Lung Cancer Screening: Now What?

Gerold Bepler, M.D., Ph.D.
Director, President & CEO


These slides are the property of the presenter. Do not duplicate without express written consent.
Lung Cancer

• #1 Cause of Cancer Death for ♂ & ♀*
• 437 deaths per day
• Only 16% survive longer than 5 years
• ~15% localized
~22% regional
~56% distant

*27.5% (159,480/580,350)

Wender et al, CA Cancer J Clin 2013

These slides are the property of the presenter. Do not duplicate without express written consent.
Lung Cancer Mortality and (Incidence)

Cancer Facts and Figures, ACS 2013

These slides are the property of the presenter. Do not duplicate without express written consent.
Strategies to Improve Outcome

- Prevention
- **Early Detection**
- Therapy
KM Survival by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Deaths/N</th>
<th>Median in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>708/1715</td>
<td>95</td>
</tr>
<tr>
<td>IB</td>
<td>991/1970</td>
<td>75</td>
</tr>
<tr>
<td>IIA</td>
<td>1098/1808</td>
<td>44</td>
</tr>
<tr>
<td>IIB</td>
<td>1028/1469</td>
<td>29</td>
</tr>
<tr>
<td>IIIA</td>
<td>1735/2175</td>
<td>19</td>
</tr>
</tbody>
</table>

LC Staging V7, Chansky et al, JTO 4:792 2009

These slides are the property of the presenter. Do not duplicate without express written consent.
Screening Requirements

High Number of Cases ✓
High Number of Deaths ✓
High Expenses* ✓
Known Natural History ✓ (?)
Effective Intervention ✓ (?)

(Screening should be inexpensive, tolerable, save, high sensitivity & specificity)

>$5.5 billion per year

*$25,000 per case
Natural History of Lung Cancer

- Well known epidemiology
- Incomplete knowledge on histopathological progression
- Evolving knowledge on molecular progression
Screening by CXR (PLCO results)

- 154,900 individual, age 55-74, smokers & NS, randomized to CXR vs usual care for 4 years
- 86% at baseline, 79-84% thereafter, 11% in usual care arm had screening
- No LC mortality reduction by CXR screening
- Data consistent with experience
  - UK Trial, Brett, Thorax 1968
  - Czech Trial, Kubik et al, Cancer 1986

JAMA 306: 1865-1873, 2011
Factors to Consider

- Incidence
- Mortality
- Survival (median or 5-y)
- Stage Shift

These slides are the property of the presenter. Do not duplicate without express written consent.
Lead Time Bias

- Screened group
- Diagnosis confirmed
- Patient dies
- Control group
- Symptoms
- Diagnosis confirmed
- Patient dies

Patz, Goodman, Bepler, NEJM 2000

These slides are the property of the presenter. Do not duplicate without express written consent.
Lead Time Bias

- Incidence
- Mortality
- Survival (median or 5-y)
- Stage Shift

These slides are the property of the presenter. Do not duplicate without express written consent.
Length Time Bias

Patz, Goodman, Bepler, NEJM 2000

These slides are the property of the presenter. Do not duplicate without express written consent.
Length Time Bias

- Incidence
- Mortality
- Survival (median or 5-y)
- Stage Shift
Overdiagnosis

Patz, Goodman, Bepler, NEJM 2000

These slides are the property of the presenter. Do not duplicate without express written consent.
Overdiagnosis

- Incidence
- Mortality
- Survival (median or 5-y)
- Stage Shift

These slides are the property of the presenter. Do not duplicate without express written consent.
## Overdiagnosis (Incident Cases)

<table>
<thead>
<tr>
<th></th>
<th>Total Cases</th>
<th>Operable Cases</th>
<th>Inoperable Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Screen</td>
<td>206</td>
<td>94</td>
<td>112</td>
</tr>
<tr>
<td>Mayo Control</td>
<td>160</td>
<td>51</td>
<td>109</td>
</tr>
<tr>
<td>Czech Screen</td>
<td>36</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td>Czech Control</td>
<td>19</td>
<td>3</td>
<td>16</td>
</tr>
</tbody>
</table>

These slides are the property of the presenter. Do not duplicate without express written consent.
Screening for Lung Cancer (until 2010)

- Not recommended
- Use in study-setting only
The Age of CT (1990 to 2010)

- ELCAP
- Mayo
- Muenster
- Japan
- Moffitt

Indeterminate pulmonary nodule detection:
Mayo 51%, Swenson et al, Am J Respir Crit Care Med 165: 508, 2002
Germany 43%, Diederich et al, Radiology 222: 773, 2002
Moffitt 32%, Tockman et al, unpublished

These slides are the property of the presenter. Do not duplicate without express written consent.
SUMMARY for single arm CT studies

