Bronchoscopic Innovations for Diagnosis of Early Lung Cancer

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Lung Cancer Screening – Transformative Change in Lung Cancer Outcome

• Lung cancer is the most common cause of cancer death worldwide – >1.6 million deaths per year (>340,000 in China)

• Modest improvement in 5 year survival over the last two decades (<18%)

• Screening with low dose CT scan shown to reduce lung cancer mortality by 20% in high risk smokers
NLST - 20% Reduction In Lung Cancer Mortality With CT Screening

53,454 Participants
- 55 to 74 years;
- ≥ 30 pack-years
- Median follow-up 6.5 years
- 6.7% reduction all cause mortality

NLST. NEJM 2011; 365:395-409
Risk Prediction - PLCO_{M2012}

Predictors: Risk $\uparrow$
- age
- $\Delta$ race/ethnicity
- $\downarrow$ education (SES)
- $\downarrow$ BMI
- $\uparrow$ personal history of cancer
- $\uparrow$ family history of lung cancer
- $\uparrow$ COPD
- $\uparrow$ smoking status, $\uparrow$ intensity, $\uparrow$ duration & $\downarrow$ quit-time

Predictive performance: in validation set - PLCO intervention arm AUC = 0.80

NEJM 2013;368:728-36
Improving Accuracy of PLCOm2012

• Adjust predictor coefficients for different age groups or ethnicity or adjust risk threshold (e.g. Ontario, Canada)

• Improve the prediction model (e.g. refine family history of cancer, personal history of cancer, alcohol use, biomass combustion, radon exposure, air pollution) – requires prospective study
Nodule Management Pathway
Lung-RADS Classification

<table>
<thead>
<tr>
<th>Lung-RADS Category</th>
<th>Baseline Screening</th>
<th>Subsequent Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No nodules; nodules with calcification</td>
<td>No nodules; nodules with calcification</td>
</tr>
<tr>
<td>2</td>
<td>Solid/part solid: &lt;6 mm</td>
<td>Solid/part solid: &lt;6 mm</td>
</tr>
<tr>
<td></td>
<td>GGN: &lt;20 mm</td>
<td>GGN: &lt;20 mm or unchanged/slowly growing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Category 3-4 nodules unchanged at ≥3 mo</td>
</tr>
<tr>
<td>3</td>
<td>Solid: ≥6 to &lt;8 mm</td>
<td>Solid: New ≥4 to &lt;6 mm</td>
</tr>
<tr>
<td></td>
<td>Part solid: ≥6 mm with solid component &lt;6 mm</td>
<td>Part solid: New &lt;6 mm</td>
</tr>
<tr>
<td></td>
<td>GGN: ≥20 mm</td>
<td>GGN: New ≥20 mm</td>
</tr>
<tr>
<td>4A</td>
<td>Solid: ≥8 to &lt;15 mm</td>
<td>Solid: Growing &lt;8 mm or new ≥6 and &lt;8 mm</td>
</tr>
<tr>
<td></td>
<td>Part solid: ≥8 mm with solid component ≥6 and &lt;8 mm</td>
<td>Part solid: ≥8 mm with new or growing solid component &lt;4 mm</td>
</tr>
<tr>
<td>4B</td>
<td>Solid: ≥15 mm</td>
<td>Solid: New or growing and ≥8 mm</td>
</tr>
<tr>
<td></td>
<td>Part solid: Solid component ≥8 mm</td>
<td>Part solid: ≥6 mm with new or growing solid component ≥4 mm</td>
</tr>
<tr>
<td>4X</td>
<td>Category 3 or 4 nodules with additional features; imaging</td>
<td>Category 3 or 4 nodules with additional features; imaging</td>
</tr>
<tr>
<td></td>
<td>findings that increase suspicion of malignancy</td>
<td>findings that increase suspicion of malignancy</td>
</tr>
</tbody>
</table>

GGN = ground-glass nodule.

* Size is the average diameter rounded to the nearest whole number. Growth is a size increase ≥1.5 mm.

