The Diagnostic Evaluation Of Pulmonary Nodules

Gerard A. Silvestri, MD, MS  
Hillenbrand Professor in Thoracic Oncology  
Medical University of South Carolina  
Charleston, SC  
Email: Silvestri @musc.edu
Disclosures

- NOTE: All are Research Funding only
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  - Auris Medical
  - Boston scientific Corporation
  - Exact Sciences
  - Integrated Diagnostics/Biodesix
  - Olympus America
  - Oncimmune
  - Oncocyte
  - Prolung
  - Veracyte
  - Veran
When it comes right down to it, what is the singular question we are attempting to answer?
Is this cancer or not?
Management Alternatives

- Surgery
  - “When in doubt, cut it out”
- Biopsy
  - “When cancer is the answer, tissue is the issue”
- Wait and watch
  - “Don’t just do something…stand there!”
For any nodule

First step: Assess likelihood of malignancy
Clinical judgment vs. risk calculator

Surveillance vs No work-up

INTERMEDIATE RISK

HIGH RISK

Serial CT

Further diagnostic testing: PET scan +/- Biopsy

Surgical Resection

Probability of cancer

0% 15% 30% 45% 60% 75%
Pulmonary nodules

- Radiomics
- Blood tests
- Biopsy options
- VOCs

Risk Prediction Calculators
ARS Question 1

A 70 year old female with a 1 pack per day smoking history for 50 years presents with a 1.4 cm spiculated nodule in the Right upper Lobe. She has family history of cancer.

The probability that this nodule is cancer is?

1. < 5%
2. Somewhere between 5% and 65%
3. > 65%
4. The probability of cancer can’t be calculated given the information provided
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4. The probability of cancer can’t be calculated given the information provided
SPN Management

- Pre-test probability of cancer and management recommendations

  - **Low** < 5% risk of cancer
    - Serial CT’s
  
  - **Intermediate** is 5 – 60%
    - Consider PET, TTNA, Bronch

  - **High** is > 60%
    - Excisional biopsy with frozen section
Solitary Pulmonary Nodule
Differential Diagnosis: Benign SPN

- Non-specific or healed granulomas (25%)
- Infectious granulomas (15%)
- Benign neoplasms (15%)
  - Hamartoma
  - Lipoma, fibroma, countless others (rare)
- Others: lung abscess, pseudotumor, round atelectasis, AVM, infarct, mucoid impaction, hematoma, rheumatoid nodule, Wegener’s
Differential Diagnosis: Malignancy in a pulmonary nodule

- Adenocarcinoma (~50%)
  - Bronchoalveolar cell carcinoma (~5%)
- Squamous cell carcinoma (~20%)
- Solitary metastasis (~10%)
- Undifferentiated NSCLC (~10%)
- Small cell carcinoma (<2%)
Current Model 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
  - Spiculation
  - Upper lobe location

George Box: “All models are wrong but some are useful”

Swensen et al. Arch Intern Med 1997;157:849
### Predictors of Cancer in Screen Detected nodules

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>1.03 (.99-1.07)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>female sex</strong></td>
<td>1.82 (1.1-3.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>family hx of lung cancer</td>
<td>1.83 (.83-2.17)</td>
<td>0.23</td>
</tr>
<tr>
<td>Emphysema</td>
<td>1.34 (.78-2.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>larger nodule size</td>
<td>2.06 (1.3-2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper lobe</td>
<td>1.93 (1.1-3.3)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>higher nodule count</strong></td>
<td>0.92 (.85-1.00)</td>
<td>0.049</td>
</tr>
<tr>
<td>Spiculation</td>
<td>2.187 (1.16-4.05)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**AUC > .90**

<table>
<thead>
<tr>
<th>Size</th>
<th>% malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-5 mm</td>
<td>1%</td>
</tr>
<tr>
<td>6-10 mm</td>
<td>24%</td>
</tr>
<tr>
<td>11-20 mm</td>
<td>33%</td>
</tr>
<tr>
<td>21-45 mm</td>
<td>80%</td>
</tr>
</tbody>
</table>

CT: Edge Characteristics

<table>
<thead>
<tr>
<th>Border type</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Smooth</td>
<td>0.2</td>
</tr>
<tr>
<td>2. Lobulated</td>
<td>0.5</td>
</tr>
<tr>
<td>3. Spiculated</td>
<td>5.0</td>
</tr>
<tr>
<td>4. Corona radiata</td>
<td>14</td>
</tr>
</tbody>
</table>

Siegelman et al. Radiology 1986;160:307
Management of Pulmonary Nodules by Community Pulmonologists
A Multicenter Observational Study

Nichole T. Tanner, MD, MSCR; Jyoth Aggarwal, MHS; Michael K. Gould, MD; Paul Kearney, PhD; Gregory Diette, MD, MHS; Anil Vachani, MD; Kenneth C. Fang, MD; and Gerard A. Silvestri, MD

33 Geographically Diverse Outpatient Pulmonary Clinics

Chest 2015:148(6):1405-14
Diagnosis and procedure use categorized by nodule pretest probability for cancer

