Objectives

• Risk stratify a pulmonary nodule(s) from the medical record
• What are appropriate studies/evaluation to establish benignity?
• When should an applicant undergo LDCT screening for lung cancer?
• Key elements of a comprehensive screening program
• Implementing a screening model
• Realize the challenge of cost effectiveness
Solitary Pulmonary Nodule (SPN)

- Well-circumscribed, radiographic opacities measuring ≤ 3 cm in diameter
- Surrounded by aerated lung
- Not associated with atelectasis or pleural fluid
- Solitary or Multiple
- Many are “incidental” vs. “with sx” vs. “screening” of high risk
- Opacities ≥ 3 cm are called lung masses and are malignant until proven otherwise

The Solitary Pulmonary Nodule

- Definition
- Nodule characteristics
- Growth rates
- Length of follow up
- Management algorithm
Differential Diagnosis of SPN
(Solitary Pulmonary Nodule)

**Benign**
- Granulomas/old TB/Histio
- Inflammatory nodules (active infection)
- Fibrotic nodules
- Harmatomas
- Rounded atelectasis
- Hemangiomas
- AVM, Wegener’s, RA
- Healed pulmonary infarcts

**Malignancy**
- Lung cancer (NSCLC and SCLC)
- Metastatic disease
- Carcinoid tumors

---

**The Problem**

- Lung cancer is the leading cause of cancer related death.
- Large population at risk:
  - > 90 million with history of smoking
- Worrying trends of smoking among adolescents and young adults.

---

**TABLE 3** Age-standardized Death Rates for All Cancers Combined, 2000 to 2004, and Estimated Deaths* from All Cancers Combined and Selected Sites by State, United States, 2006

<table>
<thead>
<tr>
<th>State</th>
<th>Death Rate</th>
<th>All Sites</th>
<th>Brain &amp; Other Nervous System</th>
<th>Female Breast</th>
<th>Colon &amp; Rectum</th>
<th>Leukemia</th>
<th>Liver</th>
<th>Lung &amp; Bronchus</th>
<th>Non-Hodgkin Lymphoma</th>
<th>Ovary</th>
<th>Pancreas</th>
<th>Prostate</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td>198.8</td>
<td>29,370</td>
<td>560</td>
<td>2,180</td>
<td>2,580</td>
<td>1,060</td>
<td>830</td>
<td>8,230</td>
<td>1,160</td>
<td>810</td>
<td>1,320</td>
<td>1,430</td>
</tr>
</tbody>
</table>

---

[Image of table and text continued]
Lung Cancer – Projected incidence in the US

<table>
<thead>
<tr>
<th>Stage</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/II</td>
<td>50,000</td>
</tr>
<tr>
<td>III</td>
<td>50,000</td>
</tr>
<tr>
<td>I-III</td>
<td>100,000</td>
</tr>
<tr>
<td>IV</td>
<td>80,000</td>
</tr>
<tr>
<td>LTD</td>
<td>15,000</td>
</tr>
<tr>
<td>NSCLC</td>
<td>180,000</td>
</tr>
<tr>
<td>SCLC</td>
<td>45,000</td>
</tr>
<tr>
<td>SCLC</td>
<td>45,000</td>
</tr>
<tr>
<td>NSCLC</td>
<td>180,000</td>
</tr>
<tr>
<td>SCLC</td>
<td>45,000</td>
</tr>
<tr>
<td>Lung Ca</td>
<td>225,000</td>
</tr>
</tbody>
</table>

Role of Smoking

Peto et al., BMJ 2000
Screening Goals—Amplify smoking cessation benefit

Prevent Deaths
Early Detection
Minimize Harms

Benign Patterns of Calcification
Nodule Size

- > 3 cm – Mass ► should be biopsied/ removed

- Size                        Likelihood of malignancy
  – < 3 mm                     0.2%
  – 4-7 mm                     0.9%
  – 8-20 mm                    18%
  – > 20 mm                    50%

Midthun et al. Lung cancer 2003

Nodule Morphology

- Opacification of underlying parenchyma
  – Solid ➔ Ground Glass
- Borders
- Calcification
- Fat - benign
- Cavitation
- Air bronchograms
- Location in the Upper Lobes

malignant
Spiculated-margined SPN

This lesion demonstrates the “corona radiata” sign which is highly associated with malignancy.

