Screening Populations: COPD or Lung Cancer or Both? Risk in High-Risk Populations

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Disclosures:

National Lung Cancer Advisory Board, Genentech Consultant (Clinical Trial Design), Olympus America
Outline:
1) Risks in a screening population
2) COPD and emphysema as risks for lung cancer
3) Non-nodular CT features as risks for lung cancer death
Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team

Aged 55-74, 30 pk-yr (quit <15 yr prior), annual CT x 3 years
≥ 4mm considered positive

<table>
<thead>
<tr>
<th>Table 7. Cause of Death on the Death Certificate, According to Screening Group.</th>
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</thead>
<tbody>
<tr>
<td>Cause of Death</td>
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<tr>
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<tr>
<td>Neoplasm of bronchus and lung†</td>
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<tr>
<td>Other neoplasm</td>
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<tr>
<td>Cardiovascular illness</td>
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<tr>
<td>Respiratory illness</td>
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<tr>
<td>Complications of medical or surgical care</td>
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<tr>
<td>Other</td>
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</tbody>
</table>
Risks: Benefits and harms of CT screening

20% relative risk reduction, 0.33% absolute risk reduction

649 cancers (3.6% of positive tests)

NNS: 320, NNH: 52 (potentially avoidable invasive procedure)

New Definition (LungRADS): ≥ 6mm considered positive
Sensitivity decreases from 94% to 85%

However even at the ≥4mm cutoff, 29% of lung cancer deaths occurred in non-screen detected cases*


* based on years T0-T2, NLST-163 PI: Kinsey
A low-risk nodule...

Lung-RADS 2—Continue annual screening with LDCT in 12 months

Difficult to evaluate RLL nodule due to low-dose technique.
Risk: Small changes may threaten the screening benefit

Monte-Carlo simulation may be used to estimate changes in lung cancer mortality in the setting of lung cancer screening.

An upper bound estimation argues that increasing nodule size alone may result in a small increase in LC deaths
Moving forward can we use features other than those of the nodule to help define lung cancer risk?

Prevent Cancer Foundation Executive Summary 2015: “With lung cancer screening however, there are new opportunities to have a greater impact with such efforts, as the information obtained with a lung CT contains three-dimensional information that is much more informative than the usual two-dimensional information obtained with standard mammography.”
COPD: Reduced FEV1 is associated with lung cancer

10-40% of patients with CT emphysema have normal lung function, making emphysema a potentially more sensitive biomarker for LC

Quantitative emphysema (%LAA) is only weakly associated with lung cancer

Table 5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model 1†</th>
<th>Model 2‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>1.09 (1.05, 1.13)</td>
<td>1.09 (1.05, 1.13)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.58 (1.06, 2.37)</td>
<td>1.62 (1.09, 2.42)</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>1.03 (1.02, 1.03)</td>
<td>1.03 (1.02, 1.04)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.95 (0.91, 0.98)</td>
<td>0.95 (0.91, 0.98)</td>
</tr>
<tr>
<td>History of adult asthma</td>
<td>0.16 (0.05, 0.43)</td>
<td>0.22 (0.08, 0.57)</td>
</tr>
<tr>
<td>History of COPD or emphysema</td>
<td>3.41 (1.78, 6.94)</td>
<td>1.95 (1.03, 3.79)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are 95% confidence intervals.

† $R^2 = 0.142, P < .0001, c = 0.74$

‡ $R^2 = 0.128, P < .0001, c = 0.73$

NOTE: Weights are from random effects analysis

Smith et al. Lung Cancer. 77; 58-63 (2012)
Emphysema is emphysema, right?

Densitometric emphysema does not capture all potentially important information.
Patterns of Emphysema in COPD

Centrilobular Emphysema

Panlobular Emphysema

Paraseptal Emphysema

Courtesy of Raul San José Estépar
Radiographic Classification

Non emphysema
  - Mild centrilobular
  - Moderate centrilobular

Severe centrilobular
  - Panlobular
  - Paraseptal

Secondary Lobule
Schematic Description

Radiologic expression in HRCT

Incorporate spatial statistical structure (texture) of low density regions.

