Lung Cancer Screening: Clinical Trials, Screening Recommendations, and What’s Next

CLAUDIA I HENSCHEK PHD, MD
MOUNT SINAI HEALTH SYSTEM, NEW YORK, NY
Disclosures

- I am a named inventor on a number of patents and patent applications relating to the evaluation of pulmonary nodules on CT scans of the chest which are owned by Cornell Research Foundation (CRF).
- As of April 2009, I signed away any financial benefit including royalties and any other proceeds related to the patents or patent applications owned by CRF.
- I am the President of the Early Diagnosis and Treatment Research Foundation.
The ELCAP Approach: A cohort paradigm
how to integrate technologic advances

Diagnostic Mission

- Everyone Screened
- CT and CXR
- Lung Cancer Distribution (Stage/Size)

Intervention Mission

- Rx
- No Rx
- Cure Rates*
- No Rx
- Cure Rates*

Two years

* specific to stage and size

In future compare CT with potential biomarkers or other tests
Individualized CT screening depends on indicators of risk e.g., current smokers, former smokers, never smokers

Largest CT Screening Cohort in the World
ELCAP to NY-ELCAP to International-ELCAP

- Study design
- Screening protocol
- Pathology protocol
- Regimen of screening
- Lung cancer size, stage, cure rate

ELCAP
WCMC
NYUMC
NY-ELCAP
SUNY-Downstate
SUNY-Stonybrook
Roswell Park
Mount Sinai
NY Medical
North Shore
Long Island Jewish
Our Lady of Mercy
MSKCC

NY-ELCAP
100+ investigators
75 institutions in 9 countries
80,000+ participants

I-ELCAP

Israel
Switzerland
Spain
Italy

Japan
China

Brazil, Canada
United States

Conferences @ 6 months
Computer analytics
Continuous Quality Improvement
Publications 200+

We have been working with Delaware since the start of I-ELCAP
ELCAP Management System

- Started in 1992, C Henschke programmed the first system.
- In 2000, AP Reeves brought it into the web-based environment.
- Now providing an open source system for the Veterans Administration and the world.
Goal of ELCAP in initial NCI grant

- Probability of detecting a noncalcified nodules (NCNs) on LDCT
- Probability of diagnosing lung cancer in an NCN
- Probability of cure after treatment, given a diagnosis of lung cancer
1990’s: images on film
2000: computer monitors
After 2010: bigger monitors
Goal of ELCAP in initial NCI grant

- Probability of detecting a noncalcified nodules (NCNs) on LDCT
  
  **ANSWER:** On initial CT scans in 1992-1999: 23% had NCNs

  On TODAYs CT scans: > 50%

- Probability of diagnosing lung cancer in an NCN
  
  **ANSWER:** Depending on smoking and age and round of screening:

  **BASELINE:** 1% to 3%

  **ANNUAL REPEAT:** 0.25% to 0.75%

- Probability of cure after treatment, given a diagnosis of lung cancer
  
  - All cases diagnosed under screening: 80%
  - Pathologic Stage I > 90%
How to Differentiate Malignant from Benign NCNs: Volumetrics

- We introduced it in 1997 in NCI grant and publications in 1999
- Showed results and images to NLST and NELSON
- NELSON used and recommended volumetrics
Baseline HRCT (CU0138)

Jun 17 1996, (X,Y) resolution: 0.68359 mm, Slice thickness : 1 mm

Images ©1998, ELCAP Lab, Cornell University Medical College
Three Month Repeat HRCT (CU0138-2)

Oct 25 1996, (X,Y) resolution: 0.68359 mm, Slice thickness : 1 mm
Baseline and 3-month Repeat HRCT
Comparison of Baseline and Three Month Repeat CT

Images ©1998, ELCAP Lab, Cornell University Medical College
Measurement Uncertainty
Within seconds, 44%

Perfect sphere had a 172 day volume doubling time

FDA Approved CT Scanner has one slice – considerable distortion

Resected clinical Stage I: 92% (95% CI: 88%-95%)

All cases: 80% (95% CI: 74%-85%)
20-year Kaplan-Meier LC Survival Curve:

N = 1149

Resected clinical Stage I: 91.3% (95% CI: 88.8-93.8%)

All cancers: 85.3% (95% CI: 83.0-87.6%)
IMPORTANCE OF THE PROTOCOL
The protocol can reduce unnecessary tests and particularly invasive procedures.
I-ELCAP and NLST Survival Rates

The benefit of having a regimen of screening with continuous updates together with a web-based electronic structured management system is shown by the results below.

