Incidental Pulmonary Nodules

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What is a (Solitary) Pulmonary Nodule?
- Nodule: A rounded opacity, well or poorly defined, measuring up to 3 cm in diameter
- Mass: >3 cm
- Micronodule: 0-5 mm
- Often are incidentally found
  - Pre-operative chest X-rays
  - CT pulmonary venograms (atrial fibrillation pre-ablation)
- In the Emergency Department
  - Abdominal CT scans (kidney stones, abdominal pain)
  - Chest CT scans (pulmonary embolism evaluation)
- OFTEN reported at the end of the CT report; OFTEN forgotten!
Epidemiology

- 2010 Adult population: 234.5 million
- Estimate of Chest CT scans: 4.8 million
  In adults per year
- Estimate of lung nodules: 1.57 million per year
- New lung cancer diagnosis (within 2 years): 63,000
- Approx 72,000 of 224,210 lung cancer cases in 2014 in the US were <30mm
- Roughly 4% of lung nodules turned out to be malignant

Etiology of Pulmonary Nodules

- **Benign >> Malignant**
  - **Benign etiologies:**
    - Fungal infection (acute, chronic, or remote)
    - Benign neoplasms (ie hamartoma)
    - Vascular pathology (pulmonary arteriovenous malformation)
    - Inflammatory nodules (sarcoidosis, rheumatoid arthritis, vasculitis)
    - ‘Other’ (intrapulmonary lymph node, mucoid impaction, rounded atelectasis)
  - **Malignant etiologies:**
    - Bronchogenic carcinoma (ie primary lung cancer)
    - Metastatic cancer (breast, testicular, germ cell, melanoma, sarcoma, renal cell)
    - Carcinoid tumors

Nodule Textures

- Benign Textures:
  - Benign etiologies:
    - Fungal infection (acute, chronic, or remote)
    - Benign neoplasms (ie hamartoma)
    - Vascular pathology (pulmonary arteriovenous malformation)
    - Inflammatory nodules (sarcoidosis, rheumatoid arthritis, vasculitis)
    - ‘Other’ (intrapulmonary lymph node, mucoid impaction, rounded atelectasis)

Nodule Attenuation

- **Benign Features**
  - Lamellar Calc.
  - Central Calc.
  - Fat
Nodule Margins

Why is the Solitary Pulmonary nodule Important?
- Malignant nodules represent a potentially curable form of lung cancer
  - 5 year survival for patients with malignant SPN 65%-80%
  - 5 year survival for unselected patients with lung cancer 17%

Current Models used to Predict Cancer in Nodules
Six independent predictors of malignancy in SPN
- Patient characteristics:
  - Age
  - Smoking status
  - History of extrathoracic malignancy
- Nodule characteristics:
  - Diameter
  - Borders
  - Location

George Box: "All models are wrong but some are useful"
Swensen et al. Arch Intern Med 1997;157:849

CT Size matters
т

Size % malignant
<4 mm 0%
4-7 mm 0.8%
8-20 mm 22%
>20 mm 63%

CT: Edge Characteristics

Border type LR
1. Smooth 0.2
2. Lobulated 0.5
3. Spiculated 5.0
4. Corona radiata 14

Siegelman et al. Radiology 1986;160:307

Risk prediction calculators

<table>
<thead>
<tr>
<th>Model</th>
<th>Population</th>
<th>Number</th>
<th>Validation</th>
<th>Prevalence of malignancy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo</td>
<td>Incidental nodules, single institution</td>
<td>629 patients</td>
<td>210 patients</td>
<td>23%</td>
<td>Useful for incidental nodules</td>
</tr>
<tr>
<td>Brock</td>
<td>Pan-Canadian multicenter screening trial</td>
<td>1871 patients</td>
<td>7008 nodules</td>
<td>1090 patients</td>
<td>52021 nodules</td>
</tr>
<tr>
<td>Herder</td>
<td>Single institution, cohort referred for PET</td>
<td>106 None</td>
<td>57%</td>
<td>Additive to Mayo</td>
<td></td>
</tr>
</tbody>
</table>

