartoma</td>
</tr>
<tr>
<td>Carcinoid tumor</td>
<td>Round pneumonia</td>
</tr>
<tr>
<td>Primary lung lymphoma</td>
<td>A-V malformation</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid nodule</td>
</tr>
<tr>
<td></td>
<td>Wegener’s granulomatosis</td>
</tr>
<tr>
<td></td>
<td>Pseudonodule</td>
</tr>
</tbody>
</table>

**SPN: Prevalence of Malignancy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Total # of nodules</th>
<th>Malignant Nodules (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steele et al (1963)</td>
<td>887</td>
<td>36</td>
</tr>
<tr>
<td>VA Cooperative Study (1975)</td>
<td>1134</td>
<td>32</td>
</tr>
<tr>
<td>Toomes et al (1983)</td>
<td>955</td>
<td>49</td>
</tr>
<tr>
<td>Rubins et al (1996)</td>
<td>370</td>
<td>79</td>
</tr>
<tr>
<td>Early Lung Cancer Action Project (ELCAP)</td>
<td>233</td>
<td>8.6</td>
</tr>
<tr>
<td>Mayo Clinic Study (2002)</td>
<td>782</td>
<td>1.8</td>
</tr>
</tbody>
</table>
SPN Management: An Approach Based on the Probability of Malignancy

Calculating Probability: Art or Science?

- Informal estimate by clinician or radiologist based on risk factors, test results and experience
- Bayesian analysis
  - Uses likelihood ratios of various risk factors and imaging results to calculate the probability of cancer
  - Bayesian models assume variables are independent i.e., no interaction
  - Probability can be determined using Bayesian model at this free website: www.chestx-ray.com
- In general, assessments by prediction models are similar to those of experienced clinicians
SPN: Risk Assessment

- Assess the risk of malignancy in each individual patient based on H+P and simple non-invasive tests:
  - Clinical risk factors
  - Radiographic finding on CXR and/or CT
- Use additional testing if necessary
  - Contrast enhanced CT and/or PET
  - Transthoracic needle biopsy or bronchoscopy
- Based on the above risk assessment decide on the next step:
  - VATS or thoracotomy
  - Close observation with serial radiographic imaging

Clinical Risk Factors for Ca

- Age
  - Risk of malignancy increases with age
  - Malignancy very uncommon in patients < 35 yrs old
- Smoking history
  - Risk increases with # pack-years
  - Ex-smokers still at risk
- Prior history of malignancy
  - 70-80% of SPNs are malignant (solitary metastasis or lung primary)
- Symptoms
  - Most patients are asymptomatic
SPN: Imaging

- CXR/CT characteristics
  - Size
  - Edge/margin characteristics
  - Presence of calcification and/or fat
  - Growth rate

Prevalence of Malignancy Based on Size

Calcifications in SPNs

• The presence of a benign pattern of calcification is indicative of benignity (LR=0.01)

• Detection of calcifications on CXR (Berger et al. AJR 2001)
  • Sensitivity: 50%
  • Specificity: 81%

• Thin-cut CT is gold standard for detection of and characterization of calcification within SPNs

• 6% of malignant nodules have Ca++ detected on CT
  - 85% of these tumors are >3 cm
  - Often punctate or eccentric pattern

Patterns of Calcifications

- DIFFUSE
- CENTRAL
- LAMINAR
- POPCORN
- ECCENTRIC
- STIPPLED
Nodule Margins in SPNs

Smooth

Lobulated

Irregular

Spiculated

Margin Characteristics of SPNs

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Spiculated</th>
<th>Lobulated</th>
<th>Smooth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary lung carcinoma</td>
<td>257 (84%)</td>
<td>112 (28%)</td>
<td>21 (11%)</td>
</tr>
<tr>
<td>Solitary metastasis</td>
<td>13 (4%)</td>
<td>62 (16%)</td>
<td>34 (18%)</td>
</tr>
<tr>
<td>Benign nodule</td>
<td>36 (12%)</td>
<td>222 (56%)</td>
<td>132 (71%)</td>
</tr>
</tbody>
</table>

Pooled data from Zerhouni et al, Radiology 1986; 160: 319-327
and Siegelman et al, Radiology 1986; 160: 307-312
**SPN: Other Radiological Signs**

- Intranodular fat on CT is a reliable indicator of a hamartoma
  - 20/20 nodules with fat or fat and Ca++ seen on CT scan were hamartomas (Siegelman et al, Radiology 1986)

- Cavitation can be seen with both benign and malignant nodule (Woodring et al, AJR 1983)
  - 95% of lesions with wall thickness < 5mm were benign
  - 84% of lesions with wall thickness > 15mm were malignant

