Lung Cancer Surveillance using low Dose CT scanning – where are We Now?

Scott Swanson
Professor Thoracic Surgery
Brigham and Women’s Hospital and Harvard Medical School
Disclosures

These slides were kindly provided by Dr Michael Jaklitsch
# U.S. Cancer Incidence by Site, 2012

## Estimated New Cases*

<table>
<thead>
<tr>
<th>Site</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>192,280</td>
<td>192,370</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,090</td>
<td>103,350</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>75,590</td>
<td>71,380</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>52,810</td>
<td>42,160</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>39,080</td>
<td>29,640</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>35,990</td>
<td>29,990</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>35,430</td>
<td>27,200</td>
</tr>
<tr>
<td>Leukemia</td>
<td>25,630</td>
<td>22,330</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>25,240</td>
<td>21,550</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,050</td>
<td>21,420</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>766,130</strong></td>
<td><strong>713,220</strong></td>
</tr>
</tbody>
</table>

## Estimated Deaths

<table>
<thead>
<tr>
<th>Site</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>88,900</td>
<td>70,490</td>
</tr>
<tr>
<td>Prostate</td>
<td>27,360</td>
<td>40,170</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>25,240</td>
<td>24,680</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,030</td>
<td>17,210</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,590</td>
<td>14,600</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>12,090</td>
<td>9,670</td>
</tr>
<tr>
<td>Esophagus</td>
<td>11,490</td>
<td>9,280</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>10,180</td>
<td>7,780</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>9,830</td>
<td>6,070</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,160</td>
<td>5,590</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>292,540</strong></td>
<td><strong>269,800</strong></td>
</tr>
</tbody>
</table>
Lethality of Cancer Affected by Screening

- Breast CA: breast exam, mammograms
- Colon CA: occult fecal blood, colonoscopy
- Prostate CA: rectal exam, PSA
- Lung CA: ?
Why No Lung Cancer Screening Prior to 2011?

- Failed trials in 1960’s to 1980’s using sputum cytology and chest x-ray

- Different disease demographics:

<table>
<thead>
<tr>
<th>Year</th>
<th>Lung Cancer</th>
<th>TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984</td>
<td>84,000</td>
<td>24,000</td>
</tr>
<tr>
<td>2012</td>
<td>226,160</td>
<td>11,545</td>
</tr>
</tbody>
</table>
New Technology Advancements

- Low-dose CT scanners
- Minimally invasive surgery for detected CA
- Reduced risk of intervention
- Accurately detect, safely intervene
Recent History LDCT Screening in the United States

- 1970-1980s: Failed CXR screening trials
- 2006: I-ELCAP demonstration project
- August 2011: NEJM publication NLST
- Spring to Fall 2012: Professional Society Position Statements
- December 2013: USPSTF endorsement at “B” level
- April 30, 2014: MEDCAC hearing at CMS
- November 10, 2014: CMS vote for coverage
Use of Low Dose CT Scan to Screen: ELCAP and I-ELCAP

- Non-randomized trial 1993: LDCT could screen for lung cancer
- 60 years of age, 10 pack years
- 484 cancers in 31,567 subjects
- 85% stage I
- 88% 5-year survival
- Surgical mortality 0.05% using board certified thoracic surgeons

I-ELCAP investigators. NEJM 2006
National Lung Screening Trial (NLST)

- NCI sponsored phase III randomized trial

- 3 eligibility criteria
  - Age 55 to 74 years
  - 30 pack year smoking history
  - If quit, smoked within last 15 years
Lung Cancer Screening Reduces Lung Cancer Mortality by 20%

- 3 annual screens, then observation for 4 years (LDCT versus CXR)
- 53,454 participants from 8/02 – 4/04
- Trial stopped early: 20% reduction in lung cancer specific mortality

NLST Research Team. NEJM 2011
Clearly there will be variable rates of national implementation of screening across various countries." 

“In light of these positive developments, each nation will decide how to integrate lung cancer screening into its existing healthcare structure.”
Guidelines from Professional Societies in North America

- National Comprehensive Cancer Network: January 2012, strongly recommended screening ages 55 to 74.

- AATS: May 2012, strongly recommended screening and included up to age 79.

- ASCO/ACCP: June 2012, weaker recommendation for ages 55 to 74.
AATS
Recommendation 1

- Annual lung cancer screening with LDCT from age 55 to age 79 for patients with 30 pack-year history of tobacco.

- Screening should not be offered if treatment impractical due to co-morbidity or functional status, regardless of age.

- This recommendation expands the age and the frequency of screening of the NLST.

