Lung Cancer Screening: Nodule Management

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Nodule Management

• Make sure the nodular opacity is significant.
• Perifissural nodules can be excluded.

Perifissural Nodules

• Solid nodule along fissure
• Triangular or lentiform
• Broadest base along fissure
• 794 identified in NELSON trial
• None were malignant

Nodule Management

• Size
• Margins
• Attenuation
• CAD
**Size**

- NLST protocol
- NCCN guidelines

**NLST Screen Interpretation**

- Positive Screen
  - Non-calcified nodule(s) ≥4 mm in greatest transverse dimension
  - Any other suspicious finding (e.g., lobar collapse, enlarged hilar/mediastinal lymph nodes, endobronchial lesion)

- Negative Screen
  - Non-calcified nodule <4 mm or benign calcified nodule
  - Other minor abnormality (e.g., emphysema, gallstones) or abnormality requiring further evaluation (e.g., other mass)
  - No abnormality

**Evaluation of Positive Screens**

- **4-10 mm nodules:** 3-6 month follow-up low dose CT
- **10 mm or larger:** Immediate more aggressive evaluation
- Modified by margin, attenuation

**Larger Nodule Threshold**

- ELCAP group – 21,136 screened
- 5 mm threshold – 3,396 positives
  - 119 cancers
- 9 mm threshold – 838 positives
  - 111 cancers
- Decreased positives from 16% to 4% - 8 “missed” cancers all Stage I
  
  Henschke, Ann Inter Med, 2013, 158

**NCCN Guidelines**

- Different recommendations for follow-up based on nodule size than NLST
- Different recommendations for follow-up based on nodule attenuation
- Recommended by ACR in interim

**NCCN Guidelines**

- Solid/Part Solid nodules
  - < 6 mm – annual screening
  - 6-8 mm – LDCT in 3 months and 6 months if no growth
  - > 8 mm – consider PET/CT or biopsy
Nodule Management

- Size
- Margins
- Attenuation
- CAD

CT Nodule Margins

- Smooth
- Lobulated
- Irregular/spiculated

Likelihood Ratios CT

- Smooth – 0.3
- Lobulated – 0.74
- Spiculated – 5.54

Nodule Management

- Size
- Margins
- Attenuation
- CAD

CT Nodule Attenuation

- Solid
- Semi-solid
- Ground glass

Lung Cancer Risk

- Semisolid – 63%
- Ground glass – 18%
- Solid – 7%

Gurney, Radiology, 186; 1993
Henschke, AJR, 18; 2002
NCCN Guidelines

- Ground Glass Nodules
  - < 5mm – annual screening
  - 5-10 mm – LDCT in 6 months
  - > 10mm – LDCT in 3-6 months
    Stable – F/U LDCT in 6 months or consider biopsy

- Multiple GGOs
  - < 5 mm – annual screening
  - > 5 mm without dominant lesion – LDCT in 6 months
  - > 5 mm with dominant lesion or with part solid component – LDCT in 3-6 months

Nodule Management

- Size
- Margins
- Attenuation
- CAD

CAD Nodule Management

- Morphology
- Volume Doubling Time

CAD Morphologic Analysis

- Computerized output using 56 morphological features improved radiologist discrimination of malignant nodules
  Li, AJR, 2004; 183
- Computerized output improved resident performance, but did not improve radiologist performance
  Awai, Radiology, 2006; 239

CAD Volumetry

- More accurate and reproducible in predicting nodule malignancy
  Yankelevitz, Radiology, 2000; 217
  Revel, Radiology, 2004; 231
  Jennings, Radiology, 2004; 231
  Reeves, Acad Radiol, 2007; 14
  Ko, Radiology, 2012; 262
**CAD in Screening Studies**

- NELSON
- Use volumetric measurements to determine growth rate of 4-10 mm nodules detected at screening
- VDT < 400 days positive
- VDT > 400 days negative

**Volumetry Limitations**

- Nodule size
- Segmentation - Nodule attachments (vessels, pleura)
- Radiation dose
- Inspiratory effort
- Algorithms

**Size Limitations**

- Smaller nodules have increasing absolute percentage of error for nodule volumetry
- Increasing percentage of surface area voxels result in increasing partial volume artifact

Goo, Radiology, 2005; 235
Petrou, AJR, 2007; 188

**Segmentation Limitations**

- Nodule contact with adjacent vessels or pleura makes accurate segmentation difficult
- Absolute percentage volume error for pleural nodules higher than other types of nodules

Das, Eur Radiol, 2007; 17

**Dose Limitations**

- Mean absolute error was smaller for standard dose images vs low dose images
- Important to measure on similar dose images

Ko, Radiology, 2003; 228

**Inspiratory Effort Limitations**

- Changes in overall lung volume affect nodule volume measurements
- Mean percentage difference in nodule volume was 23% between exams done in inspiration and expiration

