Low-dose CT Screening for Lung Cancer
Goals & Objectives

• Lung cancer statistics
• What comprises a good screening test
• The big studies
  – National Lung Screening Trial (NLST)
  – Early Lung Cancer Action Program (ELCAP)
• Current recommendations and rationale
Lung Cancer – The Statistics

- Second most common cancer for both men and women
- Far and away the most common cause of cancer death
  - 27% of all cancer deaths
  - More than colon, breast and prostate combined
- 224,000 new cases estimated for 2014
  - 116,000 men
  - 108,000 women
  - Gap between genders has been closing for years
- 159,000 deaths estimated for 2014

American Cancer Society
www.cancer.org
Lung Cancer – The Statistics

• Tobacco association
  – Male smokers 23X more likely to develop than never smokers
  – Female smokers 13X more likely to develop than never smokers
  – Secondhand smoke
    – Home or work exposure leads to an estimated 20-30% increased risk for developing lung cancer
    – Estimated 7,330 lung cancer deaths per year attributable to secondhand smoke

• Other risk factors
  – Radon – est. 21,000 cancer deaths per year
  – Occupational exposure (asbestos, etc.)
Initial staging

Percent of Cases by Stage

- Localized
- Regional spread (lymph nodes)
- Distant (metastases present)
- Unknown

National Cancer Institute/SEER database
5-year survival by stage

Overall = 16.6%

National Cancer Institute/SEER database
What comprises a good screening test?

- **Disease factors**
  - Disease must have an adequate prevalence
    - Contributes to negative predictive value
  - Must have a detectable pre-clinical period
  - Must be curable during pre-clinical period
    - Patient must be able to tolerate the treatment
  - Must be more successfully treated during pre-clinical period
What comprises a good screening test?

- **Test factors**
  - High sensitivity
  - Reasonable specificity
  - High predictive value
  - Broadly available/acceptable
    - Cost
    - Risk
    - Patient tolerance
What is a low dose CT?

- CT dose is determined by many factors, including:
  - Tube current (mAs)
  - X-ray voltage (kVp)
  - Pitch
  - Slice thickness
  - Patient factors
- The lung is intrinsically high-contrast, allowing the dose to be reduced (particularly the tube current)
Low dose vs. standard dose
(as a reference, a standard CXR view = 0.06 mSv)

Low-dose CT = 0.9 mSv
Standard CT = 6.7 mSv
Low dose CT protocol (Scott & White)

- No IV contrast
- Axial thin sections (1.5 mm)
- Axial and coronal reconstructions at 3 mm
- Axial, coronal and sagittal MIP images
- Takes about 5-10 minutes and two breath-holds

All from single acquisition
Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team∗

ABSTRACT
Please note

- Screening data and recommendations to follow are largely confined to non-small cell cancer
- Small cell carcinoma is clinically treated differently, is more rare, and more aggressive
The NLST

- Large, multicenter trial comparing low-dose CT (LDCT) with conventional radiographs for screening for lung cancer
- 53,454 patients
- 33 U.S. medical centers
- Patients randomized to either low-dose CT or a single PA chest radiograph
- Patients received 3 studies separated by one year intervals (T0, T1, T2)
NLST - Participants

• 55-74 years old

• At least 30 pack-year history of smoking
  – 48% current smokers
  – 52% previous smokers (must have quit within last 15 years)

• Excluded
  – Those with previous history of lung cancer
  – Those with a CT within the previous 18 months
  – Those with current hemoptysis, unexplained weight loss
NLST - Screening

- Positive CT = any non-calcified nodule $\geq 4\text{mm}$
- Positive radiograph = any non-calcified nodule or mass “suspicious for cancer”
- Malignant-appearing adenopathy or effusion could also be scored positive
- Findings stable at the third round were classified as a minor abnormality instead of a positive study
- No standardized follow up for the nodules was performed
  - None existed at the time
  - Nodules were managed as per institutional practices
# NLST - Results

## Table 2. Results of Three Rounds of Screening.*

<table>
<thead>
<tr>
<th>Screening Round</th>
<th>Low-Dose CT</th>
<th>Chest Radiography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No. Screened</td>
<td>Positive Result</td>
</tr>
<tr>
<td>T0</td>
<td>26,309</td>
<td>7191 (27.3)</td>
</tr>
<tr>
<td>T1</td>
<td>24,715</td>
<td>6901 (27.9)</td>
</tr>
<tr>
<td>T2</td>
<td>24,102</td>
<td>4054 (16.8)</td>
</tr>
</tbody>
</table>