“Ground-glass” SPNs

Ground-glass infiltrate on left has a 1:5 chance of malignancy. The ground-glass + solid component lesion on the right has a 2:3 likelihood of malignancy. Any ground-glass SPN may ultimately prove to be AIS and serial CT > 2 years may be needed.
Radiology of Benign v. Malignant SPN

<table>
<thead>
<tr>
<th>Radiologic Feature</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>&lt; 5 mm</td>
<td>&gt; 10 mm</td>
</tr>
<tr>
<td>Border</td>
<td>Smooth</td>
<td>Irregular or spiculated</td>
</tr>
<tr>
<td>Density</td>
<td>Dense, solid</td>
<td>Variegated, &quot;ground-glass&quot;</td>
</tr>
<tr>
<td>Calcification</td>
<td>Central, concentric, popcorn, or homogeneous</td>
<td>Non-calcified or “eccentric” calcification</td>
</tr>
<tr>
<td>Doubling Time</td>
<td>Less than 1 month, greater than 1 year</td>
<td>One month to one year</td>
</tr>
</tbody>
</table>

New Approach to SPNs

- For SPN > 8 mm and < 2 cm: PET is more sensitive than CT at identifying CA
  - + PET $\rightarrow$ likelihood of lung cancer is > 85% and cancer should be assumed
  - Negative PET $\rightarrow$ likelihood of lung cancer is low with negative predictive value > 90%
    - These nodules should be followed with serial CT imaging at 6 month intervals x 2 years
CT Imaging of SPNs

- **CT densitometry**
  - Involves measurement of attenuation values expressed in Hounsfield units
  - In one large multicenter trial only 1 nodule among 66 with Hounsfield unit > 264 ultimately proved to be malignant.
    » Zerhouni et al. Radiology 1986; 160: 319-27
- **Use of contrast enhancement**
  - An increase in attenuation of > 20 Hounsfield units may suggest a nodule to be malignant
    » Zhang and Kono. Radiology 1997; 205: 471-8

### Factors Affecting Malignant Probability of SPN

<table>
<thead>
<tr>
<th>Factor</th>
<th>Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiculated Margins</td>
<td>5.54</td>
</tr>
<tr>
<td>Age &gt; 70 years old</td>
<td>4.16</td>
</tr>
<tr>
<td>Size 2.1-3.0 cm</td>
<td>3.67</td>
</tr>
<tr>
<td>Doubling time &lt; 465 days</td>
<td>3.40</td>
</tr>
<tr>
<td>Smoker</td>
<td>2.27</td>
</tr>
<tr>
<td>Age 50-69 years old</td>
<td>1.90</td>
</tr>
<tr>
<td>Size 1.1 to 2.0 cm</td>
<td>0.74</td>
</tr>
<tr>
<td>&lt; 1 cm</td>
<td>0.52</td>
</tr>
<tr>
<td>Smooth Margins</td>
<td>0.30</td>
</tr>
<tr>
<td>Never Smoked</td>
<td>0.19</td>
</tr>
<tr>
<td>Doubling Time &gt; 465 days</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Management - SPN

- Compare OLD films
- Compare OLD films
- Compare OLD films
- Assess patient risk

SPN management strategy

- Excision
  - High risk lesion, low risk pt
- Biopsy
  - Intermediate risk
- Observation
  - Low risk lesion, high risk pt
  - Requires serial CT scans
    - PET
  - Bx if change