**SPN: Growth Rates**

- The growth rate is expressed as the doubling time which refers to the doubling of volume
  - \( \frac{4}{3} \pi r^3 \) ie, 25% increase in the diameter equals a doubling of the volume

- Most malignant tumors have doubling times between 30-450 days

- No growth over a 2 year period (730 days) usually indicates benignity (LR=0.01)
  - Can be established retrospectively (get old CXRs or CTs!)
  - Can be established prospectively in low risk patients (“watch and wait approach” with serial imaging)
“Watchful Waiting”

- To establish nodule stability/benignity prospectively in low risk patients
  - Uses 2 year rule to confirm benignity
  - Serial CXR or CT (CT measurements more accurate) X 2 yrs
    - At 3, 6, 12, 18, and 24 months
  - No growth over 2 year period = benign
  - Any growth during this period is an indication for VATS or biopsy

Non-Invasive Testing

- Contrast enhanced CT
- PET scan
Contrast Enhanced CT

- Benign and malignant nodules differ in vascularity and behave differently after contrast administration.
- Contrast-enhanced CT uses nodule enhancement to differentiate benign from malignant lesions.
- CT nodule enhancement protocol:
  - Contrast: 2 ml/sec, 300 mg iodine/ml, 420 mg/kg dose
  - Nodule is scanned pre-contrast and at 1, 2, 3, 4 min after contrast injection
  - Nodule enhancement (HU) = peak post-contrast measurement - pre-contrast measurement

Swenson SJ et al. Radiology 2000; 214: 73-80

\[
\Delta = \text{Peak Post-contrast} - \text{Pre-contrast} \\
\text{Max } \Delta = 88 - 46 = 42 \\
\text{Enhancement} = 42 \text{ HU} \\
\text{Test Interpretation:} \\
\leq 15 \text{ HU} = \text{Benign} \\
> 15 \text{ HU} = \text{Malignant}
\]
Contrast Enhanced CT

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swenson et al. 2000 *</td>
<td>98%</td>
<td>58%</td>
<td>68%</td>
<td>96%</td>
</tr>
<tr>
<td>Meta-analysis Cronin et al. 2008</td>
<td>93%</td>
<td>76%</td>
<td>80%</td>
<td>95%</td>
</tr>
</tbody>
</table>

* Cut-off used: ≤ 15 HU = Benign; > 15 HU = Malignant

Swenson SJ et al. Radiology 2000; 214: 73-80
Cronin et al. Radiology 2008; 246: 772-782

Contrast Enhanced CT: Summary

- Useful test in the evaluation of SPNs
- The absence of enhancement (≤ 15 HU) is strongly predictive of benignity (NPV=95%)
- The presence of enhancement (> 15 HU) can be seen with malignancy or active granulomas (PPV=70-80%)
- Limited data for nodules < 1 cm
Positron Emission Tomography (PET)

- 2-deoxy-2-$^{18}$fluoro-D-glucose ($^{18}$FDG) is the radiotracer most commonly used in clinical PET
- Why FDG?
  - Cancer cells have an increased glucose metabolism
  - FDG is an analogue of glucose and there is an increased uptake of FDG within cancer cells

PET: Methodology

- Patients should be fasting for at least 4 hours to minimize the physiologic glucose utilization
- Blood glucose may be measured prior to the test
  - Glucose < 200 mg/dl: proceed with the test
  - Glucose > 200 mg/dl: test is delayed or rescheduled
- IV injection of 10-15 mCi of FDG is given
- Imaging begins about 45 minutes after injection
  - Whole body scans (ears-knees) take about 45-60 minutes to complete
• PET interpretation
  - Qualitative visual assessment
    • Area of abnormality is detected by comparison with mediastinal activity
  - Semi-quantitative assessment
    • Standardized uptake value (SUV)
    • SUV ≥ 2.5 cut-off for malignancy is often used in clinical practice

• Two meta-analyses of PET imaging with results applicable to SPNs > 1 and < 3 cm

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gould et al. 2001</td>
<td>94%</td>
<td>83%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cronin et al. 2008</td>
<td>95%</td>
<td>82%</td>
<td>91%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Gould MK et al. JAMA 2001; 285: 914-924
Cronin et al. Radiology 2008; 246: 772-782
PET: SPN Imaging

**Causes of False-negatives**
- Bronchoalveolar carcinoma
- Carcinoid
- Tumors < 1 cm
- Low grade adenocarcinoma
- Hyperglycemia

**Causes of False-positives**
- Granulomatous inflammation or infection (i.e., Tuberculosis, Histoplasmosis, Sarcoidosis)
- CWP/Silicosis
- Rheumatoid nodules