- I-ELCAP: 5-year rate of 83% (95% CI: 79%-85%)
- NLST-CT Arm: 5-year rate of 62% (95% CI: 53%-63%)

**Stage I**
- Average tumor size (mm): I-ELCAP 82% 17 mm, NLST 67% 23 mm

Changes in Definition of Positive Result

1992:
- **Baseline:** any noncalcified nodule (NCN)
- **Annual:** any new or growing NCN

2000:
- **Baseline:** any NCN ≥ 5.0
- **Annual:** any new or growing NCN ≥ 3.0

2016:
- **Baseline:** a 2-step process for any solid NCN between 6.0-15.0, follow-up CT to assess growth rate
- **Annual:** no change
Subsolid Nodules: Part-solid and Nonsolid
AAH – AIS – MIA – Lepedic predominant

Nonsolid Nodule                                             Part-solid nodule
International Early Lung Cancer Action Program Firsts

Long-term survival of solitary and multiple adenocarcinomas manifesting as subsolid nodules.


Ad-BAC 100% vs. Ad-Mixed 95% (95%CI: 92%-98%) vs. Adeno-Other 75% (95%CI: 51%-100%)

Adeno by %BAC
Since then classified as AIS, MIA, Adeno-BAC

Adenocarcinoma N0M0
Single 97% vs. Multiple 100%
For nonsolid nodules

No further diagnostic tests

Only 1 year follow-up

For part-solid nodules

Follow-up based on Solid component only

Same as solid nodules

Publications on Nonsolid and Part-solid Nodules

National Lung Screening Trial: Outcomes


Meta-analyses of Long-term Outcomes of Nonsolid and Part-solid Nodules

Baseline: frequency of positive result and dx of lung cancer among 21,136 recent participants


Led to Guideline Changes

LUNG RADS, NCCN, I-ELCAP
I-ELCAP Recommendations for Baseline Workup:
Based on largest solid (solid component of PS) NCN

- Recommend annual repeat LDCT for all NCN (nonsolid, part-solid, solid)

  - Unless

    - NCN (solid or solid component of PS) is 6.0 to 15.0 mm which demonstrates growth at a malignant rate on 3-month follow-up LDCT

    - NCN 15.0+, then recommend biopsy
ELCAP Management System

- Started in 1992, C Henschke programmed the first system
- In 2000, AP Reeves brought it into the web-based environment
- Now providing an open source system for the Veterans Administration and the world
Individualized CT screening depends on indicators of risk e.g., current smokers, former smokers, never smokers

- Study design
- Screening protocol
- Pathology protocol
- Regimen of screening
- Lung cancer size, stage, cure rate
- Conferences @ 6 months
- Computer analytics
- Continuous Quality Improvement
- Publications 200+
- Nodule growth and detection
- Mediastinal masses
- Emphysema
- Coronary Artery Ca++
- Breast Diseases
### I-ELCAP, ACR-LungRADS, European baseline protocol comparison

