Distinguishing Benign From Malignant Pulmonary Nodules

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# Disclosures

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<thead>
<tr>
<th>Source</th>
<th>Research Funding</th>
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Learning Objectives

• Review the diagnostic approach to distinguish benign from malignant disease.
• Discuss when to choose surveillance, lung biopsy, PET scan, or surgery for the management of lung nodules.
• Introduce how blood biomarkers will potentially be used in this space.
When it comes right down to it, what is the singular question we are attempting to answer?
Is this cancer or not?
For any nodule

- Step 1: Assess likelihood of malignancy
  Clinical judgment vs. risk calculator

**LOW RISK**
- Surveillance serial CT vs No work-up

**INTERMEDIATE RISK**
- Further diagnostic testing: PET scan +/- Biopsy

**HIGH RISK**
- Surgical Resection

Probability of cancer
Extrapolating to the US population

- 2010 Adult population: 234.5 million
- Estimate of chest CT scans: 4.8 million
- Estimate of lung nodules: 1.57 million
- 72,000 of 224,210 lung cancer cases in 2014 (US) were ≤ 30 mm
Pulmonary nodules

- Radiomics
- Genomics Proteomics
- VOCs
- Bronchoscopic Diagnostics
- Risk Prediction Calculators
Assessing pre-test probability for malignancy

- Clinical Intuition
- Validated Risk Models
  - Highly dependent on the prevalence of malignancy
  - VA Model (40% cancer rate)
  - Mayo Model (24% cancer rate)
  - Brock Model (3-5% cancer rate)
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
Diagnosis and procedure use categorized by nodule pretest probability for cancer

<table>
<thead>
<tr>
<th></th>
<th>Low Risk &lt; 5% n=36</th>
<th>Intermediate Risk &gt;5 to &lt;65% n=300</th>
<th>High Risk &gt;65% n=41</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Outcome</td>
<td></td>
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<tr>
<td>Benign</td>
<td>36 (100% )</td>
<td>224 (75%)</td>
<td>23 (55%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Malignant</td>
<td>0</td>
<td>76 (25%)</td>
<td>18 (45%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Most Invasive Procedure Utilized</td>
<td></td>
<td></td>
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<tr>
<td>Surgery</td>
<td>6 (17%)</td>
<td>64 (21%)</td>
<td>7 (17%)</td>
<td>0.6878</td>
</tr>
<tr>
<td>Biopsy</td>
<td>10 (28%)</td>
<td>95 (32%)</td>
<td>20 (49%)</td>
<td>0.0711</td>
</tr>
<tr>
<td>Surveillance</td>
<td>20 (56%)</td>
<td>141 (47%)</td>
<td>14 (34%)</td>
<td>0.1548</td>
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Objectives:
- compare physician estimates of pretest probability to validated nodule malignancy prediction calculators
- Determine how often guideline recommended diagnostic testing was used based on pCA

Methods:
- Data part of multicenter, prospective trial
- N=337 patients with final diagnosis
- Physician assessed pCA categorized into risk and next test ordered evaluated
Physician and Model ROCs

AUC
- MD 0.849
- Mayo 0.776, p=0.011 vs MD
- VA 0.747, p<0.001 vs MD
Pulmonary nodules

- Radiomics
- Genomics Proteomics
- VOCs
- Bronchoscopic Diagnostics
- Risk Prediction Calculators
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)
Volumetric Measurement

• Volumetric Software
  – Automated or semi-automated
  – Measures volume of nodule

• NELSON trial
  – Use of Volume Doubling Time ≥ 25%
  – Reduced false positives from 30% to 2%

• Nodule prediction models
  – improve the classification of malignancy from 60% to 88%

van Klaveren, et al, NEJM 2009
Mehta et al, Chest, 2014
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
• PET is useful for Staging lung cancer and searching for metastatic Disease

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

- Radiomics
- Proteomics
- Risk Prediction Calculators
- Bronchoscopic Diagnostics
- VOCs
<table>
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<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>
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<td>34 studies 5,742 patients</td>
<td>Peripheral lesions – 78%</td>
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<tr>
<td></td>
<td>10 studies 1,367 patients</td>
<td>&lt; 2cm – 34%</td>
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<tr>
<td></td>
<td></td>
<td>&gt; 2cm – 63%</td>
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<tr>
<td>2012 Meta-analysis</td>
<td>39 studies 3,004 patients</td>
<td>Overall – 70%</td>
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<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
# Yield of Bronchoscopy for Lung Cancer

