The Diagnostic Evaluation Of Pulmonary Nodules

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Disclosures

- NOTE: All are Research Funding only
  - Patient Centered Outcomes Research Institute
  - NIH/NCI
  - 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
Pulmonary nodules

- Risk Prediction Calculators
- Radiomics
- Blood tests
- Biopsy options
- VOCs
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
  - **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

- Older age 1.03 (.99-1.07) 0.16
- female sex 1.82 (1.1-3.0) 0.02
- family hx of lung cancer 1.83 (.83-2.17) 0.23
- Emphysema 1.34 (.78-2.3) 0.29
- larger nodule size 2.06 (1.3-2.5) <0.001
- Upper lobe 1.93 (1.1-3.3) 0.02
- higher nodule count 0.92 (.85-1.00) 0.049
- Spiculation 2.187 (1.16-4.05) 0.02

AUC >.90  

CT: Size Matters

<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>

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
Management of Pulmonary Nodules by Community Pulmonologists
A Multicenter Observational Study

Nichole T. Tanner, MD, MSCR; Jyoti 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
Diagnosis and procedure use categorized by nodule pretest probability for cancer

<table>
<thead>
<tr>
<th>N=377</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 5% n=36</td>
<td>&gt;5 to &lt;65% n=300</td>
<td>&gt;65%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Benign</th>
<th>Malignant</th>
<th>Most Invasive Procedure Utilized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36 (100%)</td>
<td>5 (55%)</td>
<td>Surveillance 20 (56%)</td>
</tr>
<tr>
<td></td>
<td>224 (75%)</td>
<td>18 (45%)</td>
<td>Biopsy 10 (28%)</td>
</tr>
<tr>
<td></td>
<td>23 (55%)</td>
<td>7 (17%)</td>
<td>Surgery 6 (17%)</td>
</tr>
</tbody>
</table>

<p><span style="font-size:28px">Surgery for BENIGN DISEASE = 35%</span></p>
Nodules in the community

- 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

Tanner NT, et al. Chest.2015
Pulmonary nodules

- Radiomics
- Risk Prediction Calculators
- Blood tests
- Biopsy options
- VOCs
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
Oxnard G R et al. JCO 2011;29:3114-3119
Standard Cursor Measurements

3/05  1.3 cm

9/05  1.5 cm
Volumetrics

3/05
1.3 cm
787 mm³

9/05
1.5 cm
1.334 mm³
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>Singe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk‡</td>
<td>&lt;6 mm (&lt;100 mm³)</td>
<td>No routine follow-up</td>
</tr>
<tr>
<td></td>
<td>6–8 mm (100–250 mm³)</td>
<td>CT at 6–12 months, then consider CT at 18–24 months</td>
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<td></td>
<td>&gt;8 mm (&gt;250 mm³)</td>
<td>Consider CT, PET/CT, or tissue sampling at 3 months</td>
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<td></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>&lt;6 mm (&lt;100 mm³)</td>
<td>Optional CT at 12 months</td>
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<td>Multiple</td>
<td></td>
<td></td>
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<tr>
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<td>Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A).</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

- Biopsy options
- Risk Prediction Calculators
- Radiomics
- Blood tests
- VOCs
Transthoracic Needle Aspiration

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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<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>
</tbody>
</table>
|                        | 10 studies 1,367 patients     | < 2cm – 34%  
|                        |                              | > 2cm – 63%    |
| 2012 Meta-analysis     | 39 studies 3,004 patients     | Overall – 70%  
|                        |                              | > 2cm – 82% 
|                        |                              | < 2cm – 61%   |

Rivera et al. *CHEST* 2013  
Wang Memoli et al. *CHEST* 2012
# Yield of Bronchoscopy for Lung Cancer

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<td><strong>2015 AQuIRE registry</strong></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><strong>2015 AEGIS study</strong></td>
<td>28 sites 639 patients</td>
<td>Overall – 53% for diagnosis of cancer</td>
</tr>
<tr>
<td><strong>2018 Multicenter RCT</strong></td>
<td>5 sites 221 patients</td>
<td>Overall – 44%</td>
</tr>
<tr>
<td>standard bronchoscope with fluoroscopy (SB-F) vs thin bronchoscope with radial EBUS (TB-EBUS)</td>
<td></td>
<td>SB-F – 37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TB-EBUS – 49%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 3cm – 57%</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 bronchoscopical examination

Silvestri, NEJM, 2015
Pulmonary nodules

- Radiomics
- Risk Prediction Calculators
- Biopsy options
- VOCs
- Blood tests
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
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
Comparison of AUCs for ROCs of lung nodule malignancy risk assessment tools relative to 95% NPV zone.
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

[ROC curve diagram]

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.