Goo, Korean J Radiol, 2006; 7
Algorithm Limitations

• de Hoop, Eur Radiol, 2009; 19
• Compared six software packages
• Significant differences in mean volumes
• Nodule volumes should not be compared between different software packages

Nodule Mass

• de Hoop, Radiology, 2010; 255
• Better than volume increase alone in detection of malignant GGNs
• Nodule mass = nodule volume x mean attenuation
• May prove helpful in future

Biomarkers

• Applied after screen detection of a nodule to identify nodules that should be more aggressively worked up

Potential Biomarkers

• Promoter methylations
• Genomics
• Proteonomics
• Can be studied on blood, serum, plasma or sputum
• Volatile organic compounds in exhaled breath

Summary

• Goal is to optimize identification of malignant nodules
• Imperative to establish standardized protocols for scanning and nodule management to allow appropriate outcomes research
**Scanning Parameters**

- Thin section 2 - 3.2 mm slice
- 1.8-2mm Increments
- Low Dose NLST protocol

**Summary of Published Interscan Variability of Same-Day CT Scans for Making Volumetric Measurements**

<table>
<thead>
<tr>
<th>Author (Reference No.)</th>
<th>Year</th>
<th>No. of Subjects</th>
<th>Mean Volumetric Size</th>
<th>Slice Thickness</th>
<th>95% Limit of Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ninomiya et al. (40)</td>
<td>2014</td>
<td>151</td>
<td>7.4 mm (2.2-23.3 mm)</td>
<td>1.25 mm</td>
<td>±20-22%</td>
</tr>
<tr>
<td>Grudean et al. (40)</td>
<td>2016</td>
<td>43</td>
<td>15.5 mm (6.3-24.4 mm)</td>
<td>1.25 mm</td>
<td>±18-35%</td>
</tr>
<tr>
<td>Gitten et al. (41)</td>
<td>2007</td>
<td>218</td>
<td>123 mm (10.4-477 mm)</td>
<td>1 mm</td>
<td>±17-34%</td>
</tr>
<tr>
<td>de Hoep et al. (46)</td>
<td>2009</td>
<td>254</td>
<td>10.3 mm (1.2-16 mm)</td>
<td>1.25 mm</td>
<td>±14-37%</td>
</tr>
<tr>
<td>Zhao et al. (44)</td>
<td>2010</td>
<td>32</td>
<td>30.2 mm (10.8-10.7 mm)</td>
<td>1.05 mm</td>
<td>±12-19%</td>
</tr>
</tbody>
</table>

Note: *Upper limits of agreements from six software packages. Numbers in parentheses are size range. No. = number

http://dx.doi.org/10.3348/kjr.2011.12.2.145

**Lobulated Margins**

- Increase likelihood of malignancy vs smooth
- More lobulations → increase risk

**Spiculated Margins**

- Highest likelihood of cancer
- 90% risk by Bayesian Analysis

Gurney, Radiology, 186 1993
**Summary of Published Studies on Performance of CAD Systems for Detecting Lung Nodules**

<table>
<thead>
<tr>
<th>Author (Reference No.)</th>
<th>Year</th>
<th>No. of Nodules</th>
<th>CAD Sensitivity</th>
<th>False Positive Rate</th>
<th>CT Section Thickness</th>
<th>Nodule Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLatchy et al. [9]</td>
<td>2004</td>
<td>43</td>
<td>70%</td>
<td>8.1</td>
<td>2.5 mm</td>
<td>5-17.1 mm</td>
</tr>
<tr>
<td>Partan et al. [11]</td>
<td>2005</td>
<td>123</td>
<td>75%</td>
<td>0.55</td>
<td>0.75 mm</td>
<td>5-15.6 mm</td>
</tr>
<tr>
<td>Lee et al. [12]</td>
<td>2005</td>
<td>78</td>
<td>60%</td>
<td>3.5</td>
<td>2.5 mm</td>
<td>4-15.6 mm</td>
</tr>
<tr>
<td>Lee et al. [13]</td>
<td>2005</td>
<td>154</td>
<td>69%</td>
<td>6.6</td>
<td>3.0 mm</td>
<td>3.37 mm</td>
</tr>
<tr>
<td>Ge et al. et al. [13]</td>
<td>2006</td>
<td>204</td>
<td>70%</td>
<td>3.3</td>
<td>3.0 mm</td>
<td>—</td>
</tr>
<tr>
<td>Do et al. et al. [13]</td>
<td>2006</td>
<td>136</td>
<td>72%</td>
<td>0.5</td>
<td>3-2 mm</td>
<td>Mean: 3.4 mm</td>
</tr>
<tr>
<td>Rechtman-Johny et al. [15]</td>
<td>2007</td>
<td>92</td>
<td>65%</td>
<td>3.4</td>
<td>5.25 mm</td>
<td>4-11.9 mm</td>
</tr>
<tr>
<td>Lee et al. [2]</td>
<td>2006</td>
<td>702</td>
<td>60%</td>
<td>3.1</td>
<td>3-3.2 mm</td>
<td>&lt; 18 mm</td>
</tr>
<tr>
<td>Hinose et al. [2]</td>
<td>2008</td>
<td>48</td>
<td>71%</td>
<td>0.95</td>
<td>1 mm</td>
<td>2.3-12.3 mm</td>
</tr>
<tr>
<td>Shibano et al. [17]</td>
<td>2004</td>
<td>281</td>
<td>65%</td>
<td>8.1</td>
<td>3.29-2.0 mm</td>
<td>2-15.6 mm</td>
</tr>
</tbody>
</table>