NLST - Results

• Positive results
  – CT arm – 24.2%
  – CXR arm 6.9%

• Greater than 90% of positive results at T0 lead to a diagnostic workup
  – Large majority limited to imaging
  – Percutaneous biopsy ≈ 2%
  – Bronchoscopy ≈ 4%
  – Surgery ≈ 4%

• Subsequent years had lower rates
NLST - Results

- False positives
  - LDCT arm – 96.4% (total of 23.3% false positive among arm)
  - CXR arm – 94.5% (total of 6.5% false positive among arm)
<table>
<thead>
<tr>
<th></th>
<th>LDCT group</th>
<th>CXR group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cancers</td>
<td>1060</td>
<td>941</td>
</tr>
<tr>
<td>Cancer dx. following + test</td>
<td>649</td>
<td>279</td>
</tr>
<tr>
<td>Cancer dx. following – test</td>
<td>44</td>
<td>137</td>
</tr>
<tr>
<td>Dx. made when screening missed or after study was over</td>
<td>367</td>
<td>525</td>
</tr>
</tbody>
</table>
NLST - Results

- Both groups had higher percentage of stage 1 cancers detected than the population diagnosed after completion of the study.
- LDCT had fewer stage 4 cancers than the CXR group.
- LDCT group had a relative reduction in lung cancer death of 20% compared to CXR.
- This is estimated to be equivalent to reduction compared to community care without imaging.
  - Compared with concurrent PLCO study comparing CXR and no imaging which showed no significant difference.
NLST – Adverse events

- In general, low
  - Minor complication (minor allergic rxn., vasovagal, small pneumothorax not requiring chest tube, etc.)
    - CT arm – 1.4%
    - CXR arm – 1.6%
  - Major complication (anaphylaxis, BP fistula, cardiac arrest, respiratory arrest, death)
    - CT true positive – 11.2%
    - CT false positive – 0.06%
    - CXR true positive – 8.2%
    - CXR false positive – 0.02%
- True positives complications included more invasive procedures
- Various institutional management schemes probably led to variations
ELCAP

- Initially started in 1991 at Cornell University Medical Center
- Designed to study difference in proportion of early stage lung cancer between LDCT and CXR
- Included a well-defined strategy for workup of positive studies (unlike NLST)
  - Emphasized that screening is a clinical process, not just a test
  - More accurately determines the improvement in lung cancer cure rates attributable to screening

www.ielcap.org/ielcap
ELCAP

- Initially screened 1000 high-risk individuals
- Eventually more clinical sites and more patients were added
  - 31.456 asymptomatic participants
- Non-randomized (single arm)
  - Survival data is actuarial
- Has resulted in 46 publications

www.ielcap.org/ielcap
ELCAP study findings (selected)

- 80% of cancers diagnosed at staging were clinical Stage 1

- Lung cancer mortality reduction in two large cohorts
  - 36% and 64% for all participants
  - 31% and 63% for those still smoking
ELCAP study findings (selected)

- Sublobar resection and lobectomy may have equivalent survival in the stage 1A setting (smaller study)

- Radiation for stage 1 may be equivalent to surgery (smaller study)
What to make of all this data?

- **National Comprehensive Cancer Network (NCCN)**
  - Alliance of 25 comprehensive cancer centers in U.S. as designated by the National Cancer Institute/NIH
  - Develop and publish practice guidelines for oncology care

- **U.S. Preventive Services Task Force (USPSTF)**
  - Panel of primary care physicians and epidemiologists appointed and funded by U.S. Dept. of Health & Human Services
  - Make recommendations on preventive services
NCCN recommendations

• Annual LDCT for high-risk individuals
  – Age 55-74, ≥ 30 pack year history of smoking, quit smoking ≤ 15 years, or
  – Age ≥ 50, ≥ 20 pack year history of smoking, and additional risk factor other than second-hand smoke
  – “Category 2A” recommendation – Uniform NCCN consensus that the test is appropriate, based on lower-level evidence