<table>
<thead>
<tr>
<th>N=377</th>
<th>Low Risk (≤ 5%)</th>
<th>Intermediate Risk (&gt;5 to ≤65%)</th>
<th>High Risk (&gt;65%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>36 (100%)</td>
<td>9 (55%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Malignant</td>
<td>0 (0%)</td>
<td>18 (45%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Most Invasive Procedure Utilized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surveillance</td>
<td>20 (56%)</td>
<td>141 (47%)</td>
<td>14 (34%)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>10 (28%)</td>
<td>95 (32%)</td>
<td>20 (49%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>6 (17%)</td>
<td>64 (21%)</td>
<td>7 (17%)</td>
</tr>
</tbody>
</table>

Surgery for BENIGN DISEASE = 35%
25% of patients presenting to pulmonologists ultimately have cancer

44% of very low risk patients (pCA <0.05) underwent an invasive procedure for a benign nodule

There was no difference in the rate of surgical resection for nodules based on pretest probability of cancer

Possible explanations:

- Pulmonologists do not routinely consider pCA
- They unaware that guidelines exist for nodule management
- They choose not to follow them guidelines
Variability of Tumor Measurement on Repeat CT within 15 minutes

- 33 patients with NSCLC
- Repeat CT within 15 min.
- 57% 1mm different
- 33% 2mm different
- 23% shrinkage
- 33% growth.

- JCO 2011, 29:311
Standard Cursor Measurements

3/05
1.3 cm

9/05
1.5 cm
Management of Lung Nodules Detected by Volume CT Scanning

Rob J. van Klaveren, M.D., Ph.D., Matthijs Oudkerk, M.D., Ph.D.,

- Definition of negative baseline screen
  - No nodule (49%)
  - Calcified nodule or volume <50 mm3 (~30%)
  - Indeterminate: volume 50 to 500 mm3 (19%)
  - 95% of the indeterminate patients had nodules that resolved at 3 months, had no growth (<25% increase), or had VDT ≥400 days

- Sensitivity for lung cancer 94.6%
- NPV= 99.7% (7,341/7,361)
- Reduced false positives from 30% to 2%
### Fleischner Society 2017 Guidelines for Management of Incidentally Detected Pulmonary Nodules in Adults

#### A: Solid Nodules

<table>
<thead>
<tr>
<th>Nodule Type</th>
<th>Size</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;6 mm (&lt;100 mm³)</td>
<td>CT at 6–12 months, then consider CT at 18–24 months</td>
</tr>
<tr>
<td>Low risk‡</td>
<td>6–8 mm (100–250 mm³)</td>
<td>Consider CT, PET/CT, or tissue sampling at 3 months</td>
</tr>
<tr>
<td></td>
<td>&gt;8 mm (&gt;250 mm³)</td>
<td>Nodules &lt;6 mm do not require routine follow-up, but certain patients at high risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-month follow-up (recommendation 1A).</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>
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<td>6–8 mm (100–250 mm³)</td>
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#### Multiple

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<th>Size</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk‡</td>
<td>No routine follow-up</td>
<td>CT at 3–6 months, then consider CT at 18–24 months</td>
</tr>
<tr>
<td></td>
<td>6–8 mm (100–250 mm³)</td>
<td>CT at 3–6 months, then consider CT at 18–24 months</td>
</tr>
<tr>
<td></td>
<td>&gt;8 mm (&gt;250 mm³)</td>
<td>Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A).</td>
</tr>
<tr>
<td>High risk‡</td>
<td>Optional CT at 12 months</td>
<td>CT at 3–6 months, then at 18–24 months</td>
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FDG-PET Imaging

- Non-invasive, functional imaging test
- FDG accumulates in metabolically active tumor cells
- Sensitivity ~72-95%, specificity ~83%
- False negative results:
  - Small nodules <8 mm to 10 mm
  - Well-differentiated adenocarcinoma, BAC, carcinoid
- False positive results:
  - Granulomatous infection/inflammation

Gould et al, Chest 2013
Cronin. Radiology, 2008
Pulmonary nodules

- Radiomics
- Blood tests
- Risk Prediction Calculators
- VOCs
- Biopsy options
11 studies with data about accuracy in SPN:

- Median sensitivity 90% (range 65% to 94%)
- Median specificity 100% (range 96% to 100%)
- Specificity assumed to be 100% in some studies
- Non-diagnostic results 5x more common in benign than malignant nodules, but non-diagnostic biopsy does not rule out malignancy
- Median probability of PTX 15% (range 15% to 43%)
- ~6% required chest tube (range 4% to 18%)

ACCP recs: In patients with an indeterminate SPN (10 mm) it is appropriate to perform a TTNA or bronchoscopy in the following circumstances:

- when clinical pre-test probability and findings on imaging tests are discordant, for example, when the pre-test probability of cancer is high and the lesion is not hypermetabolic by PET
- when a benign diagnosis requiring specific medical treatment is suspected
- when a fully informed patient desires proof of a malignant diagnosis prior to surgery, especially when the risk of surgical complications is high.
- Patient non operative and need tissue to treat
# Yield of Bronchoscopy for Lung Cancer

