Screening for Lung Cancer: Update
Caroline Chiles, MD

Lung cancer screening: a 2010 update
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What we do know…

- The odds of surviving lung cancer are better if the cancer is detected earlier, before it has spread to lymph nodes or distant sites.
- The majority of lung cancers detected in trials of screening with CT are Stage I.

What we don’t know…

- Will screening with CT change the outcome for the patient?
- If it does change the outcome, will the costs of CT (not just $) be worth the risks?

Lung cancer & criteria for screening

- Affects a large number of people
- Can choose a population at increased risk
  - 19.8% of US adults are current smokers
  - 43.4 million current smokers in US
  - 47.3 million former smokers in US
- Preclinical phase of disease is detectable
- Early stage disease is curable

How do we determine if screening with CT can change the outcome?

- The goal of cancer screening is a reduction in morbidity or mortality, not just early case detection.
- This requires a randomized controlled trial to calculate.
Randomized controlled trial

- 2 populations, matched for age, gender, smoking history
- One is screened with CT
- One is not
- Calculate the number of deaths from lung cancer in each population
- Calculate the deaths from all causes in each population

If screening is effective,

- There should be fewer deaths from lung cancer in the screened population and/or
- There should be fewer deaths from all causes in the screened population

Survival vs. Mortality

- Longer survival is not an adequate surrogate for reduction in mortality - by definition a cancer screening test will advance the date of diagnosis. (lead time bias)

Lead time bias

- No screening
- Screening

<table>
<thead>
<tr>
<th>Survival</th>
<th>DEATH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs or symptoms</td>
<td></td>
</tr>
<tr>
<td>Lead Time Bias</td>
<td></td>
</tr>
<tr>
<td>Positive test</td>
<td>DEATH</td>
</tr>
<tr>
<td></td>
<td>Survival</td>
</tr>
</tbody>
</table>

Length time bias

- Faster growing tumors have a shorter asymptomatic phase and are less likely to be detected at screening
- Slowly growing malignancies are over represented in screening trials

On-going lung cancer screening trials (RCT)

<table>
<thead>
<tr>
<th></th>
<th>NLST</th>
<th>NELSON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>53,461</td>
<td>19,627</td>
</tr>
<tr>
<td>Screening</td>
<td>CT vs. CXR</td>
<td>CT vs. usual care</td>
</tr>
<tr>
<td>Ages</td>
<td>55-74</td>
<td>50-75</td>
</tr>
<tr>
<td>Smoking hx</td>
<td>≥ 30 pack-years</td>
<td>15-18.75</td>
</tr>
<tr>
<td>Exsmokers</td>
<td>Quit &lt; 15</td>
<td>Quit &lt; 10</td>
</tr>
<tr>
<td>Final analysis</td>
<td>2009</td>
<td>2016</td>
</tr>
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</table>
Other randomized controlled screening trials of note

<table>
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<tr>
<th></th>
<th>ITALUNG</th>
<th>DANTE</th>
<th>DEPISCAN</th>
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<tbody>
<tr>
<td>participants</td>
<td>3,206</td>
<td>2,472</td>
<td>765</td>
</tr>
<tr>
<td>screening arms</td>
<td>CT vs. usual care</td>
<td>CT vs. usual care</td>
<td>CT vs. CXR</td>
</tr>
<tr>
<td>Final analysis</td>
<td>2012</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Screening completed in 2006
- Medical record collection through 2009
  - Diagnosis of lung cancer or other cancer
  - Other diagnosis
  - Medical resource utilization
  - Quality of life
  - Vital status
  - Cause of death (death certificate)

- Deaths recorded through 12/31/09
  - Lung cancer deaths
  - All deaths
  - Data analysis in 2010
  - Publication of results...

