LUNG CANCER SCREENING: UPDATE AND IMPLICATIONS FOR PRACTICE

Theresa C. McLoud, M.D.
LUNG CANCER

- Leading cause of death from malignancy
  - 1.3 million deaths / year worldwide
  - U.S. >/60,000 deaths – 2010
  - Approximately 70% of cases have incurable disease at presentation, metastatic or locally advanced

- 14% overall 5 year survival
LUNG CANCER CONT’D

- Risk factors
  - Smoking – 85%
  - Occupational exposure
    - Asbestos, radon, arsenic, etc.
  - Second hand smoke
Early lung cancer survival data

- NSCLC Stage IA > 65%

- Small < 1 cm Stage IA > 80%
RATIONALE FOR SCREENING

- Diagnosis early in preclinical stages
- Higher cure rate
- Intuitively makes sense to screen high risk asymptomatic individuals
DETERMINANTS OF SCREENING EFFECTIVENESS

- Survival subject to biases
- Endpoint must be decrease in mortality
- Requires randomized control trial (comparison of mortality rates between screened individuals and nonscreened control group.)
NEWER DIAGNOSTIC TESTS FOR EARLY DETECTION

- Molecular markers ?

** Low-dose helical and MDCT

Early lung cancers are usually peripheral nodules, nodule detection improves with CT

Low dose CT -- 20-25% of standard dose
Mixed solid/GGO SPN

Adenocarcinoma noninvasive with BAC features (thoracotomy)
OBSERVATIONAL TRIALS WITH LOW-DOSE HELICAL CT (SINGLE ARM)

- Purpose
  - Feasibility studies
  - Analyze sensitivity for early lung cancer
  - Test diagnostic algorithms for workup
  - Reduce incidence of advanced stage NSCLC
OBSERVATIONAL TRIALS WITH LOW-DOSE HELICAL CT CONT’D

- Japan, No. America, Europe
- High risk groups, annual low dose CT
- Single arm trials
RESULTS OF OBSERVATIONAL CT TRIALS

- Similar results
- Detection of early stage lung cancer higher than chest radiograph (2-4X)
- Annual exam
- False positives 3x that of standard radiograph
RESULTS OF OBSERVATIONAL CT TRIALS CONT’D

- Management of nodules (suspected lung cancer) – size
  - F/U CT < 8-10 mm
  - More complex studies >8-10 mm
    - (PET, contrast CT, biopsy, resection)
    - Invasive procedures (< 30% done for benign lesions)
SCREENING: PROOF OF EFFICACY

RCT - PROSPECTIVE

- Screening arm with diagnostic test
- Control arm without diagnostic test
- Comparison of cancer mortality
PROSPECTIVE RANDOMIZED CONTROL TRIALS (RCT)

- Nelson trial – Europe (Netherlands and Belgium (n >15,000))
- NLST – USA (NCI and ACRIN) n>30,000.
NLST

- Randomized national study
- Smoking history $\geq 30$ pack years
- Ages 55-74
- 3 annual screens
NLST – (NCI)

- 50,000 current or former smokers
- Medical outcomes 4-6 years from randomization
- 2 arms – CXR & CT
END POINTS OF NLST

- Lung cancer specific mortality
  90% power to detect
  20% reduction in lung cancer mortality in CT screened group
END POINTS OF NLCST CONT’D

- Secondary end points
  - All cause mortality
  - Stage distribution at diagnosis
  - Medical resources use in positive studies
  - Overall performance of 2 screening tests
SECONDARY END POINTS
ACRIN

- Quality of life issues (anxiety in positive screens)
- Medical resource use, cost effectiveness
SECONDARY END

POINTS

ACRIN CONT’D

- Influence on smoking behavior
- 10,000 participants
  - biomarkers – blood, urine, sputum
Persons at Risk ("Healthy" Smokers, Former Smokers) → Screening (Chest X-ray vs. Helical CT) → Early Lung Cancer Detection → Intermediate Outcomes
- Surgery for cure
- Decreased late stage disease → Health Outcomes
- Lung Cancer Mortality
- Overall Mortality
- Quality of Life