When in doubt, take it out.
Screening Principles

- High prevalence of detectable disease in asymptomatic patients

- Detect disease that responds better to early vs. late treatment

- Provide benefits in treating the small number of patients diagnosed with disease, outweighing the harm associated with screening a large number of healthy individuals
Historical Radiographic Studies for Lung Cancer Screening

- 4 Randomized Clinical Trials in 1970s
  - Mayo Clinic Study
  - Czech Study
  - Sloan Kettering study
  - Johns Hopkins study

CXR + Sputum cytology vs. Usual Care

CXR + Sputum cytology vs. CXR alone

NO BENEFIT TO SCREEN

National Lung Screening Trial

- NCI/ACRIN 2002-2004
  - 54,000
  - Age 55-74 30pyr

CT

CXR

Year 0 1 2 3 4 5 6 7

National Lung Screening Trial
NCI/ACRIN 2002-2004
54,000
Age 55-74 30pyr
CT
CXR
Year 0 1 2 3 4 5 6 7

American College of Radiology Imaging Network (ACRIN)
NLST – Study population

Inclusion criteria
- 55 to 74 years
- At least 30 pack-year smoking history
- If former smokers, had quit within previous 15 years

Exclusion criteria
- Previous lung cancer
- CT chest within 18 months before enrollment
- Hemoptysis
- Unexplained weight loss of more than 15 lbs in last year

60% Males
90% Whites
50% former smokers
75% less than 64 years old

NLST- results across 3 years of screening

<table>
<thead>
<tr>
<th></th>
<th>Positive Screens</th>
<th>False Positives</th>
<th>Major complication (if no lung cancer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDCT</td>
<td>24.2%</td>
<td>96.4%</td>
<td>0.06%</td>
</tr>
<tr>
<td>CXR</td>
<td>6.9%</td>
<td>94.5%</td>
<td>0.02%</td>
</tr>
</tbody>
</table>

- 16 deaths occurred in LDCT group (vs 10 in CXR group) within 60 days after an invasive diagnostic test was performed.
- Small cell cancers were not detected in early stages in either group.
NLST- Results

20% reduction in lung cancer mortality
7% reduction in overall mortality

Number Needed to Screen – 320

Implementing a Feasible Screening Program

Feasibility = Lower cost + High cancer detection

- LDCT
- Integrated Program
- Duration
- High risk population
- Adherence
- Education
Key Elements of a Screening Program

- Physicians
- Navigators
- Patient counselling
- Medical community
- Pulmonary
- Radiology
- Surgery
- Oncology
- Behaviour
- Medical

Subject Selection
Societal Recommendations

<table>
<thead>
<tr>
<th>Age</th>
<th>Tobacco</th>
<th>Other Risk factors</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Am Col Chest Physicians Am So Clin Oncology (ACCP/ASCO)</td>
<td>55-74</td>
<td>&gt; 30 pyr</td>
<td>Not defined</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network (NCCN)</td>
<td>55-74</td>
<td>&gt; 30 pyr</td>
<td>Not defined</td>
</tr>
<tr>
<td></td>
<td>50-74</td>
<td>&gt; 20 pyr</td>
<td>Occupational, radon</td>
</tr>
<tr>
<td>Am Asso for Thoracic Surgery (AATS)</td>
<td>55-79</td>
<td>&gt; 30 pyr</td>
<td>Lifelong</td>
</tr>
<tr>
<td>American Cancer Society (ACS)</td>
<td>55-74</td>
<td>&gt; 30 pyr</td>
<td>Lifelong</td>
</tr>
</tbody>
</table>

USPTF: 55-80 yrs, 30 pyr. Stop once quit >15 yrs

Risk Prediction Model Based Selection

- Several lung cancer risk prediction models
  - Spitz, Liverpool Lung Project, Etzel etc.
- Modified PLCO: Increased risk predictors:
  - ↑ Age
  - ↑ Tobacco exposure
  - ↑ COPD
  - ↑ Family history of lung cancer
  - ↑ Personal history of lung cancer
  - ↓ BMI
  - ↓ Education