Solitary Pulmonary Nodule (SPN): Malignancy Risk Score (Mayo Clinic Model)
Summary of Fleischner Guidelines for SOLID, SOLITARY Nodules

<table>
<thead>
<tr>
<th>&lt;6 mm (&lt;100 mm³)</th>
<th>6-8 mm (100-250 mm³)</th>
<th>&gt;8 mm (&gt;250 mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No routine follow-up</td>
<td>CT at 6-12 months; then consider CT at 18-24 months</td>
<td>Consider CT at 3 months, PET/CT; or tissue sampling</td>
</tr>
<tr>
<td>High Risk</td>
<td>Optional CT at 12 months</td>
<td>CT at 6-12 months, then CT at 18-24 months</td>
</tr>
</tbody>
</table>

**Fleischner Criteria Exclusions?**

- Exclusions:
  - Patients with unexplained fever
  - Patients with known or suspected metastases
  - Patients <35 years of age
  - Lung cancer screening (use LUNG-RADS)

**Management**

- CT scan surveillance
  - NON-contrast, THIN cuts, LOW-dose radiation CT scan is preferred
  - If any interval growth, likely will need to proceed to PET scan, biopsy, resection, etc

- **Positron emission tomography (PET) scan**
  - Measures the ‘metabolic activity’ of nodules
    - Nodule/lesion can be ‘PET-avid’ if malignant, infectious, or inflammatory (like sarcoidosis)
  - Typically reserved for SOLID nodules GREATER than 8 mm (or even 10 mm)
    - High false negative rates in nodules < 8 mm or pure subsolid (ground glass) nodules
    - Can be helpful to determine best site to biopsy (ie diagnose AND stage simultaneously)
Management

• Biopsy
  – Bronchoscopic biopsy
    • Endobronchial Ultrasound (EBUS) Transbronchial Needle Aspiration (TBNA)
      – Useful for centrally-located lesions and if adenopathy present
    • Electromagnetic Navigational bronchoscopic biopsies
      – Useful for peripherally-located nodules that may not be amenable to transthoracic needle biopsy
    – Transthoracic needle biopsy (ie ‘CT-guided’ biopsy)
      – Depends on size of nodule, presence of other ‘biopsyable’ sites (ie lymph nodes), location of nodule (ie peripheral vs central)

Bronchoscopic vs CT-guided Biopsies

• Bronchoscopic biopsies (EBUS or navigational bronchoscopy)
  – Require at least moderate sedation (though often performed under general anesthesia)
  – 1-3 hours in duration
  – Minimal risks
    • Most risk is from anesthesia itself
    • Low rates of bleeding and pneumothoraces
• Transthoracic needle biopsies
  – Relatively quick procedures done using local anesthetic
  – Comparably higher risks of bleeding and pneumothoraces
**Management**

- Biopsy via surgical resection
  - Theoretically can be diagnostic and curative
  - Reserved for:
    - Nodules with high pre-test probability for cancer
      - Enlarging, >1 cm, spiculated, high-risk patient (ie smokers)
    - NO evidence of concerning adenopathy or distant metastatic lesions (ie would diagnose but NOT stage)
    - Patients that are good surgical candidates
  - In theory, can proceed directly from CT scan to surgical resection (without a PET scan or a biopsy)
    - In practice, PET scans are usually obtained to evaluate for:
      - A) PET-avidity in the nodule itself
      - B) ensure there are no other PET-avid lesions

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**Next Steps?**

- FIGURE 2 (Section 4.1) Factors that influence choice between evaluation and management alternatives for indeterminate, solid nodules 8-15 mm in diameter.

