Pulmonary Nodules: Evaluation and Management

David F. Yankelevitz, MD

Disclosure

- Dr. David Yankelevitz is a named inventor on a number of patents and pending patent applications relating to the evaluation of diseases of the chest including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF) are non-exclusively licensed to General Electric. As an inventor of these patents, Dr. Yankelevitz is entitled to a share of any compensation which CRF may receive from its commercialization of these patents.
**Historical Perspective**

- **1972: Prototype CT**
  - Several hrs per slice acquisition; days for reconstruction
- **1974: 1st Generation CT**
  - 2.5 min/slice
- **1976: Whole-body CT**
  - 5 sec/slice
- **1989: Helical/Spiral CT**
  - 0.3 sec/slice; 40 sec for entire chest (40cm Z-axis)
- **1998: 4-row MDCT**
  - 10 sec for entire chest
- **2002: 16-row MDCT**
  - 8 sec for entire chest
- **2004: 64-row MDCT**
  - 5 sec for entire chest
- **2009: 64-row MDCT**
  - <1 sec for entire chest
- **2011: 128-row/dual energy**
  - ???

**Advances in CT**

- **Improvements in image quality**
  - Spatial resolution
  - Temporal resolution
  - Artifact reduction
- **Dual energy**
  - Spectral analysis
  - Iodine enhanced
- **Improvements in radiation dose**
  - Iterative reconstruction
  - Model based
Ultra Low-dose CT

10mm Slice Thickness

© ELCAP 2002
1mm Slice Thickness

Increased Detection

- Increased use of CT
- Screening
Small < 5mm nodule

Right Lung

Trachea (main airway)

Small < 5mm nodule

Right Lung

Trachea (main airway)
One Year Later

Blood vessels

Adenosquamous carcinoma

The Challenge

- To develop useful criteria to efficiently diagnose these small nodules. Currently, many small nodules are being dismissed as not being clinically important, however scientific criteria needs to be applied before making this decision.
When Do We Know for Sure?

- Calcification in a benign pattern
- No change in size over two years

Patterns of Calcification

- Central
- Ring or Laminated
- Popcorn
- Diffuse
Pleural Plaque

- Pleural Plaque
- Pleural fissure

Pleural Plaque

- Subtle pleural fissure
Pleural Plaque

Intrapulmonary Lymph Node
Non-invasive Imaging Tests

- Contrast Enhancement
- PET/CT imaging
- Growth
- Morphologic features

Diagnosis: Invasive

- Minimally Invasive
  - Bronchoscopy
  - Transthoracic Needle Biopsy

- Invasive
  - Thoracoscopy
  - Thoracotomy
Choice of Work-up

- Wide range of sensitivity/specificity
- Availability of equipment
- Ability to perform procedures
- Varying reimbursements

Definition of a Positive Result

- The concept of a positive result must be confined to findings that justify further diagnostic workup
- Calcified nodules
- Small nodules
Further Considerations by Size

- For some given size nodule (<5mm, perhaps as small as 1 mm), the frequency with which they occur in a screening population will approach 100%
- Once this occurs, finding a nodule of this size no longer has any meaning in terms of diagnosis
  - A single red blood cell in a stool specimen
  - A single PVC on a 24 hour Holter monitor

Positive Result of Initial Test

- Baseline:
  - ≥ 5mm solid
  - ≥ 8mm nonsolid

- Repeat:
  - any new nodule
  - growth
Three Point Scale

- **Negative Result**: No workup required
- **Semi-positive Result**: Annual screen required
- **Positive Result**: According to protocol

<table>
<thead>
<tr>
<th>Result</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>&lt;1 mm</td>
</tr>
<tr>
<td>Semi-positive</td>
<td>~1 mm</td>
</tr>
<tr>
<td>Positive</td>
<td>5 mm</td>
</tr>
</tbody>
</table>

Comparison of Protocols

- **Similarities**
  - Nodule size is primary determinant on baseline
  - Growth estimation is primary follow-up determinant
- **Differences**
  - PET/CT and biopsy
  - Size estimation
  - Size criterion
  - Time to follow-up
  - Antibiotic
PLuSS Conclusions

CT detects many indeterminate lung nodules, as well as early stage lung cancer... Our results indicate a tendency, in our community, towards overly aggressive diagnostic evaluation, including thoracotomy and VATS lung resection of CT screen-detected lung nodules. These results underscore the importance of adhering to diagnostic algorithms for managing CT screen-detected nodules.

Wilson DO et al. Am J Respir Crit Care Med. 178; 956-61

Fleischner Society Guidelines

<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 mo if unchanged, no further follow-up.</td>
</tr>
<tr>
<td>&gt;4-6</td>
<td>Follow-up CT at 12 mo if unchanged, no further follow-up.</td>
<td>Initial follow-up CT at 6-12 mo then at 18-24 mo if no change.</td>
</tr>
<tr>
<td>&gt;6-8</td>
<td>Initial follow-up CT at 6-12 mo then at 18-24 mo if no change.</td>
<td>Initial follow-up CT at 3-6 mo then at 9-12 and 24 mo if no change.</td>
</tr>
<tr>
<td>&gt;8</td>
<td>Follow-up CT at around 3, 9, and 24 mo, dynamic contrast-enhanced CT, PET, and/or biopsy.</td>
<td>Same as for low-risk patient.</td>
</tr>
</tbody>
</table>