Modified PLCO Model

<table>
<thead>
<tr>
<th></th>
<th>NLST criteria</th>
<th>PLCO2012</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>71.1%</td>
<td>83.0%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Specificity</td>
<td>62.7%</td>
<td>62.9%</td>
<td>p=0.536</td>
</tr>
<tr>
<td>PPV</td>
<td>3.4%</td>
<td>4.0%</td>
<td>p=0.011</td>
</tr>
</tbody>
</table>

• PLCO model missed 115 cancers relative to 196 cancers missed by NLST criteria – 41% fewer.

• C:\Documents and Settings\rxk032\Desktop\LCriskCalculatorSMKonly-Tammemagi-2SEP13-Locked.xlsx

Implementing the Model
Commonly Practiced Model

The Pulmonologist Gatekeeper Model
Advantages of the Pulmonary Model

- Subjects meet a pulmonary physician **BEFORE** screen study
  - Ensures compliance to criteria (NLST)
  - Reassurance to individuals not meeting criteria
  - Promotes patient education
  - Chance to discuss implications of findings if detected same day
  - Reduces patient anxiety

Most Important Link – Patient Navigator
Fleischner Society Guidelines

 Recommendations for Follow-up and Management of Nodules Smaller than 8 mm Detected Incidentally at Nonscreening CT

<table>
<thead>
<tr>
<th>Nodule Size (mm)</th>
<th>Low-Risk Patient</th>
<th>High-Risk Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This does not apply to.....

Patients with known or suspected metastatic disease.
Patients < 35 yrs
Ground Glass Nodules
Patients with unknown fever

Note: Newly detected indeterminate nodule in persons 35 years of age or older.

SPN Calculators

- [www.chestx-ray.com/spn/spnprob](http://www.chestx-ray.com/spn/spnprob)
- [www.nucmed.com/nucmed/SPN_Calculator](http://www.nucmed.com/nucmed/SPN_Calculator)
- I entered the following into each calculator
  - 70 year old
  - Never-smoker
  - Size: 1 cm
  - Location: Upper/middle zone of lung
  - Contour: Smooth
- Likelihood of malignancy
  - First calculator = 12%
  - Second calculator = 11.6%
Costs and Cost Effectiveness of Screening
Cost Challenges

- Most insurance companies not paying yet
  - $99 to $1000 self pay
- No CPT code for LDCT
  - Most institutions charge $800 for non-contrast CT
- Cost of technicians, coordinators, physician fees
- Smoking Cessation Program costs
  - Pharmacological interventions are expensive
  - Nicotine replacement is not covered by most prescription plans

How to minimize costs

- Improvise actual scan timing
  - Scan between PET infusions and downtime
- Should initial scans be free?
  - Use downstream revenue from follow up of positive findings to offset cost
- Integrated program
- Lobby CMS to approve screening
  - Cost effectiveness
Cost effectiveness

Increases
- Higher risk population
- High Quit rates
- High surgical effectiveness
- Less frequent scans

Decreases
- Higher false positives
- More futile procedures
- Higher complications
- ? Radiation Risks

• Population:
  – Age 50-64 current and former smokers with 30 pyr exposure
  – 18 million
• ELCAP based
• Average annual cost of screening - $247
• Positive scans – 21%
• Assumes most screen detected cases are resectable

A Cost-Utility Analysis of Lung Cancer Screening and the Additional Benefits of Incorporating Smoking Cessation Interventions

Andrea C. Villanti1,2, Yiding Jiang3, David B. Abrams1,2,4, Bruce S. Pyenson5

PLoS ONE 8(8): e71379
Results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>ELCAP stage shift (cost/ QALY saved)</th>
<th>NLST stage shift (cost/ QALY saved)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDCT</td>
<td>$28,000</td>
<td>$47,000</td>
</tr>
<tr>
<td>LDCT Light smoking cessation</td>
<td>$23,000</td>
<td>$35,000</td>
</tr>
<tr>
<td>LDCT Nicotine replacement</td>
<td>$16,000</td>
<td>$22,000</td>
</tr>
<tr>
<td>LDCT Varenicline</td>
<td>$17,000</td>
<td>$24,000</td>
</tr>
</tbody>
</table>