- Primary objective:
  To determine whether lung cancer screening using low-dose helical CT reduces lung-cancer specific mortality relative to screening with CXR in a high-risk cohort
  - # of lung cancer deaths in CT arm vs. # of lung cancer deaths in CXR arm

- Secondary objective: to assess differences in stage distribution between the two arms of the study

<table>
<thead>
<tr>
<th></th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT arm</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td>CXR arm</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
</tr>
</tbody>
</table>

- to compare lung cancer-related medical resource utilization between the two arms of the study
to assess the psychological impact of screening as well as the impact of a positive screening test, and the differential effects on quality of life between the two arms of the study
- to assess the economic consequences of screening with CT versus CXR
- to develop a tissue bank from individuals at high risk of lung cancer both with and without pathologically proven lung cancer

**NELSON trial**
- Key differences between NELSON and NLST
  - CT vs usual care – no screening in control population
  - Three rounds of screening – but at baseline, + 1 year, + 3 years
  - 10 years of follow-up
  - 80% power to detect lung cancer mortality reduction of 25% or more 10 years after randomization

**Limited contamination in the Dutch-Belgian randomized lung cancer screening trial (NELSON)**
- contamination = screening in the control arm
- Questionnaires sent to sample of 1,460 male participants in control arm
- 17% had received either CXR or CT for any reason in last 24 months
- 3.1% had received a lung cancer screening examination, either CT (20%) or CXR (80%)

Bneeke F et al, Lung Cancer 2009

**Smooth or attached solid indeterminate nodules detected at baseline screening in the NELSON study: cancer risk during 1 year of follow-up**
- Noncalcified nodules between 5 and 10 mm were retrospectively evaluated at 3 months and 1 year to assess volume doubling time
- 16 detector CT, 0.75 m section thickness, pitch of 1.5
- Volume calculation with 3D software, with radiologist override for inappropriate segmentation


- 8% of nodules had a VDT < 400 days at 3 months – of these 68 nodules, 10 were malignant, and 58 were benign
- 1% of nodules had a VDT < 400 days at 12 months – of these 10 nodules, 5 were malignant and 5 were benign


- All 16 cancers were smooth, nonspherical, and purely intraparenchymal without attachment to vessels, pleura, or fissures
- A volume of 130 mm$^3$ or larger with 3 month or 12 month VDT < 400 days were predictive of malignancy
The Danish Randomized Lung Cancer CT Screening Trial – Overall Design and Results of the Prevalence Round

- 4,104 participants; CT vs. usual care
- Accrual 2004-2006, 5 rounds of screening
- ≥ 20 pack years
- 179 of 2,052 (8.7%) CTs showed noncalcified nodule > 5 mm; most rescanned after 3 months
- 17 were lung cancer (10 were stage I)
- False positive rate was 7.9%

Pederson et al, J Thorac Oncol 2009; 4:608-614

CT characteristics of resolving ground glass opacities in a lung cancer screening program

- 280 participants, annual low-dose CT
- 75 GGOs in 37 participants
- 55% present at baseline, 45% on annual CT
- At follow-up, 56% persisted, 44% disappeared
- Resolving GGOs: more often lobular, polygonal, mixed, larger

Pederson et al, J Thorac Oncol 2009; 4:608-614

FDG uptake measured by PET and SUV predicts long-term survival of CT screening detected lung cancers in heavy smokers

- All patients in screening trial with nodules ≥ 7 mm underwent PET-CT
- PET-CT in 68 patients (1.4%)
- PET-CT in 34/38 lung cancer patients
- 32/34 were positive (SUV > 2.0)

Pastorino et al, J Thorac Oncol 2009: 4:1352-1356

<table>
<thead>
<tr>
<th>TABLE 1. Results of PET</th>
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<tbody>
<tr>
<td>SUV</td>
</tr>
<tr>
<td>≥2.5</td>
</tr>
<tr>
<td>&gt;2.5, &lt;8</td>
</tr>
<tr>
<td>≥8</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>All cancers</td>
</tr>
<tr>
<td>Stage I</td>
</tr>
<tr>
<td>Stage II-IV</td>
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<tr>
<td>Adenocarcinoma</td>
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<tr>
<td>Other types</td>
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</tbody>
</table>

Pastorino et al, J Thorac Oncol 2009: 4:1352-1356

Decisions we need to make

- Is screening with low-dose helical CT effective at reducing mortality?
- How do we predict future behavior of a lung cancer, and distinguish indolent cancers from aggressive cancers?

“FDG-PET using SUV can predict long-term survival of screening detected lung cancer

- Metabolic assessment of biologic behavior might improve clinical management of CT-detected lung cancer and reduce the risk of unnecessary treatments for indolent disease”

Pastorino U, Landoni C, Marchiano A et al.