• Not recommended for lower risk individuals
NCCN recommendations

• Benefits
  – Decrease in mortality
    – 40-60% by 7995 patient ELCAP cohort
    – 20% by NLST
    – May be higher than stated if carried out more than two years
  – Quality of life – not yet available
  – Reduced treatment-related morbidity
    – More stage 1 cancers
    – More lung-conserving therapy
  – Screening may reinforce smoking cessation, reduce anxiety – little data
NCCN recommendations

• Cost-effectiveness
  – Few analyses at present
  – Length of time needed to screen and the cost of false-positives are estimates
  – Original ELCAP estimated a 0.1 year increased survival at an incremental cost of $230
NCCN recommendations

• Risks
  – Significant false-positive rate
    – Some have complications
    – NCCN guidelines try to limit invasive interventions found on baselines in order to limit this
  – “Overdiagnosis” – futile detection of indolent cancers
    – Many experts believe invasive lung cancer is uniformly fatal if untreated
      » Limited data – all 8 untreated stage 1 cancers in one ELCAP cohort were dead in less than 5 years
  – AIS/MIA are fairly recently defined
    » Future studies may be able to establish more accurate imaging criteria
NCCN recommendations

- Risks – radiation dose
  - LDCT ≈ 0.6 - 1 mSv
  - Conventional CT ≈ 6 mSv
  - CXR single view ≈ 0.06 mSv
  - Estimation of harms is very difficult
    - One study suggests 1.8% increase in cancer if half of all current and former US smokers got annual LDCT’s between 50-75 years
  - Doses may be reduced in future with techniques like spectral shaping and iterative reconstruction
    - Dose may drop to 0.1 – 0.2 mSv
The Task Force Recommendation on Lung Cancer Screening With Low-Dose Computed Tomography

The USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in persons age 55 through 80 years with a 30 pack year history of smoking who are currently smoking or have quit within the past 15 years. Screening should be discontinued once the individual has not smoked for 15 years or develops a health problem significantly limiting either life expectancy or ability or willingness to undergo curative lung surgery.

http://www.uspreventiveservicestaskforce.org/uspstf13/lungcan/lungcanfinalrs.htm
USPSTF recommendations

• Recommends high-risk individuals age 55-80 get LDCT annually, until:
  – Have quit smoking for ≥ 15 years
  – Develops health problems precluding lung surgery
  – Unwilling to undergo lung surgery

• Proposed risks and benefits very similar to what NCCN published
Other societies

• LDCT screening recommended by:
  – American Cancer Society
  – American College of Chest Physicians
  – Society of Thoracic Surgeons
  – American College of Radiology

• American Academy of Family Physicians
  – “I” recommendation
    – “The AAFP concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.”
AAFP recommendation

• Reluctance to recommend from following points
  – NLST data from large medical centers, and results may not be applicable to community setting
    – European (non-RCT) studies showed less benefit
  – Risks of false-positives
  – NLST data collected over short period of time
Costs

- At present, CMS has yet to render a decision on reimbursement for LDCT screening
- This typically follows a positive USPSTF recommendation, but is not currently forthcoming
- Offered on a cash basis in many locations
  - $100-$300
Future directions

- Lower CT radiation dose on horizon
- CMS (and insurer) reimbursement will make study more available
- Follow up uniformity will be more established
  - NCCN guidelines are already an improvement
  - ACR working on Lung RADS to establish a uniform lexicon and follow up scheme
    - Similar to BI-RADS for mammography
- Longer-term benefits from screening will hopefully be established
What to do?
(Editorialized view follows)

- LDCT good if:
  - Your patient has access to radiology services that are prepared to do it
  - You are able to help patient negotiate follow up (or refer to pulmonary, etc.)
  - **Screening is coupled with smoking cessation assistance**
    - Every study and recommendation makes particular emphasis about this – there is no replacement
  - Your patient can undergo the necessary follow up and/or surgical treatment
Helpful resources

• **NCCN guidelines**
  - Free web site, but you need to sign up and get a login ID and password

• **USPSTF guidelines**
  - [http://www.uspreventiveservicestaskforce.org/uspstf13/lungcan/lungcanfinalrs.htm](http://www.uspreventiveservicestaskforce.org/uspstf13/lungcan/lungcanfinalrs.htm)

• **ACR Lung RADS**
Helpful resources

• **Link for NLST paper in NEJM**

• **ELCAP site**
  - [http://www.ielcap.org/](http://www.ielcap.org/)