Jaklitsch et al. JTCVS 2012;144:33-38.
Justification for Annual Screens

- Annual increase in risk due to age.
- Divergence of survival graphs in NLST during screening period, but parallel course of survival during observation. Mortality reduction would have exceeded 20% if continued annual scans.
- NLST 20% reduction in mortality with just 3 annual screens, followed by 4 years of observation.
- AATS Task Force: No scientific evidence to stop screening after 3 annual screens.

NLST Research Team. NEJM 2011
Justification for Increasing Age of Screening from 74 to 79

- Median age of Lung Cancer 74 years.
- Average life expectancy US 78.6 years
- Lung Cancer incidence increases beyond 74.
- Screening should add 7 years of life expectancy
Lung Cancer Risk is a Function of Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence (per 100,000)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 – 70 years</td>
<td>336</td>
<td>248</td>
<td></td>
</tr>
<tr>
<td>71 – 75 years</td>
<td>490</td>
<td>350</td>
<td></td>
</tr>
<tr>
<td>&gt; 75 years</td>
<td>517</td>
<td>307</td>
<td></td>
</tr>
</tbody>
</table>

Exponential Lung Cancer Risk for Elderly Smokers

SEER Database Shows Increase in Stage I cancer with age: N = 14,555

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Males, %</th>
<th>Stage I, %</th>
<th>Histology, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 yrs (n=5057)</td>
<td>55</td>
<td>79</td>
<td>26</td>
</tr>
<tr>
<td>65 - 74 yrs (n=6073)</td>
<td>57</td>
<td>83</td>
<td>35</td>
</tr>
<tr>
<td>≥75 yrs (n=3425)</td>
<td>54</td>
<td>87</td>
<td>35</td>
</tr>
<tr>
<td>P</td>
<td>0.0062</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Squamous cell cancers have higher rates of local disease, lower recurrence rates, and longer survival times.

Mery. Chest 2005
The United States Preventive Services Task Force (USPSTF) issued a Recommendation B* (December 2013):

- Annual screening (LDCT)
- Adults aged 55 to 80 years
- 30 pack-year smoking history
- Currently smoke
- Have quit within the past 15 years

Because of this, private insurance plans, **must** cover Lung Ca Screening by January 1st, 2015

This recommendation also encourages Medicaid plans to provide screening services with no cost sharing; however, **Medicare is not required** to follow this recommendation

*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*
Medicare Evidence Development & Coverage Advisory Committee

Voted between low and intermediate confidence that the benefits outweigh the harms of LDCAT screening

Considerable press in May 2014 that LDCT “was dead”
To qualify for the once-per-year benefit (annual), patients must be 55 to 77 years old.

Additionally, Medicare beneficiaries must

- currently smoke tobacco products or have quit within the past 15 years,
- have smoked an average of one pack of cigarettes a day for 30 years, and
- have a physician or other health care professional's written order requesting the test.
So, Where are we now?
How will LDCT screen look?

- Annual scan for selected patients age 55-77 with 30 pack years, smoked within 15 years, able to withstand treatment.
- ACR provides site accreditation
- LUNGrads guides subcentimeter nodule workups
- Surgery within insurance networks with second opinions at academic centers
- Data audits and re-evaluation of guidelines every 7 years.
Screening CT Resolution

Screening CT

Diagnostic CT – Adenocarcinoma
## Size as Risk Factor for Cancer

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>2-5</th>
<th>6-10</th>
<th>11-20</th>
<th>20-45</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>99</td>
<td>46</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>%</td>
<td>1</td>
<td>24</td>
<td>33</td>
<td>80</td>
</tr>
</tbody>
</table>

Henschke C. Lancet 1999; 354
### Fleischner Society Small Nodule Followup

<table>
<thead>
<tr>
<th>Nodule Size</th>
<th>Low Risk Pt</th>
<th>High Risk Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=4 mm</td>
<td>None</td>
<td>12 m No ∆ - stop</td>
</tr>
<tr>
<td>4 – 6 mm</td>
<td>12 m No ∆ - stop</td>
<td>6-12 m; No ∆ then 18-24 m</td>
</tr>
<tr>
<td>6 – 8 mm</td>
<td>6-12 m If no ∆ then 18-24 m</td>
<td>3-6 m If no ∆ then 18-24 m</td>
</tr>
<tr>
<td>&gt; 8 mm</td>
<td>CT 3, 9, 24 m or CE CT; PET; or biopsy</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3: AATS Lung Cancer Screening Guidelines for Solid Nodules

Solid or part solid nodule

- ≤ 4 mm → Annual LDCT screening to age 79
- >4-6 mm →
  - 6-8 mm → LDCT in 3 mo → Increase → Surgery recommended
  - >8 mm → Consider PET/CT →
    - Low suspicion →
    - High Suspicion → Surgery recommended
- Solid Endobronchial → Bronchoscopy recommended
**INDETERMINATE NODULE 4-7 mm**

Thin-section CT at 6 m.