- > 12,000 individuals screened
- Age is an important determinant of LC risk

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-39</td>
<td>0.03 (1 in 3,646)</td>
<td>0.03 (1 in 3,185)</td>
<td>0.93 (1 in 108)</td>
<td>0.77 (1 in 130)</td>
</tr>
<tr>
<td>40-59</td>
<td>2.29 (1 in 44)</td>
<td>1.74 (1 in 57)</td>
<td>6.70 (1 in 15)</td>
<td>4.90 (1 in 20)</td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Smoking and COPD are important determinants of LC risk
- Indeterminate Nodules are found in 23-51% of (ex)smokers age ≥40 years

These slides are the property of the presenter. Do not duplicate without express written consent.
CT Screening: NLST (overview)

- NLST Study
- Prospective Randomized Study
- Duration: 8/02 – 9/07 (F/U to 12/31/2009)
- 33 Centers in the US
- N = 53,454 (PLCO and ACRIN)
- First published June 6, 2011


These slides are the property of the presenter. Do not duplicate without express written consent.
CT Screening: NLST (design)

- **Eligibility:** age 55-74, (wo)men >30 PY, quit <15 y, no active cancer or h/o LC, no CT ≤18m

<table>
<thead>
<tr>
<th>T0 (entry)</th>
<th>T1 (12 months)</th>
<th>T2 (24 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR</td>
<td>→ CXR</td>
<td>→ CXR</td>
</tr>
<tr>
<td>CT</td>
<td>→ CT</td>
<td>→ CT</td>
</tr>
</tbody>
</table>

- **Test:**

- **Other:** biospecimens, survey, spirometry


These slides are the property of the presenter. Do not duplicate without express written consent.
• Definition: any solitary nodule that is
  • non-calcified
  • non-fat attenuation
  • new (stable < 2y)

• Work up:
  • <4 mm  no intervention
  • 4-10 mm repeat q3m or enhanced or Bx
  • >10 mm TTNA or VATS-Bx
CT Screening: NLST (results)

- Follow-up diagnostic procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>CT (27%)</th>
<th>CXR (9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; One procedure</td>
<td>90% (N=297)</td>
<td>93% (N=121)</td>
</tr>
<tr>
<td>Chest CT</td>
<td>73%</td>
<td>66%</td>
</tr>
<tr>
<td>PET</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>4.3%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Transthoracic Bx</td>
<td>2.2%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Surgery (diagnostic)</td>
<td>4.2%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>
CT Screening: NLST (results)

- Median follow-up: 6.5 years
- Adherence: 95% for CT, 93% for CXR
  - Annual CTs done on CXR arm: 4.3%
### CT Screening: NLST (results from 2011)

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td># subjects</td>
<td>26,722</td>
<td>26,732</td>
</tr>
<tr>
<td># cancers</td>
<td>1,060</td>
<td>941</td>
</tr>
<tr>
<td># resectable cancers</td>
<td>692</td>
<td>472</td>
</tr>
<tr>
<td>Mortality Reduction*</td>
<td>2.47 /1000 prs-y</td>
<td>3.09 /1000 prs-y</td>
</tr>
<tr>
<td>Unresectable Disease</td>
<td>348</td>
<td>457</td>
</tr>
<tr>
<td>Reduction (=stage shift)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive CT (CXR) test</td>
<td>24.2%</td>
<td>6.9%</td>
</tr>
<tr>
<td>(≥4 mm non-calcified)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False positive test</td>
<td>96.4%</td>
<td></td>
</tr>
</tbody>
</table>

*20% risk reduction p=0.004; 6.7% risk reduction from all cause mortality

Mayo CXR Trial Mortality: CXR:3.2 vs Control:3.0/1000 prs-years
Unresectable Disease: CXR:112 vs Control: 109

NEJM 365: 395, 2011
The Michigan Cancer Consortium has concluded that the current scientific evidence supports the use of annual low-dose spiral computed axial tomography (CT scans) for lung cancer screening in asymptomatic individuals who smoke or who have quit smoking (quit smoking for ≤ 15 years), who have a 30 pack-year history of tobacco use (pack-year history is equal to the average number of packs smoked per day times the number of years smoked), and are 55-74 years of age.

MCC Early Detection Working Group
- Co-Chairs: Gregory Kalemkerian and Gerold Bepler
- Members: Kevin Berger, Paul Kvale, Vicki Rakowski, Farid Shamo, Mary Jo Voelpel
- Staff: Carol Garlinghouse, Steve Springer, May Yassine
CT Screening: NLST (results)

- Number of cancers detected

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>292</td>
<td>190</td>
</tr>
<tr>
<td>T1</td>
<td>186</td>
<td>133</td>
</tr>
<tr>
<td>T2</td>
<td>237</td>
<td>144</td>
</tr>
<tr>
<td>Total</td>
<td>715</td>
<td>467</td>
</tr>
</tbody>
</table>

- **Note**: Lung cancer detection appears to continue at a stable rate per year, suggesting that screening should continue (annually?).