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<th>Sites/Patients</th>
<th>Yield/Sensitivity</th>
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<tr>
<td>2015 AQuIRE registry</td>
<td>15 sites 531 patients</td>
<td>Flexible bronchoscopy – 64%</td>
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<tr>
<td></td>
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<td>Radial EBUS – 57%</td>
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<td></td>
<td></td>
<td>EMN – 39%</td>
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<tr>
<td>2015 AEGIS study</td>
<td>28 sites 639 patients</td>
<td>Overall – 53% for diagnosis of cancer</td>
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<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>
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<tr>
<td></td>
<td></td>
<td>SB-F – 37%</td>
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<tr>
<td></td>
<td></td>
<td>TB-EBUS – 49%</td>
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<tr>
<td></td>
<td></td>
<td>&gt; 3cm – 57%</td>
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Ost et al. *AJRCCM*, 2015
Silvestri et al. *NEJM*, 2015
Tanner et al. *CHEST*, 2018
Pulmonary nodules

- Radiomics
- Genomics
- Proteomics
- Bronchoscopic Diagnostics
- Risk Prediction Calculators
- VOCs
Pretest probability of cancer and where biomarker fits best

Recommendations for Intermediate risk for cancer: Further diagnostic testing:
PET scan +/- Biopsy

Pretest probability of cancer and where blood biomarker may fit

Rule out biomarker

Recommendations for Intermediate risk for cancer: Further diagnostic testing:
   PET scan +/- Biopsy

Serial CT

Surgical Resection

Probability of cancer

0%  15%  30%  45%  60%  75%

Pretest probability of cancer and where blood biomarker may fit

Patient moves to Surveillance

Recommendations for Intermediate risk for cancer: Further diagnostic testing:
PET scan +/- Biopsy

Pretest probability of cancer and where blood biomarker may fit

Rule in biomarker

Recommendations for Intermediate risk for cancer: Further diagnostic testing: PET scan +/- Biopsy

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Surgical Resection

Probability of cancer

0%  15%  30%  45%  60%  75%

Pretest probability of cancer and where blood biomarker may fit

Recommendations for Intermediate risk for cancer: Further diagnostic testing:

PET scan +/- Biopsy

Serial CT

Patient is Operated on

Probability of cancer

0% 15% 30% 45% 60% 75%

Surgical Resection

• **Design:** prospective, multi-center trial (33 North American sites), 685 patients

• **Eligibility:** Age ≥ 40 with new lung nodule ≥8mm and ≤30mm

• **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**

Silvestri, Chest 2018
Results

• 178 patients had pCA ≤ 50%; 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, G; Tanner NT, et al, Chest 2018
Nodify XL2 Blood-Based Test

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

Silvestri, G; Tanner NT, et al, Chest 2018
Nodify XL2 Test Result Example

MAGNITUDE OF RISK REDUCTION DEPENDS ON pCA & TEST RESULT

SPN Calculator Pre-test
Risk of Malignancy

Nodify XL2 Test Result

Post-Nodify XL2 Risk of Malignancy

98% NPV
Likely Benign
Altitude Study

Intervention arm – investigators will receive result of biopsy. Control arm they will not

Randomize Lung nodules

Intervention Arm

Likely benign → Recommend surveillance

Indeterminate → Standard of care

Control Arm

Standard of care

Reduction in Invasive biopsies Futile surgery For benign dz
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
The perfect biomarker and my challenge for the next 5 years

• Both a high sensitivity and specificity (>95%).
  – If I have to pick one, would go with high sensitivity, NPV and rule out test.

• Reliable, reproducible, and provides useful Information on the majority of patients.
  – Indeterminate test results in majority of patients are problematic

• Fast turnaround

• Results portrayed in an easy to understand manner

• Low cost
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.
• Answer probably comes with escaping from silos combining technologies and utilizing deep machine learning/ Artificial intelligence.