Other Outcomes/Trade-Offs
- Healthcare Utilization
- Cost Effectiveness

Adverse Effects of Screening
Adverse Effects of Treatment
NLST CONT’D

- Study group – low dose CT
- Control group – standard radiograph
- Initial screen & end of first and second years
NLST

- Follow-up for another five years
- All deaths documented & also cancer as cause of death
- Preliminary results (November, 2010)
FINAL RESULTS

METHODS

Enrollment period  8/2002-4/2004
Population  53,454
  Low dose CT  26,722
  Chest radiography  26,732
Yearly screening rounds  3
Data collection (deaths)  12/31/2009
RESULTS

Adherence rate 90%

Positive test (3 rounds)

Low dose CT 24.2%
Radiography 6.9%
## RESULTS (CONT’D)

<table>
<thead>
<tr>
<th>Incidence lung cancers</th>
<th>CT group</th>
<th>Radiography group years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>645 (100,000 person years)</td>
<td>572 (100,000 person years)</td>
</tr>
<tr>
<td></td>
<td>1060 cancers</td>
<td>941 cancers</td>
</tr>
</tbody>
</table>
RESULTS (CONT’D)

Relative mortality reduction

Lung cancer-CT compared to radiography 20%

Overall death rate any cause - CT group compared to radiography 6.7%
FALSE POSITIVES

- 40% participants positive finding of small indeterminate nodules on any screens.
  - Follow up
  - Further imaging
  - Invasive procedures
FALSE POSITIVES
(CONT’D)

- 96.4% of positive findings in CT group --false positives
- Complications during follow-up CT group
  - Overall 1.4%
  - 11.2% lung cancer
- Cancers detected on screening mostly adenocarcinoma

- **Staging**
  
  **CT group**
  
  Stages I & II 70%
  
  Stage IA 52%

  **Radiography group**
  
  Stages I & II 51%
  
  Stage IA 33%
CONCLUSION

- Objective evidence of benefits of low dose CT screening in high risk older population
- Potential to save many lives

DISADVANTAGES

- Cumulative effects of radiation (long term follow up of indeterminate nodules)
- Surgical & medical complications in patients who do not have lung cancer – additional testing
- Anxiety – false positives
- Risks associated with work up other discovered disease
- COST!! (CT scan 94 million smokers US. --$30 billion annual at Medicare rate)
THE FUTURE (publications from NLST 2011-12)

- Diagnostic evaluation and follow-up
- Radiation risk
- ACRIN – quality of life and cost effectiveness analysis
- Future research--biomarkers
QUESTIONS TO BE ANSWERED

- Number of screening rounds
- Optimum interval
- Length of follow-up
- Modeling studies suggest more screening rounds and longer follow-up increases mortality reduction
QUESTIONS TO BE ANSWERED

- Is there overdiagnosis in lung cancer screening? (small peripheral ground glass nodule)—indolent and slow growing
- Risk stratification for current and former smokers
- Improved CAD and volumetric software

SCREENING GUIDELINE DEVELOPMENT
SUMMARY

- Lung cancer mortality calls for screening
- CT highly sensitive for nodules
- CT detects more cancers than CXR
- CT screening for lung cancer has meaningful mortality benefit—should be recommended
SUMMARY CONT’D

- High % are early stage
- CT screened lung cancers – mortality benefit
Set up a program—follow guidelines (NLST parameters)

- Physician referred, educate physicians
- Provide information to patients (risks and benefits)
- Follow up of nodules—suspected cancer—Fleischner guidelines
- Medicare rate—patient charged directly
Implications for your practice

- Increased workload
- Tools to increase productivity
  - CAD
  - GROWTH OF NODULES ON FOLLOW UP-VOLUMETRIC ANALYSIS