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**'Ground Glass' Nodules**

- Gould M, CHEST 2013
Incidental Solitary Subsolid Pulmonary Nodules ('ground glass')

- Incidental solitary subsolid (pure ground glass or part-solid) pulmonary nodule.
- Search medical record for prior CT images of the chest. Is the nodule unchanged on CT for over five years?
  - Nodule unchanged
  - Unknown or equivocal
  - Nodule growing?
  - No further follow-up
  - Biopsy or resection
  - Malignancy Study

Enlarging Ground Glass Nodules

- Assess nodule size and attenuation (ground glass versus part-solid).
- <5 mm ground glass or part-solid
  - No further follow-up
  - Biopsy or resect if nodule grows?
- ≥6 mm ground glass
  - Perform chest CT at 6 to 12 months and then every 2 years for up to 5 years.
  - Biopsy or resect if nodule grows.
  - No further follow-up if nodule resolves.
### Management of Enlarging Ground Glass Nodules

- Malignant until proven otherwise
  - Adenocarcinoma 'in situ' (formerly known as 'bronchoalveolar carcinoma')
- PET scan vs percutaneous/transthoracic biopsy vs surgical resection
  - Compared to solid nodules, there are higher rates of false negatives with PET scans and percutaneous biopsies for ground glass nodules
  - Slow rate of growth, so not particularly metabolic active (false negative on PET scan)
  - Lesion is not solid, so needle biopsy may not be representative
  - 'if in doubt, cut it out' → referral to thoracic surgery

### Take Home Points

- Always be on the lookout for incidental pulmonary nodules
  - CT scans (both CT chest angiography as well as CT abdomen) in the ER
  - CT pulmonary venograms (often obtained in the management of atrial fibrillation)
- 1st step is ALWAYS to look for prior imaging
- Use caution if/when ordering PET scans (particularly with ground glass nodules and nodules < 1 cm)
- High rates of false positives AND false negatives
- Fine line between wanting to 'cure'/not wanting to 'miss' an early cancer and surgically resecting a benign lesion
- If ANY concern, can refer to pulmonary or thoracic surgery

### Why Do We Need Screening?

- Lung cancer is the leading cause of cancer-related death among men and women
- Worldwide → 1.6 million deaths due to lung cancer annually
- United States → 234,000 new cases of lung cancer diagnosed yearly
  - 154,000 lung cancer-associated deaths annually
- Clinical outcome for non-small cell lung cancer is directly related to stage at the time of diagnosis
- Estimated that 75% of patients with lung cancer present with symptoms due to advanced local/metastatic disease no longer amenable to curative surgery
- 5 year survival rates average 18% for all individuals with lung cancer
Pros and Cons of Screening

- Potential benefits of lung cancer screening:
  - Early detection (early stage) → potential curative surgical resection → increased survival (decreased morbidity and mortality)
  - Increased smoking cessation rates

- Potential ‘harms’ of lung cancer screening:
  - Consequences of evaluating normal findings:
    - High risk procedures (biopsy, surgery) for likely benign nodules
    - Incidental findings → asymptomatic emphysema, coronary artery disease, thyroid nodules
  - Radiation exposure (though we use ‘low dose’ radiation chest CTs for screening)
  - Patient ‘distress’ → presence of nodules (likely benign) may cause anxiety related to fear of having lung cancer
• Roughly 54,000 patients at ‘high risk’ for lung cancer were randomly assigned to undergo three annual screenings with either:
  - Low-dose chest CT
  - Chest radiograph
• Inclusion criteria:
  - Age 55 to 74 years
  - At least a 30 pack year smoking history
  - If former smoker, had to have quit within the previous 15 years
• Excluded if:
  - Previous diagnosis of lung cancer
  - Had undergone chest CT within previous 18 months
  - Any symptoms present (hemoptysis and weight loss)

#### Table 2. Results of Three Rounds of Screening.

<table>
<thead>
<tr>
<th>Screening Round</th>
<th>Low-Dose CT</th>
<th>Chest Radiography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No. Screened</td>
<td>Positive Result</td>
</tr>
<tr>
<td></td>
<td>No. (% of screened)</td>
<td>No. (% of screened)</td>
</tr>
<tr>
<td>T0</td>
<td>26,309 (100.0)</td>
<td>7191 (27.3)</td>
</tr>
<tr>
<td>T1</td>
<td>24,715 (100.0)</td>
<td>6901 (27.9)</td>
</tr>
<tr>
<td>T2</td>
<td>24,102 (100.0)</td>
<td>4054 (16.8)</td>
</tr>
</tbody>
</table>