<table>
<thead>
<tr>
<th>Category</th>
<th>I-ELCAP</th>
<th>ACR-Scenario 1</th>
<th>ACR-Scenario 2</th>
<th>European</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solid NCN, largest</strong></td>
<td>≥ 15.0 mm</td>
<td>≥ 8 mm</td>
<td>≥ 15 mm</td>
<td>≥ 10 mm</td>
</tr>
<tr>
<td><strong>Part-solid NCN, largest</strong></td>
<td>solid component ≥ 15.0 mm</td>
<td>solid component ≥ 8 mm</td>
<td>solid component ≥ 8 mm</td>
<td>NONE</td>
</tr>
<tr>
<td><strong>b. 3-month LDCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Solid NCN, largest</strong></td>
<td>≥ 6.0 mm but &lt;15.0 mm</td>
<td>-</td>
<td>≥ 8 mm but &lt;15 mm</td>
<td>≥ 5 mm but &lt;10 mm</td>
</tr>
<tr>
<td><strong>Part-solid NCN, largest</strong></td>
<td>solid component of NCN ≥6.0 mm but &lt;15.0 mm</td>
<td>entire size of NCN ≥6 mm with solid component ≥6 mm but &lt;8 mm</td>
<td>entire size of NCN ≥6 mm with solid component ≥6 mm but &lt;8 mm</td>
<td>entire size of NCN ≥5 mm</td>
</tr>
<tr>
<td><strong>Nonsolid NCN, largest</strong></td>
<td></td>
<td></td>
<td></td>
<td>≥5 mm</td>
</tr>
<tr>
<td><strong>c. 6-month LDCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Solid NCN, largest</strong></td>
<td>NONE</td>
<td>≥6mm to &lt;8mm</td>
<td>≥6mm to &lt;8mm</td>
<td>NONE</td>
</tr>
<tr>
<td><strong>Part-solid NCN, largest</strong></td>
<td>NONE</td>
<td>entire size of NCN ≥6 mm with solid component ≥6 mm</td>
<td>entire size of NCN ≥6 mm with solid component &lt;6 mm</td>
<td>NONE</td>
</tr>
<tr>
<td><strong>Nonsolid NCN, largest</strong></td>
<td></td>
<td>≥20mm</td>
<td>≥20mm</td>
<td></td>
</tr>
</tbody>
</table>

Henschke CI, Yip R, Ma T, Aguayo SM, Zulueta J, Yankelevitz DF for I-ELCAP Investigators. CT Screening for Lung Cancer: Comparison of three baseline protocols. European Radiology, 2018
Comparison of Protocols

ER = number of people requiring dx tests for each diagnosis of lung cancer

<table>
<thead>
<tr>
<th>Workup</th>
<th>I-ELCAP ER %</th>
<th>ACR-S1 ER %</th>
<th>ACR-S2 ER %</th>
<th>European ER %</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVERALL</td>
<td>13.9</td>
<td>18.3</td>
<td>18.3</td>
<td>31.9</td>
</tr>
</tbody>
</table>

# Comparison of Baseline Protocols: Estimated % participants requiring biopsies and # biopsies per LC dx

<table>
<thead>
<tr>
<th>Workup</th>
<th>I-ELCAP</th>
<th>ACR-S1</th>
<th>ACR-S2</th>
<th>European</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsies</td>
<td>1.6%</td>
<td>6.0%</td>
<td>2.3%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Henschke CI, Yip R, Ma T, Aguayo SM, Zulueta J, Yankelevitz DF for I-ELCAP Investigators. CT Screening for Lung Cancer: Comparison of three baseline protocols. European Radiology, 2018
I-ELCAP, ACR-LungRADS, European

- All protocols recommend
  - 1) immediate workup, %
  - 2) delayed workup, %
  - 3) annual repeat screening %

- All use different thresholds for recommendations
  - 6.0mm for I-ELCAP, 6mm for LungRADS, 5mm European

- ACR-LungRADS recommends PET scans for NCNs, 8 mm or larger, although 3 month follow-up CT is an alternative, therefore 2 scenarios:
  - Scenario 1: immediate PET scan
  - Scenario 2: 3 month LDCT
Conclusion

- Differences among modern protocols lead to major changes in efficiencies.

- Accumulated knowledge and data should lead to continual updating of protocols.

- Mechanisms should be place to enhance such updating.
Osteoporosis

Thyroid

Thymus

Breast

Liver

Heart

Lung

Adrenal glands

Osteoporosis
Largest CT Screening Cohort in the World
ELCAP to NY-ELCAP to International-ELCAP

Individualized CT screening depends on indicators of risk
e.g., current smokers, former smokers, never smokers

- Study design
- Screening protocol
- Pathology protocol
- Regimen of screening
- Lung cancer size, stage, cure rate

ELCAP
WCMC
NYUMC
NY-ELCAP
SUNY-Downstate
SUNY-Stonybrook
Roswell Park
Mount Sinai
NY Medical
North Shore
Long Island Jewish
Our Lady of Mercy
MSKCC