These slides are the property of the presenter. Do not duplicate without express written consent.
CT Screening: NLST (results)

- Stage Shift for T1 and T2 screens

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1-Stage I</strong></td>
<td>49.2%</td>
<td>31.8%</td>
</tr>
<tr>
<td><strong>T1-Stage IIIB/IV</strong></td>
<td>30.8%</td>
<td>48.6%</td>
</tr>
<tr>
<td><strong>T2-Stage I</strong></td>
<td>48.1%</td>
<td>33.6%</td>
</tr>
<tr>
<td><strong>T2-Stage IIIB/IV</strong></td>
<td>29.9%</td>
<td>45.5%</td>
</tr>
</tbody>
</table>
CT Screening: NLST (results)

- True and False Positive Rates (>4 mm)

<table>
<thead>
<tr>
<th></th>
<th>CT T0</th>
<th>CT T1</th>
<th>CT T2</th>
<th>CXR T0</th>
<th>CXR T1</th>
<th>CXR T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Screen</td>
<td>7,193</td>
<td>6,902</td>
<td>4,052</td>
<td>2,387</td>
<td>1,482</td>
<td>1,175</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>4% (270)</td>
<td>2% (168)</td>
<td>5% (211)</td>
<td>6% (136)</td>
<td>4% (65)</td>
<td>7% (78)</td>
</tr>
<tr>
<td>No Lung Cancer</td>
<td>96%</td>
<td>98%</td>
<td>95%</td>
<td>94%</td>
<td>96%</td>
<td>93%</td>
</tr>
</tbody>
</table>
CT Screening: NLST (results)

- Sensitivity, specificity, PPV, and NPV for CT

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>93.8%</td>
<td>94.4%</td>
<td>93.0%</td>
</tr>
<tr>
<td>Specificity</td>
<td>73.4%</td>
<td>72.6%</td>
<td>83.9%</td>
</tr>
<tr>
<td>PPV</td>
<td>3.8%</td>
<td>2.4%</td>
<td>5.2%</td>
</tr>
<tr>
<td>NPV</td>
<td>99.9%</td>
<td>99.9%</td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity = TP/(TP+FN)
Specificity = TN/(FP+TN)
PPV = TP/(TP+FP)
NPV = TN/(FN+TN)

These slides are the property of the presenter. Do not duplicate without express written consent.
CT Screening: NLST (results)

- PPV by nodule size

<table>
<thead>
<tr>
<th>Size</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4 mm</td>
<td>3.8%</td>
</tr>
<tr>
<td>4-6 mm</td>
<td>0.5%</td>
</tr>
<tr>
<td>7-10 mm</td>
<td>1.7%</td>
</tr>
<tr>
<td>11-20 mm</td>
<td>11.9%</td>
</tr>
<tr>
<td>21-30 mm</td>
<td>29.7%</td>
</tr>
<tr>
<td>&gt;30 mm</td>
<td>41.3%</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>18.5%</td>
</tr>
</tbody>
</table>
CT Screening: NLST (results)

- Other notable findings in CT arm

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV with Biopsy</td>
<td>58.2%</td>
<td>65.8%</td>
</tr>
<tr>
<td>Surgery for Benign Disease</td>
<td>18.9%</td>
<td>15.9%</td>
</tr>
</tbody>
</table>

- Total number of surgeries
  - mediastinoscopy, thoracotomy, thoracoscopy
  - 24% of surgeries for benign disease (164/673)
Impact on US Population

- 8.6 million Americans meet the NLST screening criteria
- 30% of people between 55-74 meet NLST criteria
- 12,000 lung cancer deaths could be averted each year
- 27% of all lung cancers would be detected and approximately 68% of lung cancers in people between 55-74 that meet NLST criteria

Comparison with Other Cancers

- Numbers needed to prevent one death
  - Mammography
    - age 40-49: 1,904
    - age 50-59: 1,339
    - age 60-79: 337
  - Fecal Occult Blood (annual x5): 1,374
  - Flexible Sigmoidoscopy: 871
  - PSA: 1,410
  - Chest CT (by NLST criteria): 320
• Annual screening for persons age 55-79 (yes 79)
• ≥30 PY, active or quit ≤15 years

• “B” recommendation (categories A, B, C, D, I), so insurances should cover this
• B = The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. The practice suggestion is to offer or provide this service.
ACS Recommendations

• Annual screening for persons age 55-74
• ≥30 PY, active or quit ≤15 years
• In centers with high volume, high quality, and discuss pros and cons
Other Organizations That Endorse Screening (for high-risk persons)

- American Association of Thoracic Surgery
- American College of Chest Physicians
- American Lung Association
- American Society of Clinical Oncology
- American Thoracic Society
- National Comprehensive Cancer Network
The Future of Lung Cancer Screening

• Development of a model for risk prediction.
• *The PPV depends on disease prevalence.*

Kovalchik *et al*, NEJM 369: 245, 2013

These slides are the property of the presenter. Do not duplicate without express written consent.
Thank You