Courtesy of Raul San José Estépar
Emphysema morphology partially determines physiology

N = ~9000

Is a higher proportion of a particular emphysema morphology associated with a risk for lung cancer?
Moderate centrilobular emphysema is associated with a risk for lung cancer

8355 controls vs. 275 cases

<table>
<thead>
<tr>
<th>Lung Parenchymal Feature</th>
<th>OR</th>
<th>CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%LAA -950 (density threshold alone)</td>
<td>1.01</td>
<td>[0.99, 1.02]</td>
<td>0.146</td>
</tr>
<tr>
<td>Mild centrilobular (CL1)</td>
<td>0.26</td>
<td>[0.17, 1.61]</td>
<td>0.263</td>
</tr>
<tr>
<td><strong>Moderate centrilobular (CL2)</strong></td>
<td>2.41</td>
<td>[1.09, 5.32]</td>
<td><strong>0.029</strong></td>
</tr>
<tr>
<td>Severe centrilobular (CL3)</td>
<td>6.12</td>
<td>[0.97, 38.6]</td>
<td>0.054</td>
</tr>
<tr>
<td>Panlobular (PL)</td>
<td>4.99</td>
<td>[0.23, 108.8]</td>
<td>0.306</td>
</tr>
<tr>
<td>Pleural-based (PB)</td>
<td>13.4</td>
<td>[0.00, 1137]</td>
<td>0.713</td>
</tr>
</tbody>
</table>

Each model includes one of the above lung parenchymal features and is adjusted for age, gender, pack years, and airflow obstruction.

With the exception of %LAA-950, all morphologies were measured by the LH method at the level of the secondary pulmonary lobule.
But even if we can better diagnose cancer among the many screen detected nodules, not all patients with lung cancer die of it...

17% of patients diagnosed with screen detected lung cancer died of something else*...

Can we use CT features to predict who is likely to die of lung cancer?

* Screen detected in years T0-T2; NLST-163 PI: Kinsey
Are Tumors that Occur in Regions of Emphysema Associated with a Worse Prognosis?
Regional tumor emphysema

Approach:
- 263 cases from the MGH-LCS study
- Classified tumors by region
- Compared with regional LAA-950% score
- Survival analysis

MGH-LCS: Massachusetts General Hospital Lung Cancer Susceptibility Study,
PI: DC Christiani
Tumors occurring in regions of emphysema are larger

Tumor Emphysema
Quartile (↑):

1st  2nd  3rd  4th

Diameter (cm): 3.10  3.12  3.20  3.30

Linear Trend for Tumor Size

<table>
<thead>
<tr>
<th>Tumor Emphysema</th>
<th>OR</th>
<th>CI</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>3.51</td>
<td>[0.47, 6.58]</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Tumors occurring in regions of emphysema are associated with a worse overall survival

\[ \text{OR}_{\text{adj}} \ 1.03 \ [1.01, 1.05], \ P=0.0006, \text{ adjusted for age, sex, histology, stage, central tumor location, performance score, and surgery} \]

Non-parenchymal features features of COPD and LC death

N=263
Lower pectoralis muscle area is associated with a worse prognosis for NSCLC

OR_{adj} 0.97 [0.96, 0.99], \( P = 0.002 \), adjusted for age, sex, smoking, histology, stage, performance score, and surgery

Limitations of the presented data:

1) None of these data are “predictive”

2) Many of these data are not derived from a CT screening population

3) All survival data and analyses are subject to secular trends in lung cancer care (e.g. approach to ground glass nodules, immunotherapy, etc)

Predominantly serve as examples and discussion points...

Demonstrates the need for a prospective system of evaluation which includes the ability to test interventions and continuously monitor lung cancer mortality.
Balancing Risks: Unanswered Questions and Opportunities

1) 29% of LC deaths in the NLST were not screen detected. How careful do we need to be with changes to CT screening? Changes in sensitivity need to be considered as drivers of mortality.

2) 96% of positives in the NLST were not cancer. Can we improve detection of cancer among the many indeterminate nodules? Emphysema morphology is associated with lung cancer and may make it valuable as part of a prediction model.

3) 17% with CT screen detected lung cancer in the NLST died of something else. Can we predict who will die of lung cancer? This is the actual endpoint of CT screening. Features such as regional emphysema and body composition (pectoralis muscle area) may be helpful.
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Thank you! Appreciate any questions or comments.