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University of Louisville

The Lung Cancer Epidemic
CA, Jemal (58)2, 71, 2008

- US 2002 2008
  Incidence 169,000 215,020
  Mortality 154,900 161,840

- Estimated Incidence Rate
  2008 Male Female
  US 89/100k 55/100k
  KY 138/100k 75/100k
Distribution of Non-Small Cell Lung Cancer NSCLC by Stage and Prognosis

N = 3823

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13%</td>
</tr>
<tr>
<td>II</td>
<td>10%</td>
</tr>
<tr>
<td>IIIA</td>
<td>22%</td>
</tr>
<tr>
<td>IIIB</td>
<td>22%</td>
</tr>
<tr>
<td>IV</td>
<td>32%</td>
</tr>
</tbody>
</table>


2005 Estimated US Cancer Deaths*

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>295,280</td>
<td>275,000</td>
</tr>
<tr>
<td>Prostate</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Liver and intrahepatic bile duct</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>

Men

- 27% Lung and bronchus
- 15% Breast
- 10% Colon and rectum
- 6% Ovary
- 6% Pancreas
- 4% Leukemia
- 3% Non-Hodgkin lymphoma
- 3% Uterine corpus
- 2% Multiple myeloma
- 2% Brain/ONS
- 22% All other sites

Women

- 27% Lung and bronchus
- 15% Breast
- 10% Colon and rectum
- 6% Ovary
- 6% Pancreas
- 4% Leukemia
- 3% Non-Hodgkin lymphoma
- 3% Uterine corpus
- 2% Multiple myeloma
- 2% Brain/ONS
- 22% All other sites

*ONS=Other nervous system.

Source: American Cancer Society, 2005.
Evidence on Cancer Screening

- Breast Cancer
- Colon Cancer
- Cervical Cancer
- Skin Cancer
- Bladder Cancer
- Oral Cancer
- Esophageal Cancer
- Testicular Cancer
- Prostate Cancer
- Neuroblastoma
- Gastric Cancer

Basic Requirement
- Ability to detect early, asymptomatic disease
- Detection leads to decreased mortality

Definition
- Survival: number alive at a certain time after diagnosis
- Mortality: number of deaths within population

Biases entrained by screening

- Lead time: Earlier detection increases survival, even if death is not delayed

- Length bias: Screening detects more slowly growing cancers
  - Aggressive cancer: Short biological life span
  - Indolent cancer: Longer biological life span
What do we see on CT?

- **GG (non-solid):** Nodule with hazy increased lung attenuation which does not obscure underlying bronchovascular markings.

- **Mixed (part-solid):** Nodules containing both ground glass and solid components.

- **Solid:** Nodules with attenuation obscuring the bronchovascular structures.

Relationships between Morphology and Volume Doubling Time (VDT)
Hasegawa et al Br J Radiol, 73, 1252-1259

- Calculated VDT in 61 CT-detected cancers based on serial CT’s
- VDT vary between lung cancers of different attenuation

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>VDT +/- SD</th>
<th>Visible on CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground glass</td>
<td>19</td>
<td>VDT= 813 days +/- 375</td>
<td>1</td>
</tr>
<tr>
<td>Mixed attenuation</td>
<td>19</td>
<td>VDT= 457 days +/- 260</td>
<td>1</td>
</tr>
<tr>
<td>Solid</td>
<td>23</td>
<td>VDT= 149 days +/- 125</td>
<td>16</td>
</tr>
</tbody>
</table>
Types of CT-detected lung cancers

- SEER data: BAC represents < 4% of NSCLC over 2 decades

- Observations from US CT-screening studies
  - Mayo CT 15% GG/Mixed (Lindell, Radiology 2007)
  - ELCAP 12% BAC (Flieder AM J Pathol 2006)
  - NY ELCAP 13% GG (Henschke, Radiology 2007)
  - I-ELCAP 06% BAC (I-ELCAP, NEJM 2006)

GG = Ground Glass, BAC = Bronchoalveolar Cancer
Japanese Lung Screening Trial  
Sone S British J Cancer 2001, 84, 25-32

• Mobile CT screening in general population >40 yrs
  - Incidence 0.4% (13,700 scans over 3 years, 60 LC’s)

• Equal cancer rates in smokers and non-smokers
  - High proportion stage 1
  - 70% BAC or well differentiated adenoca

• Detection rate = 11 fold ↑↑ over annual incidence rates
  - Males 2-15 fold over annual mortality rate
  - Females 10-25 fold over annual mortality rate
  - Many CT-detected cancers will not become symptomatic

Will screening cause stage shift?
Mayo Clinic CXR Screening Trial
Marcus PM JNCI 2000, 92(16)1308, Fontana RS Cancer 1990, 67, 1155

Observed stage distribution
True stage shift

CXR/Sputum q 4m vs yearly, >45 yrs smokers
Screening x 6 years, F/U for 11/24 yrs