- **Ca+**
  - Benign
  - **Indeterminate**
    - CT at 12 mo
      - ↑ size > 8mm PET or Biopsy
    - CT at 24 mo
      - ↑ size – Biopsy or PET

Inflammatory nodule - 12 month resolution
Part Solid Nodule - Ground Glass Opacity

12 MONTHS FOLLOW-UP UNCHANGED
6 month follow-up: No Change
Increase in size – Adenocarcinoma, papillary type
Growth Rate Assessment

- Malignant - doubling time of 30 days to 18 months
- Absence of growth for 2 years - benign
Plain film data cannot be applied to screening CT

CT doubling times range from 79 to 1435 days (mean 508)

Histological correlates

BAC – 567 days; Squamous – 122
Detecting Volume Change:

Small Nodules

- 4 mm
- 5 mm
- 6.2 mm

volume doubling

- 3 cm
- 3.75 cm
- 4.70 cm
Initial Scan  Adenocarcinoma  At 10 months
MAI GRANULOMA

Baseline

6 months

MAI GRANULOMA
Bronchoalveolar carcinoma
Causes Of GGO

- Slow growing bronchoalveolar carcinoma
- Atypical adenomatous hyperplasia
- Organizing pneumonia
- Inflammatory pseudotumor
- Lymphoma
GGO: CT / PATHOLOGY

- 43 GGO`s < 2 cm resected
- BAC 23; Adenocarcinoma 11; AAH 9
- GGO and solid component 93% malignant

Nakata Chest 2002
Adenocarcinoma with BAC: Features

Courtesy of Dr. David Naidich
Non-mucinous BAC

GGOs in 3 patients, RLL and LUL of 2 different patients at presentation, and recurrent tumor posteriorly in RUL
Mucinous BAC

GGOs contain prominent linear outlines within the opacities. Often associated with multifocal disease as in patients with bilateral abnormality.
Papillary Pattern

Primarily solid tumor nodule or in solid portion of nodule also exhibiting ground glass feature
Solid Pattern

Right hand images demonstrate correlation between the CT and whole mount pathology
Histologic image (4x) demonstrates areas of invasive (acinar pattern) tumor with prominent septal thickening that create appearance of bars on CT images.

Best seen with CT images that are less than 2 mm in thickness
Histologic image shows peripheral areas of lepidic growth with central foci of invasive (acinar pattern) tumor with fibrosis and septal thickening creating the appearance of holes on CT images.

Best seen with CT images that are less than 2 mm in thickness
Recommendation 2

- Long-term lung cancer survivors should have annual LDCT to detect second primary lung cancer until the age of 79.

- Surveillance for recurrence for 4 yrs, then annual LDCT.

- 400,000 lung cancer survivors are highest risk of new cancer, but were excluded from previous trials and ignored in other societal recommendations.
Cost Controversy: Radiation

- USPSTF endorsed annual scans from age 55 to 80 (25 years)
- In the NLST, average dose was 1.5 mSv
- Estimates of lung cancer risk due to radiation over 25 years range between 0.07% and 0.85%
- ACR accreditation of screening sites
Cost Controversy: False Positive Scans

- Implication of harm due to invasive tests:

  But, the program is built on repeat LDCT scans, **NOT** invasive procedures. Thus,
  
  - "Positive" scan leads to a repeat scan in 3, 6, or 12 months
  - "False positive nodules" implies that the nodule was removed, but 96% of the false positive findings were sorted out by repeat imaging

In the 6369 positive screens in the CT screening arm, only 297 (4.2%) had surgery. Furthermore, half of the "positive" scans were so labeled for nodules between 4 and 6 mm.
Methods to Reduce False Positives

1) Use of standardized protocol: LUNGrads of ACR

2) Increase threshold of “positive scan” to 6 mm

3) Use of repeat scan prior to invasive procedures, especially in subcentimeter nodules.
Cost Controversy: Lung Cancer Screening will bankrupt Medicare

- There will be inevitable and substantial financial impact to the CMS. Several website editorials reporting a cost of over $1 billion.

- Broken out per beneficiary:
  - Estimates have ranged from $1 per beneficiary per month to $3 per beneficiary per month
  - It comes out to the price of a cup of coffee once or twice a month
  - Cost of $28K per QALY about equal to colonoscopy and better than mammography
Summary

- CT screening is here and will be covered
- Use guidelines to begin program
- Most need a clinical extender to help provide follow-up
- Establish institutional database
- Must have minimally invasive option to avoid unnecessary morbidity