Note: Test CAD systems were evaluated using same dataset. CAD = computer-aided diagnosis, No. = number.


http://dx.doi.org/10.3348/kjr.2011.12.2.145

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**Risk of Lung Cancer**

- Semisolid – 63%
- Ground glass – 18%
- Solid – 7%

Henschke, AJR, 170, 2002

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**Second Reader**

- Increase number of nodules detected
- Increased interpretation time
- Not as sensitive as CAD
  - 63% vs. 76% for CAD

Rubin, Radiology, 2005; 234

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**Nodule Detection**

- Mayo Lung cancer screening study (SCTS)
  - 26% of nodules were missed on initial screen
  - 62% were < 4mm
  - 38% were > 4mm

Swensen, AJRCC, 165: 2002

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**Nodule Detection Optimization**

- CAD
- Reconstructions (MIPS)

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**CAD Detection**

- Increase number of nodules detected
- Detects nodules differently than humans
**CAD vs Radiologists**

- Better for nodules <5mm
- Better for isolated nodules
- Not as good for larger nodules
- Not as good for nodules attached to other structures
- Not as good for GGO’s

Marten, Clin Radiol, 2005; 60
Lee, Invest Radiol, 2004; 39

**CAD for Detection**

- Beyer, Eur Radiol, 2007; 17
- CAD as concurrent reader vs CAD as second reader
- CAD as second reader was more sensitive for nodule detection

**CAD Morphology**

- Attenuation makes a difference
- Non-solid nodules - lobulated border is only margin predictor of malignancy

Lee, Eur Radiol, 2009; 19

**MIPS**

- Improve nodule detection
- Limited addition to interpretation time
- Preferred method over CAD

Jankowski, Radiology, 17; 2007

**Non solid Nodules**

- Semisolid of any size should be followed up at 3 months and if persistent should be worked up more aggressively
- Proposed algorithm for GGNs

**Groundglass Followup**

- <5mm – no follow up
- 5-10mm – follow up 3-6 months
  - If growth consider more aggressive work up
  - If stable continue screening, but may need longer follow up
- >10mm – resect
Fleischner Guidelines

<table>
<thead>
<tr>
<th>Nodule Size (mm³)</th>
<th>Low-Risk Patient¹</th>
<th>High-Risk Patient²</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4</td>
<td>No follow-up needed³</td>
<td>follow-up CT at 12 mo; if unchanged, no further follow-up²</td>
</tr>
<tr>
<td>&gt;4-6</td>
<td>Follow-up CT at 12 mo; if unchanged, no further follow-up²</td>
<td>Initial follow-up CT at 6-12 mo then at 18-24 mo if no change²</td>
</tr>
<tr>
<td>&gt;6-8</td>
<td>Initial follow-up CT at 6-12 mo then at 18-24 mo if no change²</td>
<td>Initial follow-up CT at 3-6 mo then at 9-12 and 24 mo if no change²</td>
</tr>
<tr>
<td>&gt;8</td>
<td>Follow-up CT at around 3, 5, and 24 mo, dynamic contrast-enhanced CT, PET, and/or biopsy²</td>
<td>Same as for low-risk patient²</td>
</tr>
</tbody>
</table>

Radiology, 2005, 237

Nodule Management

- Size
- Margins
- Attenuation
- CAD
RC101
Lung cancer screening: How I do it

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<thead>
<tr>
<th>Current Data Summary and Recommendations</th>
<th>Ella Kazerooni, MD</th>
</tr>
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<tr>
<td>Starting a Screening Program</td>
<td>Reggie Munden, MD, DMD</td>
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<tr>
<td>Management Strategies for Screen-Detected Nodules</td>
<td>Thomas Harman, MD</td>
</tr>
<tr>
<td>Biopsy of Screen-Detected Nodules</td>
<td>David Yankelevitz, MD</td>
</tr>
<tr>
<td>Other Findings: What Do I Do?</td>
<td>Caroline Chiles, MD</td>
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