NY-ELCAP
100+ investigators
75 institutions in 9 countries
80,000+ participants

I-ELCAP

Conferences @ 6 months
Computer analytics
Continuous Quality Improvement
Publications 200+

Nodule growth and detection
Mediastinal masses
Emphysema
Coronary Artery Ca++
Breast Diseases

Israel
Switzerland
Spain
Italy

Brazil, Canada
United States

Japan
China
MANY UNANTICIPATED FINDINGS

Further areas:
Liver
Adrenals
Thyroid

Image processing software
Breast mass
Breast density
Axillary LNs
Vascular CAC
Breast
Atherosclerosis
Aorta
Stenosis
Peripheral/vascular
Hypertension
COPD
Emphysema
Chronic bronchitis
Bronchiectasis
Focal pneumonia
Interstitial disease
Lung Cancer
Lung

IELCAP Database
Ostroff JS, Buckshee N, Mancuso CA, Yankelevitz DF, Henschke CI. Smoking cessation following CT screening for early detection of lung cancer. Preventive Medicine 2001; 33:613-21 PMID:11716658


Cardiac Disease on Low-dose CT

CAC Score

- Main, LAD, circumflex, right coronary arteries
- Extent of calcification in each artery: none (0), mild (1), moderate (2), marked (3)
- CAC score: 0 -12, for any given person

Shemesh et al. Clinical Imaging 2006; 239: 181-5
Shemesh et al. Radiology 2010; 257: 541-8
Survival rates by CAC score (n = 8,872) adjusted by age, sex, smoking history and diabetes

Shemesh et al. Radiology 2010; 257: 541-548
## Cardiac Recommendations

**Endorsed by Cardiology Organizations**

<table>
<thead>
<tr>
<th>Ordinal CAC Score</th>
<th>Agatston Score</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 0                 | 0              | **Probability of cardiovascular heart disease (CHD) is low.**
|                   |                | **Reassure and keep healthy lifestyle** |
| 1-3               | 1-100          | **Probability of CHD is mild to moderately increased;**
|                   |                | **Healthy lifestyle; moderate statin; ASA** |
| 4-12              | > 100          | **Probability of CHD is moderate to high.**
|                   |                | **Healthy lifestyle; very intensive statin + second drug as needed; ASA;**
|                   |                | **Consider function testing to r/o obstruction;**
|                   |                | **Aggressive BP lowering;**
|                   |                | **Referral to internist or preventive cardiologist** |
Emphysema

- None
- Mild
- Moderate
- Severe

Zulueta JJ et al. Chest 2012; 141:1216-23
COPD-specific Survival Rates (n = 9,047) adjusted by age, sex, smoking history and diabetes

- Moderate: HR = 17.3 (9.5-52.3)
- Marked: HR = 43.7 (13.9-86.1)

Log-Rank Test: $p < 0.0001$

Zulueta et al. Chest 2012; 141: 1216-23
Lung Cancer Survival Rates (n = 9,047) adjusted by age, sex, smoking history and diabetes

Marked emphysema: HR = 3.2 (95% CI: 1.5 – 6.7)
Thickening of the bronchial walls is associated with many pulmonary diseases such as chronic bronchitis.

Task: Compare two whole-lung CT scans to evaluate if there has been any change in airway health: (thickening of airways)

Computer method
1. Identify the bronchial tree in each 3D CT image
Ascending Aorta and Aortic Arch Aneurysms

- Direct visualization of the aortic root, ascending and descending aorta
- Well seen without contrast injection
Among 1,225 consecutive screening participants, the prevalence of
- moderate AV calcifications was 2.1%
- Severe AV calcifications was 0.2%
- Recommend cardiac consultation and echocardiography
Pulmonary Hypertension

- If
  - Main pulmonary artery diameter $\geq 34$ mm or
  - Main pulmonary artery/aorta $\geq 1.0$
- Recommend pulmonary consultation and possibly echocardiogram
Among 1,949 current and former smokers in I-ELCAP, the prevalence rates were:

- Main pulmonary artery diameter $\geq 34$ mm
  - 4.2%
- Main pulmonary artery/aorta $\geq 1.0$
  - 6.9%

Recommend pulmonary consultation and possibly echocardiogram for further evaluation of pulmonary hypertension.
Interstitial Lung Disease