**PET: Summary**

- Useful test in the evaluation of SPNs
  - High negative and positive predictive value > 90%
- Can also provide staging information for malignant nodules
- Be aware of the clinical settings where false positives or false negatives are more likely
- Limited use in lesions < 1cm
  - PET spatial resolution 5-7 mm
  - Limited data on accuracy for lesions < 1cm
Invasive Testing

- Bronchoscopy
- Trans-thoracic needle aspiration
- VATS
- Thoracotomy

SPN: Bronchoscopy

- Sensitivity (20-80%) varies according to
  - Size of nodule
    - < 1.5 cm: 10%
    - 2-3 cm: 40-60%
  - Location of lesion
  - Skill of the bronchoscopist
  - Positive bronchus sign on CT (increased 30%→60%)

- A specific benign diagnosis is rarely made

- Bronchoscopy is of limited use in the evaluation of an SPN
  - Useful in the reluctant surgical patient, poor surgical candidate or inoperable patient with > 2cm nodule
SPN: Transthoracic Needle Aspirate

- Performed under CT guidance or fluoro
- Sensitivity: 60-95%  Specificity: 98-100%
  - Factors that affect yield:
    - Needle size (core vs. aspirate)
    - Number of passes
    - Size and location of lesion
    - Experience of radiologist
    - Presence of an experienced cytopathologist on-site
- Specific benign diagnosis rarely made

SPN: Transthoracic Needle Aspirate

- Utility of TTNA in the work-up of an SPN
  - In an inoperable patient for a tissue diagnosis
  - Patient who is reluctant to have surgery without a diagnosis or who is a high risk operative candidate
  - In an operable patient the decision for a TTNA should be based on:
    - The likelihood of making a specific benign diagnosis
      - Low pre-test probability for malignancy
    - Will a “negative” result alter your management?
      - What is the pretest probability of cancer?
    - Is knowing the patient has cancer prior to surgery helpful?
      - Does it shorten OR time?
Video-Assisted Thoracic Surgery (VATS)

- Most useful for small peripheral lesions
- Almost 100% sensitivity and specificity
  - If positive for malignancy on frozen section may need to convert to thoracotomy for optimal management
  - If benign then no further intervention is required
- Mortality rate: very rare
- Complication rate: 5-8%
  - Atelectasis
  - Pneumonia
  - Prolonged air leak

SPN: Thoracotomy

- The “gold standard”
- 100% sensitivity and specificity
- Diagnostic and therapeutic
- 30 day mortality: 1-4%
  - pneumonectomy > lobectomy
  - Age of patient
Small Pulmonary Nodule < 1cm

- Small pulmonary nodules (<1 cm) are an increasingly common in clinical practice
  - The routine use of multi-row detector CT increases the ability to detect small pulmonary nodules

<table>
<thead>
<tr>
<th></th>
<th>&lt; 4 mm</th>
<th>4-7 mm</th>
<th>≥ 8 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic (2003)</td>
<td>307</td>
<td>391</td>
<td>84</td>
</tr>
<tr>
<td>Nodules detected on</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline screening CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis of lung</td>
<td>0</td>
<td>2 (1%)</td>
<td>24 (29%)</td>
</tr>
<tr>
<td>cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th></th>
<th>&lt; 5 mm</th>
<th>5-9 mm</th>
<th>≥ 10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodules detected on</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline screening CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis of cancer at</td>
<td>0</td>
<td>14 (6%)</td>
<td>56 (51%)</td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Henschke et al. Radiology 2004; 231: 164-168
The Evaluation of the SPN < 1 cm

- CT imaging
  - Calcifications
  - Size
  - Nodule margins
  - Growth
    - Always obtain prior imaging for comparison, if available
- Contrast enhanced CT
  - Of limited use in SPN < 8-10 mm

The Evaluation of the SPN < 1 cm

- PET
  - Spatial resolution of most PET scanners is 5-7 mm
  - Limited data on PET for SPN < 10 mm
    - 8 malignant nodules ≤ 10mm were all PET negative (Nomori et al. Lung Cancer 2004; 45: 19-27)
    - 36 nodules ≤ 10mm (only 8 nodules were ≤ 8mm) (Herder et al. Eur J Nucl Med Mol Imaging 2004;31:1231-6)
      - Sensitivity: 93%  Specificity: 77%
  - How should PET be interpreted if a nodule < 1cm?
    - Should a cut-off SUV of 2.5 be used?
    - More research is needed
The Evaluation of the Small SPN

- **CT-guided TTNA**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients with nodules ≤ 1 cm</th>
<th>Sensitivity</th>
<th>Accuracy</th>
<th>Pneumothorax rate</th>
<th>Chest tube</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallace et al. 2002</td>
<td>61 total 51: 8-10 mm 10: 5-7 mm</td>
<td>82%</td>
<td>88%</td>
<td>62%</td>
<td>31%</td>
</tr>
<tr>
<td>Ng et al. 2008</td>
<td>55 total 50: 8-10 mm 5: 5-7 mm</td>
<td>68%</td>
<td>79%</td>
<td>52%</td>
<td>9%</td>
</tr>
</tbody>
</table>