Note.—*Nodules detected in indeterminate nodules in persons 35 years of age or older.
†Average of length and width.
‡Minimal or absent history of smoking and of other known risk factors.
§History of smoking or of other known risk factors.
§The risk of malignancy in this category (<1%) is substantially less than that in a baseline CT scan of an asymptomatic smoker.
§Nodules (ground-glass) or partly solid nodules may require longer follow-up to exclude indolent adenocarcinoma.
Fleischner Society Guidelines

- “Note that the recommendations ... apply only to adult patients with nodules that are “incidental” in the sense that they are unrelated to known underlying disease.”
- “Patients known to have or suspected of having malignant disease”
- “Patients with unexplained fever”

MacMahon H. Radiol 2005; 247: 847

ACCP Guidelines

Background: Pulmonary nodules are spherical radiographic opacities that measure up to 30 mm in diameter. Nodules are extremely common in clinical practice and challenging to manage, especially small, “subcentimeter” nodules. Identification of malignant nodules is important because they represent a potentially curable form of lung cancer.

Methods: We developed evidence-based clinical practice guidelines based on a systematic literature review and discussion with a large, multidisciplinary group of clinical experts and other stakeholders.

Results: We generated a list of 29 recommendations for managing the solitary pulmonary nodule (SPN) that measures at least 8 to 10 mm in diameter; small, subcentimeter nodules that measure ≤ 5 mm to 10 mm in diameter; and multiple nodules when they are detected incidentally during evaluation of the SPN. Recommendations stress the value of risk factor assessment, the utility of imaging tests (especially old films), the need to weigh the risks and benefits of various management strategies (biopsy, surgery, and observation with serial imaging tests), and the importance of eliciting patient preferences.

Conclusion: Patients with pulmonary nodules should be evaluated by estimation of the probability of malignancy, performance of imaging tests to characterize the lesion(s) better, evaluation of the risks associated with various management alternatives, and elicitation of patient preferences for treatment.

(CHEST 2007; 132:1088–1309)
ACCP Guidelines

- Essentially agree with Fleischner Society
  - Patient preferences should be considered
  - Nodule consistency
  - F/U using low dose scans

Gould M. Chest 2007; 132: 108S

Figure 2. Recommended management algorithm for patients with subcentimeter pulmonary nodules that measure ≤ 8 mm in diameter.
Growth

Advantages of Volume Measurements

- Greater proportional change
  - 26% diameter increase corresponds to 100% volume increase
- Measurement of asymmetric growth
- Tumor volume doubling time
Computer Aided Diagnosis

- Improves with increased resolution
- Large datasets needed to improve algorithms
- Better understanding of measurement error
- New sub-voxel approaches (cellular size)

8 mm Stable Nodule

right lung

nodule

blood vessel
Volumetric Growth Rate Analysis

- 8 mm stable pulmonary nodule at baseline and 181 days later
- MVGI = 0.57%

10 mm Malignant Nodule
10 mm malignant pulmonary nodule at baseline and 32 days later
MVGI = 22.0% -- Squamous Cell Carcinoma

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Measurement Error
Studies on commercial products

Scan subjects twice during one session and measure the lesion size difference

<table>
<thead>
<tr>
<th>Author</th>
<th># nodules</th>
<th>Slice (mm)</th>
<th>% vol. change confidence interval</th>
<th>Software</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gietema (2007)</td>
<td>218</td>
<td>0.75</td>
<td>-21.2 – 23.8</td>
<td>Siemens LungCare</td>
</tr>
<tr>
<td>Wormanns (2004)</td>
<td>151</td>
<td>1.25</td>
<td>-20.4 – 21.9</td>
<td>Siemens LungCare</td>
</tr>
</tbody>
</table>

95% Level of Agreement

Semi-Automatic Zero-Change Dataset
Sources of Measurement Uncertainty

- Scanner
  - Inherent properties
  - Adjustable parameters
- Software
  - Manual
  - Computer-assisted (hybrid)
  - Semi-automatic
- Tumor
  - Boundary definition

1mm Zone of Uncertainty/Volume

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>Uncertainty (mm)</th>
<th>1mm Zone (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>33.5</td>
<td>65.4</td>
</tr>
<tr>
<td></td>
<td>113.1</td>
<td></td>
</tr>
<tr>
<td>10.0</td>
<td>381.7</td>
<td>523.6</td>
</tr>
<tr>
<td></td>
<td>696.9</td>
<td></td>
</tr>
</tbody>
</table>
“Zone of Uncertainty”

Lungs

ambiguous borders

Normal lung

Cancer (solid)

Zhou et al Radiology

aorta

spine

cancer nodule

Fine Needle Aspiration
Large Solid Nodule

- tumor
- right lung
- blood vessels
- airway
- airway

2mm x 2mm
No Adjustment

breastbone (sternum)
heart
spine

Geometric Considerations

Patient's back
Small Nodule

Small Nodule
Small Nodule
Small Nodule

Small Nodule
Uncertainty

Predicting Needle Tip Location
Cytology

- Immediate Cytologic Evaluation (ICE)
- Specimens are quick-dried and air-dried
- Determine whether additional studies are necessary
Cytology

Tissue Procurement

- What are we trying to learn?
  - How much tissue do we need?
  - How do we get it?

- Each institution should set up protocols for small tissue samples
Cytologic Evaluation

- Morphology
- Immunohistochemistry
- Fluorescence In-situ hybridization (FISH)
- Microarray analysis
- Optical CT

Conclusions

- Increasing prevalence of small < 5mm nodules
- Conservative approaches are now recommended for f/u with careful attention to empirically driven protocols (IASLC)
- Major advances in image processing techniques and ability to process small tissue samples need to be incorporated
Global Resource for Advancing Cancer Education

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