Mayo Clinic CT Screening Study
McMahon P, Radiology,2008, 248(1), 279

1520 ex/smokers with 5 annual CT screens

4% mortality reduction at 6 years, 2% at 15 years based on simulation model
lung cancer specific mortality decreased by 28% at 6 years
CT Screening and Lung Cancer Outcomes
Bach P, JAMA, 2007, 297, 953

<table>
<thead>
<tr>
<th>N</th>
<th>3246</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standardized</td>
<td></td>
</tr>
<tr>
<td>&gt;3 annual screens</td>
<td></td>
</tr>
<tr>
<td>Person years</td>
<td>10,942</td>
</tr>
<tr>
<td>Observed</td>
<td></td>
</tr>
<tr>
<td>Expected</td>
<td></td>
</tr>
<tr>
<td>Lung Cancers</td>
<td></td>
</tr>
<tr>
<td>Lung Cancers</td>
<td></td>
</tr>
<tr>
<td>144</td>
<td>44.5</td>
</tr>
<tr>
<td>Advanced</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>33.4</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>38.8</td>
</tr>
<tr>
<td>No mortality reduction</td>
<td></td>
</tr>
<tr>
<td>10-fold more surgeries</td>
<td></td>
</tr>
</tbody>
</table>

International Early Lung Cancer Action Program (I-ELCAP)
NEJM, 2006, 355 (17), 1763

31,367 Asymptomatic participants underwent baseline screening
27,456 Annual screenings

4136 With at least 1 solid or partly solid nodule ≤3 mm in diameter or had a total 1 non-nodular nodule ≥6 mm in diameter
27,381 With no nodules or nodules not qualifying as a positive result
1406 With newly identified, nonclassified nodules
25996 With no newly identified nonclassified nodules

Baseline management algorithm
Workup within 12 mo after initial CT prompted by symptoms
Annual management algorithm
Workup within 12 mo after previous CT prompted by symptoms

403 Found to have lung cancer on baseline CT
5 Received interim diagnosis of lung cancer
74 Showed lung cancer on annual CT
None received interim diagnosis of lung cancer

404 Received a diagnosis of lung cancer

412 Had clinical stage II lung cancer
International Early Lung Cancer Action Program (I-ELCAP)
NEJM, 2006, 355 (17), 1763

Case Fatality ≠ Overall Mortality !!!!

Lessons from CT Observational Trials

• CT more sensitive for **nodule detection** than CXR

• CT picks up more **cancers** than CXR: **4:1**
  – Increase in early stage lung cancers
  – Oversampling of BAC/well differentiated adenocarcinoma

• Uncertain Stage Shift
Lessons Learned

• Measure the right endpoint

Lung cancer deaths/total lung cancers (Case Fatality Rate) is not avoiding the screening biases of lead time, length, overdiagnosis

A much better endpoint is:

total (lung cancer) deaths = best measure of screening effect
total population screened

– Comparison Trial needed to follow outcome in all screened and unscreened participants
– Verify cause of deaths by review of medical records

National Lung Screening Trial (NLST) Design and Time Posts

• RCT in ex/smokers, >50
• 1:1 randomization to CXR or CT

- NELSON Trial, RCT comparing LDCT vs Expectant Management
- 20,000 current and former smokers
- 25% reduction in mortality as endpoint
Biomarkers for Lung Cancer Screening

Rare Circulating Tumor Cells

10e-9 cell detection, 1 ml/hr blood
Exosomes and MiRNA

Exosomal microRNA: A Diagnostic Marker for Lung Cancer
Goetz H. Kloecker, Guilherme Rabinowits, Cicak Gercel-Taylor, Jamie M. Day, Douglas D. Taylor
Clinical Lung Cancer, 2008, 9(5), #7, full article in press

ISOLATION OF CIRCULATING EXOSOMES

1. Incubate plasma with anti-EpCAM coupled to magnetic beads
2. Collect fractions containing antiEpCAM binding exosomes
3. Isolate RNA circulating tumor-derived exosomes, synthesize cDNA probe for microarray hybridization
4. Hybridize labeled probe with DNA microarray
5. Analyze data and define miRNA associated with the presence of NSCLC
MiRNA from Tumor and Exosomes
Goetz H. Kloecker, Guilherme Rabinowits, Cicek Gercel-Taylor, Jamie M. Day, Douglas D. Taylor
Clinical Lung Cancer, 2008, 9(5), #7, full article in press

- Intensities for specific miRNAs derived from the tumors and from exosomes isolated from the sera of these patients.

MiRNA in Cancer Patients and Controls
Goetz H. Kloecker, Guilherme Rabinowits, Cicek Gercel-Taylor, Jamie M. Day, Douglas D. Taylor
Clinical Lung Cancer, 2008, 9(5), #7, full article in press

RESULTS
Plasma Thermogram and Lung Cancer
R Chaires, D Xiung, A Mitha, GH Kloeker, ASCO-NCI-EORTC Meeting 2008, #77

Any Questions?