*The screenings were performed at 1-year intervals, with the first screening (T0) performed soon after the time of randomization. Results of screening tests that were technically inadequate (7 in the low-dose CT group and 26 in the radiography group, across the three screening rounds) are not included in this table. A screening test with low-dose CT was considered to be positive if it revealed a nodule at least 4 mm in any diameter or other abnormalities that were suspicious for lung cancer. A screening test with chest radiography was considered to be positive if it revealed a nodule or mass of any size or other abnormalities suspicious for lung cancer.*

#### False positive rates:
- CT group: 96.4%
- CXR group: 94.5%

#### Table 3. Diagnostic Follow-up of Positive Screening Results in the Three Screening Rounds.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low-Dose CT</th>
<th>Chest Radiography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>number</td>
</tr>
<tr>
<td>Lung cancer confirmed</td>
<td>211 (3.8)</td>
<td>640 (3.8)</td>
</tr>
<tr>
<td>Lung cancer not confirmed</td>
<td>865 (96.2)</td>
<td>573 (6.4)</td>
</tr>
</tbody>
</table>

This screening was performed at 1-year intervals, with the first screening (T0) performed soon after the time of randomization. FIDG PET denotes 18F-fluorodeoxyglucose positron emission tomography.

† Positive tests with incomplete information on diagnostic follow-up are included in this category (142 at T0, 161 at T1, and 141 at T2 in the low-dose CT group and 39 at T0, 26 at T1, and 25 at T2 in the radiography group).


9/9/2021
Table 5. Stage and Histologic Type of Lung Cancers in the Two Screening Groups, According to the Result of Screening.

<table>
<thead>
<tr>
<th>Stage and Histologic Type</th>
<th>Low-Dose CT Positive Screening Test (N=1060)</th>
<th>Chest Radiography Negative Screening Test (N=941)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>329/635 (51.8)</td>
<td>90/275 (32.7)</td>
</tr>
<tr>
<td>IB</td>
<td>71/635 (11.2)</td>
<td>41/275 (14.9)</td>
</tr>
<tr>
<td>IIA</td>
<td>26/635 (4.1)</td>
<td>14/275 (5.1)</td>
</tr>
<tr>
<td>IIB</td>
<td>20/635 (3.1)</td>
<td>11/275 (4.0)</td>
</tr>
<tr>
<td>IIIA</td>
<td>59/635 (9.3)</td>
<td>35/275 (12.7)</td>
</tr>
<tr>
<td>IIIB</td>
<td>49/635 (7.7)</td>
<td>27/275 (9.8)</td>
</tr>
<tr>
<td>IV</td>
<td>81/635 (12.8)</td>
<td>57/275 (20.7)</td>
</tr>
</tbody>
</table>

More Lung Cancers Detected With CT

Cumulative Number

Years Since Randomization


Lung Cancer Screening

Less Lung Cancer Deaths With CT

relative reduction in the rate of death from lung cancer with low-dose CT screening of 20%!!!

Number needed to screen with LDCT to prevent one death from lung cancer was 320

### Table 3. Lung-Cancer Stage and Histologic Type of All First-Detected Lung Cancers in Male Participants at 10 Years of Follow-up or on December 31, 2015.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Screening Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants (percent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA (n=203)</td>
<td>95 (46.8)</td>
<td>10 (7.1)</td>
</tr>
<tr>
<td>IB (n=241)</td>
<td>24 (11.8)</td>
<td>10 (7.1)</td>
</tr>
<tr>
<td>IIA (n=104)</td>
<td>8 (3.9)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>IIB (n=107)</td>
<td>11 (5.4)</td>
<td>6 (4.3)</td>
</tr>
<tr>
<td>IIIA (n=34)</td>
<td>20 (9.9)</td>
<td>14 (9.9)</td>
</tr>
<tr>
<td>IIIB (n=27)</td>
<td>13 (6.4)</td>
<td>14 (9.9)</td>
</tr>
<tr>
<td>IV (n=19)</td>
<td>19 (9.4)</td>
<td>73 (51.8)</td>
</tr>
</tbody>
</table>