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<tr>
<th>Study</th>
<th>Sites/Patients</th>
<th>Yield/Sensitivity</th>
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<tr>
<td>2013 ACCP Guidelines</td>
<td>35 studies, 4,507 patients</td>
<td>Central lesions – 88%</td>
</tr>
<tr>
<td></td>
<td>34 studies, 5,742 patients</td>
<td>Peripheral lesions – 78%</td>
</tr>
<tr>
<td>10 studies, 1,367 patients</td>
<td>&lt; 2cm – 34%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 2cm – 63%</td>
<td></td>
</tr>
<tr>
<td>2012 Meta-analysis</td>
<td>39 studies, 3,004 patients</td>
<td>Overall – 70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 2cm – 82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 2cm – 61%</td>
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Rivera et al. *CHEST* 2013  
Wang Memoli et al. *CHEST* 2012
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<td>2015 AQuIRE registry</td>
<td>15 sites 531 patients</td>
<td>Flexible bronchoscopy – 64%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radial EBUS – 57%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EMN – 39%</td>
</tr>
<tr>
<td>2015 AEGIS study</td>
<td>28 sites 639 patients</td>
<td>Overall – 53% for diagnosis of cancer</td>
</tr>
<tr>
<td>2018 Multicenter RCT standard bronchoscope with fluoroscopy (SB-F) vs thin bronchoscope with radial EBUS (TB-EBUS)</td>
<td>5 sites 221 patients</td>
<td>Overall – 44%</td>
</tr>
</tbody>
</table>

Ost et al. *AJRCCM*, 2015  
Silvestri et al. *NEJM*, 2015  
Tanner et al. *CHEST*, 2018
Rationale: Bronchoscopy is often non-diagnostic in patients with pulmonary lesions leading to additional invasive testing.

Objective: Evaluate the effectiveness of a bronchial-airway gene-expression classifier on the diagnostic performance of bronchoscopy.
Results

- N= 639
- Gene-expression classifier measured in epithelial cells collected from normal-appearing mainstem bronchus
- 43% of bronchoscopies non-diagnostic
- 35% with benign lesions underwent invasive procedures
- The combination of the classifier plus bronchoscopy had a sensitivity of 96% (95% CI, 93 to 98) in AEGIS-1 and 98% (95% CI, 96 to 99) in
- Independent of lesion size and location.
- In 101 patients with an intermediate pretest probability of cancer, the negative predictive value of the classifier was 91% (95% CI, 75 to 98) among patients with a non-diagnostic bronchoscopic examination

Silvestri, NEJM, 2015
- **Design:** prospective, multi-center trial (33 North American sites), 685 patients
- **Eligibility:** Age $\geq 40$ with new lung nodule $\geq 8$mm and $\leq 30$mm
- **Methods:** 2 plasma proteins, LG3BP and C163A, were integrated with a clinical risk prediction model to identify likely benign nodules
- **Clinician assessment of nodule pre-test probability for malignancy was provided at enrollment**
Results

- 178 patients had pCA ≤ 80%; prevalence of cancer was 16%
- The integrated classifier:
  - Sensitivity of 97%
  - Specificity 44%
  - NPV 98% in distinguishing benign from malignant nodules
- Had results been used to direct care, 40% fewer procedures would have been done on benign nodules
  - 3% of malignant nodules would have been misclassified

Silvestri, Chest 2018
Comparison of AUCs for ROCs of lung nodule malignancy risk assessment tools relative to 95% NPV zone.

Silvestri, Chest 2018
EarlyCDT®-Lung

Rule in Test: Early CDT Oncimmune

- autoantibodies can aid early detection and nodule risk stratification in lung cancer patients
  - Absent or low concentrations in benign cohorts
  - 7 panel ELISA
  - p53, NY-ESO-1, SOX2, HuD, GBU4-5, CAGE & MAGE A4
  - ~40% sensitivity & 93% specificity for all stages of lung cancer

Personal communication courtesy of Jim Jett, MD
Volatile Organic Compounds

- **Origin**
  - Endogenous (end-products of metabolic pathways)
  - Exogenous (contaminants from environment)

- **VOCs detected in various lung diseases**
  - Combination, rather than single

- **Analyzers**
  - Gas chromatography/mass spectrometry
  - Portable devices
  - Canine detection
Canine and Electronic Nose to Detect Lung Cancer

- Canine Detection:
  - 3 studies with 280 subjects
    - Sensitivity range 71%-99%
    - Specificity range 82%-99%

- Electronic Nose:
  - 7 studies with 30 subjects
    - Sensitivity range 7%-86%
    - Specificity range 72%-99%

- Dent et al, J Thorac Dis 2013
Conclusions

- Common Radiologic Problem with an Increasing incidence
- Multiple Imaging Strategies
- Multiple minimally invasive and surgical approaches
- Management Decisions Often Based on Pre-test Probability of Malignancy
- Biomarkers will help build physician confidence
- Bronchoscopy may not be as useful as we think
- Answer probably comes with escaping from silos Deep machine learning/ Artificial intelligence.