Lung Cancer

219,440 new cases/year in U.S. (2009)
169,390 deaths/year in U.S.
  mortality greater than from breast, colon, prostate CA combined
  28% of all cancer deaths

19.8% (43.4 million) US adults current smokers
20% (47.3 million) are former smokers
Lung Cancer

Overall 5 year survival = 16%
Resected early stage survival = $\geq 70\%$

If detect disease in early preclinical stage
surgical resection most likely to
prolong life
reduce lung cancer mortality
• Diagnose more patients at an early stage
• Reduce number of patients with late-stage disease
• Result in fewer deaths
Screening Test

- Always generates both benefits and harms
- Remember that target population is asymptomatic individuals
Lung Cancer Screening

CT more sensitive than chest radiography, by at least 3:1 higher percentage are early stage
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchogenic carcinoma detected</td>
<td>3.4%</td>
</tr>
<tr>
<td>Prevalence</td>
<td>2.7%</td>
</tr>
<tr>
<td>(mammography)</td>
<td>0.7%</td>
</tr>
<tr>
<td>Stage I</td>
<td>85%</td>
</tr>
</tbody>
</table>

Henschke, ELCAP, 1999
CT: Lung Cancer Screening
Potentially Ideal

- Affects large number of people
- Can select population at increased risk
- Preclinical phase is detectable
- Early stage disease potentially curable
CT: Lung Cancer Screening

Mayo Clinic  1520 individuals

50 years or older; 20 pack years

1 prevalence
3 incidence
Nodule 4 mm or greater
49 % prevalence
20 % more with incidence

97.4% benign
60% cancers Stage IA *
6 died from lung cancer

20% resected were benign
grew or positive PET
Nodule Follow-up Recommendations

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Follow-up Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4mm</td>
<td>12 month (stop if stable)</td>
</tr>
<tr>
<td>&gt; 4-6</td>
<td>6-12 months (then 18-24)</td>
</tr>
<tr>
<td>&gt; 6-8</td>
<td>3-6 months (9-12 and 24)</td>
</tr>
<tr>
<td>&gt; 8</td>
<td>3, 9, and 24 months</td>
</tr>
<tr>
<td></td>
<td>?PET ?Biopsy</td>
</tr>
</tbody>
</table>
Nodule Characterization
Rarely If Ever Malignant

- Smooth and solid
- Pleural based ovoid or triangular intrapulmonary lymph node scar
Mayo: Ancillary Findings

76%
(include emphysema and RBILD)

33% potential high significance

Severe coronary calcification
AAA
Lymphadenopathy
Breast mass
Renal, gastric, adrenal mass

Further testing suggested
Incidentalomas

Pandemic now, with CT the main vector

Exacerbated when do screening CT
Lung Cancer Screening
Spiral CT

Proponents:
- save lives
- shift stage
- ancillary findings
Lung Cancer Screening
Spiral CT

Antagonists
false “positives”
financial and psychological costs
no proven change in mortality
lead time bias
length time bias
overdiagnosis bias
co-morbidities (may preclude surgery)
morbidity, mortality
associated with surgery, testing
Screening Test
Survival Statistics Biases

• Lead Time
• Length Time
• Overdiagnosis
  (Overtreatment)

• Co-morbidities
Survival increased relative to historical controls (typically symptom-detected) e.g., alive 5 years later.

Mortality is a distinctly different measure. It accounts for lead and length time bias and overdiagnosis.
Survival vs Mortality

Diagnosis age 68, die age 70
2 year survival

Screening diagnosis age 63, die age 70
7 year survival
but no real benefit (worry longer)

Screening diagnosis age 63, die age 75
12 year survival
definite benefit
Length Time Bias

Slowly growing carcinoma,
less likely lethal,
more likely to be discovered
especially on initial screening

Interval symptomatic cancers are a failure of screening
Overdiagnosis (Overtreatment) Bias

- **Type I**
  does not progress

- **Type II**
  progresses slowly without harming patient
  (may depend upon competing causes of death)
Survival vs Mortality

**Survival**
- inherently biased (not a surrogate for)

**Mortality**
- free of bias
- benefit if both
  - ↑ early stage cancers
  - ↓ late stage cancers
Survival vs Mortality

Increase in the detection of early stage tumors
Does not necessarily translate to a decrease in the number of aggressive, advanced stage cancers
Survival vs Mortality

Demonstration of increased survival is insufficient evidence of a screening benefit.

A screening benefit must demonstrate a decrease in lung cancer specific mortality.
Lung Cancer Screening
Risk Benefit Ratio

Benefit: a good thing

But must be balanced against the
Risks (Harms)

costs (including psychological)
shift resources from true disease
complications of
downstream tests, surgery
CT: Lung Cancer Screening

Can we reduce mortality (and morbidity) at a “reasonable cost”? Are benefits worth the risks?

Requires a randomized controlled trial
Randomized Controlled Trial

- Two populations matched for age, gender, smoking history
- One screened with CT, the other not
- Calculate number of deaths from lung cancer plus all causes in both populations

If screening effective, fewer deaths from lung cancer and/or all causes
Randomized Controlled Trials

• Eliminate biases
• Difficult, expensive to set up
• Contamination a major problem
• Take a very long time
• In interval, technology often changes
NLST (and Nelson Trial)

Designed to compare differences in lung cancer specific mortality between screened and unscreened populations (control arm to overcome screening biases)

Also will measure medical resource utilization significance of non-cancer findings and associated costs and morbidity/mortality
<table>
<thead>
<tr>
<th><strong>National Lung Screening Trial (NLST)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
</tr>
<tr>
<td><strong>Screening</strong></td>
</tr>
<tr>
<td><strong>Accrual</strong></td>
</tr>
<tr>
<td><strong>Ages</strong></td>
</tr>
<tr>
<td><strong>Smoking Hx</strong></td>
</tr>
<tr>
<td><strong>Ex-smokers</strong></td>
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<tr>
<td><strong>Medical record collection</strong></td>
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<tr>
<td><strong>Data analysis</strong></td>
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<tr>
<td><strong>Publication of results</strong></td>
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In 2010, the efficacy of spiral CT for lung cancer screening remains unproven.

No data available to demonstrate that screening reduces lung cancer specific or overall mortality.
Even if spiral CT lung cancer screening reduces mortality somewhat, it may be less effective and more costly than smoking cessation efforts. Economically, we have to ask not only “does it work” but “can we afford it”
Conceivable, that some subpopulations, at truly high risk, familial history (genetic predisposition) pack years, lung function, might benefit.

At present, the most important thing a smoker can do regarding his/her cancer risk is to stop smoking.