### Medicare Part B covers an annual lung cancer screening and LDCT scan (at 100%) if all of the following apply:

- Age 55 to 77 years
- Currently smoke or quit within the past 15 years
- 30 pack year smoking history
- No signs/symptoms of lung cancer
- Receive the screening/LDCT at a Medicare-approved radiology facility

**Cost to Patient?**

- Out of pocket cost for annual LCS? → $400-600
- Cost of pack per day smoking over a year? → $2300

### Before the 1st screening, patient MUST have a shared decision-making conversation with ordering physician (risks/benefits)

- Ordering physician will also provide counseling on smoking risks/smoking cessation services (when appropriate)
Cost Effectiveness of Lung Cancer Screening

- Milliman actuarial studies from 2010-14:
  - In terms of cost per life-year saved:
    - Colonoscopy → $12,000-$26,000
    - Mammography → $31,000-$51,000
    - Pap smears → $50,000-$75,000
    - LDCT for lung cancer screening → $12,000-$26,000
      - well below the $100,000 threshold experts consider to be a reasonable value

Is the False Positive Rate too High?

- Majority of ‘false positives’ on screening CT scans do NOT result in an invasive procedure
  - For example:
    - A 4 mm nodule found on initial LCS would be considered a false positive if stable/resolved on repeat imaging at the 12 month interval
  - False positive rate likely greatly exaggerated...

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Table 1. Comparison of mean effective radiation dose

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mean Effective Radiation Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray</td>
<td>0.15 mSv</td>
</tr>
<tr>
<td>Low dose chest</td>
<td>0.5 mSv (1.8 mSv at High Flags)</td>
</tr>
<tr>
<td>Routine chest</td>
<td>0.7 mSv (5.0 mSv at High Flags)</td>
</tr>
<tr>
<td>mammography</td>
<td>0.4 mSv</td>
</tr>
<tr>
<td>Natural Background Radiation</td>
<td>3.6 mSv/year (5.5 mSv per year in Colorado)</td>
</tr>
<tr>
<td>Transcontinental Flight</td>
<td>0.03 mSv</td>
</tr>
</tbody>
</table>
Lung Cancer Screening Uptake in the U.S.

- Lung Cancer Screening with Low-Dose Computed Tomography in the United States – 2010 to 2015 (JAMA Oncology, 2017)
- According to 2010 National Health Interview Survey (NHIS), only 2-4% of high-risk smokers received LDCT for cancer screening in the previous year.
- This study examined whether the 2013 USPSTF recommendation for screening had made a meaningful difference.

<table>
<thead>
<tr>
<th>Pre-guidelines screening rates</th>
<th>Post-guidelines screening rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

Screening rate for ELIGIBLE patients in 2015: 3.9%
Screening rate for INELIGIBLE patients in 2015: 2.7%
Why Is Uptake So Poor?

- ‘Knowledge of, Attitudes Toward, and Use of Low-Dose Computed Tomography for Lung Cancer Screening Among Physicians’ (Cancer, Aug 2016)
Barriers to LCS

- Patients:
  - Unawareness of screening programs
  - Fear of cancer diagnosis
  - Cost concerns
  - Access to screening/imaging sites
- Physicians/providers:
  - Unfamiliarity with screening guidelines/insurance coverage
  - Insufficient time/knowledge to conduct shared-decision making
  - Lack of guidance for managing lung cancer screening results
  - Skepticism about benefits of screening
  - Concerns over 'false positive' rates

How to Improve Screening Uptake?

- Early detection is great, but PREVENTION will always be better! (i.e. smoking cessation)
- New USPSTF guidelines are a great step in the right direction to expand the screening pool, but we need insurance companies to buy in!
- Remember, lung cancer screening is ANNUAL (and basically life-long until patient no longer meets criteria), not a ‘one and done’ venture
- Be persistent! Empower your patients!

Summary/Key Points
References