• Based on Lung Cancer Policy Model
• 3.5 - 8.0 million screen eligible persons
• Ages 55-74 year with at least 20 pack years exposure
• Estimated 18-25% reduction in lung cancer mortality

• Cost to screen: $126,000 to $169,000/ QALY
• If cessation rate increases from 3% to 6% this number reduces to $75,000/ QALY
**NLST Cost Effective Analysis- Prelim**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDCT</td>
<td>$300</td>
</tr>
<tr>
<td>Non Med</td>
<td>$100</td>
</tr>
<tr>
<td>Per 3 screens</td>
<td>$1200</td>
</tr>
<tr>
<td>F/U CT</td>
<td>$320</td>
</tr>
<tr>
<td>Total</td>
<td>$1520</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of screening</th>
<th>Cost</th>
<th>QALYs</th>
<th>ICER/ QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose CT</td>
<td>$2,770</td>
<td>11.0143</td>
<td>$72,916</td>
</tr>
<tr>
<td>Chest X ray</td>
<td>$1,730</td>
<td>10.9924</td>
<td>NA</td>
</tr>
<tr>
<td>None</td>
<td>$1,170</td>
<td>10.9924</td>
<td>NA</td>
</tr>
</tbody>
</table>

ICER: Incremental cost effectiveness ratio

**Comparison: LDCT with other Preventive Health Interventions**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>$/ QALY (2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer Screening with LDCT (age 50-64 for 15 yrs)</td>
<td>$28,000-$47,000</td>
</tr>
<tr>
<td>Biennial Mammography (age 50-75)</td>
<td>$53,000</td>
</tr>
<tr>
<td>Colonoscopy (age 50-75 every 10 yrs)</td>
<td>$9,000</td>
</tr>
<tr>
<td>Pap test for cervical cancer (age 20-65 every 3 yrs)</td>
<td>$19,000</td>
</tr>
<tr>
<td>Annual fecal occult blood testing</td>
<td>$28,000-$32,000</td>
</tr>
<tr>
<td>Annual HIV testing in high risk population</td>
<td>$150,000</td>
</tr>
<tr>
<td>Diabetes Type 2, age 25+</td>
<td>$105,000</td>
</tr>
<tr>
<td>Statin vs Diet</td>
<td>$220,000+</td>
</tr>
</tbody>
</table>
Cost effectiveness of LDCT is likely favorable, but will continue to be evaluated

Recent Data from a High Volume center

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Overall</th>
<th>NLST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>916</td>
<td>114</td>
<td>500</td>
<td>~26,000</td>
</tr>
<tr>
<td>Average age (y)</td>
<td>60.1</td>
<td>60.5</td>
<td>62.5</td>
<td>61.4</td>
</tr>
<tr>
<td>Smoking history (pack-years)</td>
<td>53.4%</td>
<td>42.1%</td>
<td>51.2%</td>
<td>59%</td>
</tr>
</tbody>
</table>

Note: NLST = National Lung Screening Trial.

- FREE scans
- 3 lung cancers diagnosed
- 25% had nodules
- No data on complications
Risks of Screening

- Understand Overdiagnosis
  - cancers that otherwise would not have been detected during an individual's lifetime
  - Overdiagnosis rate of 13% (1-1060/941)
    - Will be higher in the community
- Procedural Risks
  - Expect more procedures
  - Higher complication rates
- Harmful effects of Radiation
  - Projected 1 new cancer for every 2000 spiral CT scans performed

Controversies to Screen

- Cost effectiveness
  - 3.5 million screening eligible persons
  - >$2 billion / year (assuming 75% screening rate – 95% in NLST)
  - Additional annual cost of screening to avoid 1 lung cancer death is about $240,000
- Money can be directed towards prevention
  - Cost to screen 55-74 yr (20pyr) - $126,000 to $169,000/ QALY
  - If prevalence of smokers is halved this number reduces to $75,000
- Duration of Screening
So, is screening feasible?....... 