- Can be detected early and there are new treatments
- Early findings, typically peripherally located at lung bases
  - Traction bronchiectasis
  - “ground-glass opacities”
  - reticulations
- Late findings
  - honeycombing
Liver Findings: moderate to severe hepatic steatosis

- If CT attenuation < 40 HU, recommend seeing hepatologist for further evaluation

Liver Findings:
moderate to severe hepatic steatosis

- Particulate Matter may play an important role in abnormal liver function tests
- In the lung cancer screening, the prevalence was 5.3%
- Higher frequency in World Trade Center responders (16.2%)
- A higher frequency was also reported for the Fire Fighters in NYC
Moderate to severe hepatic steatosis (<40 HU) is associated with progressive liver disease that can lead to cirrhosis, liver failure, and hepatocellular carcinoma.

On the other hand, liver attenuation can change rapidly due to alcohol intake.

Focus is on persistent hepatic steatosis.

Diameter: >30 mm or shows growth, recommend further workup

Baseline: 0.45% (41/9263) participants, only 5 were larger than 30 mm
- 1 thymic carcinoma, 4 non-invasive thymomas

Annual: No new or growing thymic lesions

Grade 3 or 4 according to BI-RADS, report on CT, as masses are obscured on mammography

Grade 3: heterogeneously dense

Grade 4: extremely dense


If maximum transverse diameter > 40 mm: recommend further evaluation

Baseline: 4% (202/4776) had adrenal enlargement
- only 2 were >40 mm
- remaining 200 were followed on annual repeat to assess change, none showed a change

Annual: 0.004% (5/11591) were new, all 5 <40 mm
- No growing adrenal glands among those being followed

Thyroid Gland

- Nodules $\geq 15$ mm, recommend thyroid sonography
- Nodules $< 15$ mm, annual repeat screening
Osteoporosis

- Developing quick visual assessment using specific window settings
- Recommend consultation and further workup
Immediate Quantitative CT Report
Protocol:
www.IELCAP.org
Initiative for Early Lung Cancer Research on Treatment
Prior IELC ART Conferences

- January 31, 2015
- February 27-28, 2015
  - History of surgical innovations
    - Evidence needed to change from pneumonectomy to lobectomy
    - Used multiple institutional data
  - Identification of key areas of investigation
IELCART Workshops and Conferences

- Workshop I: January 30 and 31, 2015
- Workshop II: February 27-28, 2015
- Workshop III: June 26, 2015
- Workshop IV: September 18, 2015
- 33rd International Conference and 1st Conference on Research for Lung Cancer Treatment: December 4 and 5, 2015
- Workshop V: March 18, 2016
- 34th International Conference and 2nd Conference on Research for Lung Cancer Treatment: March 6 and 7, 2016
- Workshop VI: June 24, 2016
- Workshop VII: September 23, 2016
- 35th International Conference and 3rd Conference on Research for Lung Cancer Treatment: November 18 and 19, 2016
- Workshop VIII: March 17, 2017
- 36th International Conference and 4th Conference on Research for Lung Cancer Treatment: May 5 and 6, 2017
- Workshop IX: June 23, 2017
- 37th International Conference and 5th Conference on Research for Lung Cancer Treatment: September 15 and 16, 2017
- 38th International Conference and 6th Conference on Research for Lung Cancer Treatment: March 16 and 17, 2018
- Workshop X: June 15, 2018
- 39th International Conference and 7th Conference on Research for Lung Cancer Treatment: October 16 and 17, 2018
- 40th International Conference and 8th Conference on Research for Lung Cancer Treatment: April 12 and 13, 2018
IELCART Primary Endpoints: A Prospective Cohort Study

- Long term survival, recurrence rates, and QoL of different treatments and mediastinal lymph node resection
  - Sublobar vs. lobectomy vs. SBRT
- Watchful waiting and Q of L
  - Includes people being watched by CT screening
  - Includes people who decided not to have surgery, either with or without biopsy
Some Surgical Subtopics

- Lobectomy vs. sublobectomy
- When to perform mediastinal lymph node resection/sampling
- Assessment of resection margin in sublobar resections
- Watchful waiting vs. resection for certain subtypes of cancers
Quality Control Considerations

- Weekly review of complications with surgeons