- **VATS**
  - Can be a challenge finding nodules
    - Special techniques may be required to localize small nodules

The Evaluation of the Small SPN

- **Follow-up of nodules**
  - Increase in nodule diameter needs to exceed 1.5-2.0 mm to be 95% sure that the nodule has increased in size
  - 3-D volumetric assessment may be the answer in the future
Rationale for the Fleischner Society Guidelines for Small Nodules < 1 cm

- Low prevalence of malignancy in small nodules in patients without a history of cancer
  - < 1% in nodules < 5 mm in diameter
  - < 10% in nodules 5-9 mm in diameter
  - Even lower in low risk individuals (e.g., non-smokers)
- Experience gained from the management of small nodules detected during CT screening studies
  - Short term f/u exams @ 3-6 mos for nodules < 5 mm are unnecessary
  - Frequent f/u exams @ 3, 6, 12, and 24 mos are unnecessary for nodules < 9 mm
- Limited utility of PET and TTNA for small nodules

Fleischner Society Guidelines for the Management of Small SPNs

<table>
<thead>
<tr>
<th>Nodule size (mm)</th>
<th>Low risk patient*</th>
<th>High risk patient**</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4</td>
<td>No follow-up needed</td>
<td>Follow-up CT at 12 months; if unchanged, no further follow-up</td>
</tr>
<tr>
<td>&gt;4-6</td>
<td>Follow-up CT at 12 months; if unchanged, no further follow-up</td>
<td>Initial follow-up CT at 6-12 months then at 18-24 months if no change</td>
</tr>
<tr>
<td>&gt;6-8</td>
<td>Initial follow-up CT at 6-12 months then at 18-24 months if no change</td>
<td>Initial follow-up CT at 3-6 months then at 9-12 and 24 months if no change</td>
</tr>
<tr>
<td>&gt;8</td>
<td>Follow-up CT at around 3, 9, and 24 months; may consider dynamic contrast enhanced CT, PET, and/or biopsy</td>
<td>Follow-up CT at around 3, 9, and 24 months; may consider dynamic contrast enhanced CT, PET, and/or biopsy</td>
</tr>
</tbody>
</table>

*minimal or absent smoking history and other known risk factors
**history of smoking or other known risk factors

The Fleischner Society Guidelines for the Management of Small Nodules

- Guidelines do not apply to the following groups:
  - Patients with active or previous extrapulmonary malignancy
    - Higher likelihood of malignancy (60-80%)
    - Biopsy or VATS may be indicated depending on
      - Cell type, stage of primary tumor, and prognosis after metastectomy
  - Young patients < 35 years old
  - Patients with unexplained fever

Nodule Attenuation

Solid  Part-Solid  Non-Solid or Ground Glass Opacity
Part-Solid and Non-Solid Nodules

- ELCAP CT screening study

<table>
<thead>
<tr>
<th>Nodule Type</th>
<th>Number of Nodules (Total n=233)</th>
<th>Number of Malignant Nodules (% prevalence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid</td>
<td>189 (81%)</td>
<td>14 (7%)</td>
</tr>
<tr>
<td>Part-solid</td>
<td>16 (7%)</td>
<td>10 (63%)</td>
</tr>
<tr>
<td>Non-solid or GGO</td>
<td>28 (12%)</td>
<td>5 (18%)</td>
</tr>
</tbody>
</table>

- Higher prevalence of cancer in part-solid and GGO than solid opacities (34% vs. 7%)
- Malignant part-solid lesions or GGO often represent bronchioloalveolar carcinoma (BAC) or adenocarcinoma with bronchioloalveolar features

Henschke et al. AJR 2002;178; 1053-7

The Evaluation of the Part-Solid or Ground Glass Opacity (GGO)

- PET scan for part-solid and GGO
  - Sensitivity 10% and specificity 20%
- CT-guided TTNA and VATS may be problematic
- Follow-up with serial thin cut CT
  - Usually best course of action for small lesions < 1 cm
  - Overall size may not change, but the lesion may become more solid
    - Change in size or change in density is an indication for biopsy
  - Follow-up duration may need to be longer because of slower growing tumors such as BAC
SPN Management: Summary

- All SPNs must be regarded as potentially malignant and require prompt evaluation
- The management of SPNs should be guided by the probability of malignancy in an individual patient
- The management of small nodules < 1 cm should be based on risk and size as delineated in the Fleischner Society guidelines