YES

Depends on the choices we make about
Who to screen: based on risk prediction models
How to screen: integrated team based approach

Will we use it as a “teachable moment” for smoking cessation

The Programs at Jefferson

• Lung Cancer Screening Program
  – Low dose CT
  – Pulmonary function testing
  – Smoking cessation
  – Visit with Pulmonologist

• Lung Nodule Clinic
  – Nodule Line: 215 955 2584

• Emphasis on fast, timely access and evaluation
• Coordination among Radiology, Thoracic Surgery and Oncology
• Research and database development
Jefferson’s Program

- Intake – NLST criteria
- Cost – $350
- Includes
  - Low dose CT
  - Visit with Pulmonologist
  - Screening PFT
  - Smoking cessation
- Team Approach: Radiology, Oncology, Thoracic Surgery and Pulmonary Medicine

Patients

<table>
<thead>
<tr>
<th></th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>14</td>
</tr>
<tr>
<td>Gender</td>
<td>9F:5M</td>
</tr>
<tr>
<td>Nodules</td>
<td>6</td>
</tr>
<tr>
<td>2 need earlier scans</td>
<td></td>
</tr>
<tr>
<td>Incidental findings</td>
<td>Thyroid nodules, Atherosclerosis, Liver cysts</td>
</tr>
<tr>
<td>Procedures</td>
<td>1</td>
</tr>
</tbody>
</table>

Jefferson Medical College

Ongoing Trials

<table>
<thead>
<tr>
<th>TRIALS</th>
<th>No.</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson (Danish-Belgium)</td>
<td>16,000</td>
<td>No imaging</td>
</tr>
<tr>
<td>includes 5 yr LC survivors</td>
<td>20/7000 at 2 yr</td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>4,000</td>
<td>No imaging</td>
</tr>
<tr>
<td>French</td>
<td>600</td>
<td>CXR</td>
</tr>
<tr>
<td>ITA-Lung CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>German - LUSI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DANTE</td>
<td>2400</td>
<td>CXR/ sputum</td>
</tr>
<tr>
<td>At 33 months</td>
<td>4.5%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>
Tools for Lung Cancer Screening

Summary

- Assess patient risk profile as initial step for nodule work up
- Any enlarging nodule needs tissue diagnosis
- Fleishner criteria is a useful way to follow solid nodules
- Sub solid/ Ground glass nodules need longer follow up
Conclusions

• Evaluating lung nodules will become an ever-greater problem for Life/Disability/LTC insurance underwriters
  • Increasing incidence of lung cancer – already the #1 cause of cancer death in both men and women
  • Increasing use of CT imaging of both chest and abdomen/pelvis + increasing ability of these scans to reveal smaller and earlier nodules
  • Should Routine CT Lung imaging for at-risk population become accepted, the number will rise even further

Conclusions

• Some lung nodules have sufficient “benign” characteristics to allow these findings to be a “non-issue”
  • Benign patterns of calcification
  • Rentgenographically stable on CXR > 2-3 years
• Other nodules will demand more evaluation
  • Nodules > 8 mm especially in “at-risk” applicants
  • Documented new nodules (old CXR w/o nodule seen)
  • Spiculated borders, eccentric calcification, ground-glass nodules especially with solid components
Conclusions

• Thoughtful and correct underwriting of nodules will require being able to assess quality of evaluation and quality of subsequent follow-up evaluation of a lung nodule, and to be able to estimate when an offer of insurance might be made if the nodule is still under evaluation