- Potentially avoid 46% to 52% follow-up chest CTs for false-positive CTs and reduce invasive diagnostic procedure by 23% compared to NLST
- lung-RADS missed 9.2% to 16.2% lung cancers compared to NLST – 44% ground-glass nodules <20 mm

PanCan Lung Nodule Malignancy Risk Calculator

Nodule Calculator

- **Age:**
- **Sex:** Male, Female
- **Family history of lung cancer?** No, Yes
- **Emphysema?** No, Yes
- **Nodule Size:** (Dimension in millimeters)
- **Nodule Type (choose only one):**
  1. Groundglass/nonsolid
  2. Semisolid
  3. Solid
- **Upper Lobe Location?** No, Yes
- **Spiculation?** No, Yes
- **Nodule Count:** Enter the total number of nodules.

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**AUC**

<table>
<thead>
<tr>
<th></th>
<th>≤10 mm</th>
<th>GGN</th>
<th>Sub-solid</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>0.94</td>
<td>0.92</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Principle of OCT

OCT or Optical Coherence Tomography is the optical analogue to ultrasound imaging with:
- Higher resolution (10μm)
- Decreased penetration (2-3 mm)

OCT requires interferometric detection to achieve high axial resolution.
AF-OCT Extends Range of Examination with Improved Image Resolution

OCT probe diameter with plastic sheath = 0.9 mm
Histology Correlation - Pig Airways

Movat’s pentachrome vs. post-formalin ex vivo OCT imaging

- Low Scattering
- Cartilage (C)
- Smooth Muscle (SM)
- Epithelium (E)
- Lamina Propria (LP)
- High Scattering
Histology Correlation - Human Airways

Masson’s trichrome

post-formalin ex vivo OCT imaging

- Glands (G)
- Cartilage (C)
- Smooth Muscle (SM)
- Epithelium (E)
- Lamina Propria (LP)

Low Scattering

High Scattering
OCT Images of Bronchioles With and Without Surrounding Emphysema

15 μm axial resolution

Non-smoker normal

Smoker without emphysema

Mild emphysema

Moderate

Severe
3D Vascular Imaging Of Large & Small Blood

pullback 16mm @ 1mm/s
frame rate = 6.25fps, frame pitch = 160um
Doppler OCT Identifies Blood Vessels
Diagnostic Confirmation

Suspicious lesions on screening CT needs to be biopsied for diagnostic confirmation

Size of screening CT-detected lung cancers* (NLST)
- 60% to 78% ≤ 20 mm
- 20% to 35% ≤ 10 mm

CT-Guided Transthoracic Lung Biopsy (CT-TTLB)

<table>
<thead>
<tr>
<th>Diagnostic Yield (Nodule &lt; 15mm)</th>
<th>Complication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 - 80%</td>
<td>60 - 70%</td>
</tr>
<tr>
<td>15% (Pneumothorax)</td>
<td>1% (Pneumothorax)</td>
</tr>
<tr>
<td>1% (Bleeding)</td>
<td>&lt;1% (Bleeding)</td>
</tr>
<tr>
<td>0.4% (Severe/Fatal)</td>
<td></td>
</tr>
</tbody>
</table>

Transbronchial Biopsy (TBBx)

McWilliams, 2013; Wiener, 2011
Bronchoscopic Biopsy Safer But Accuracy Needs Improvement

- Fluoroscopy
- Electromagnetic Navigational Bronchoscopy (ENB)
- Radial Endobronchial Ultrasound (R-EBUS)
- Virtual Bronchoscopic Navigation (VBN)
- Guide Sheath (GS) Technique
Limitations Of Current Bronchoscopic Biopsy Methods

• Spatial accuracy of existing techniques for biopsy guidance is poor
  – Image guidance (R-EBUS) and sample collection are serial procedures (sample collection is blind)
  – Guide sheath can move and/or stretch 10’s of mm
  – ENB resolution is limited (tidal breathing, sensor registration)
Poor Image Resolution of R-EBUS Especially For Small Sub-solid Nodules

- Solid
- Semi-Solid
- Non-Solid

20% nodules sub-solid

No Doppler function to visualize blood vessels
Existing Biopsy Tools Are Unsuitable Except for End-on Tumor Bronchus Geometry
Changing Lung Cancer Care

• Early detection in high risk individuals improve outcome while keeping costs under control
• Shifting from palliative treatment to curative treatment
• Decrease symptom burden & hospital resource utilization
• Optimize lung cancer care pathway – reduce costs and improve outcome
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