LUNG CANCER SCREENING UPDATE

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Disclosures

- No conflicts of interest to disclose
Topics of Discussion

- **The Basics**
  - Epidemiology and Causes of Lung Cancer

- **Screening (not in that order)**
  - Who
  - What
  - Why
  - Where
  - When
A Huge Problem

- Lung Cancer is the most common cause of cancer deaths in the US.
- 1.8 million new lung cancer cases/year worldwide
- 1.6 million deaths/year (more than TB, malaria and HIV)
Etiologies

- Cigarette Smoking
- Cigarette Smoking
- Cigarette Smoking
- Cigar and Pipe Smoking
- Secondhand Smoking
- Asbestos
- Radon
- Occupational Exposure
Cigarette Smoking

- responsible for 90% or more of lung cancers
- risk increased for all types of lung cancer
- small cell and squamous types are nearly 100% smoking-related
- adenocarcinoma, though less strongly correlated with smoking, is 6.7 times more common in smokers than non-smokers
Secondhand Smoking

- Approximately 50% increase in risk of lung cancer for non-smokers living with smokers, representing about 1/3 of all lung cancer in non-smokers.
- Epidemiological studies documenting this phenomenon are responsible for ban of smoking in public places.
Prevention

- Most effective strategy for reducing the burden of lung cancer
- Smoking cessation is KEY to prevention
  - Behavioral counseling
    - 1-800-QUIT-NOW
    - County Driven
  - Pharmacologic treatments
    - Varenicline or Bupropion
  - Alternative treatments
    - Acupuncture, hypnosis
Incidence By Stage

Adapted from Kraut et. al
Screening

- Evaluation of a disease in an asymptomatic, at risk individual

- **GOALS:**
  - Detect disease EARLY
  - Benefit outweighs harm
  - Screening leads to improved survival
Why Screen for Lung Cancer

- High morbidity and mortality
- Significant prevalence
- Identified risk factors allowing targeted screening for high-risk individuals
- Lengthy preclinical phase for some types of lung cancer
- Early treatment means better survival
National Lung Screening Trial

- Large Randomized Trial
  - Eligible patients:
    - Asymptomatic
    - 55-74 years old
    - ≥30 pack years of smoking current smoker or quit within 15 years
    - 53,454 randomized to 3 annual LDCTs vs. 3 annual CXRs
Positive Findings
- Noncalcified nodule $\geq 4\text{mm}$ on LDCT (24.2%)
- Any noncalcified nodule on x-ray (6.9%)

False Positives
- LDCT 96.4% $\rightarrow$ 92% lead to another test
- X-ray 94.5% $\rightarrow$ 92.7% lead to another test
Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team®

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low-Dose CT</th>
<th></th>
<th></th>
<th></th>
<th>Chest Radiography</th>
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<tbody>
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<td></td>
<td>T0</td>
<td>T1</td>
<td>T2</td>
<td>Total</td>
<td>T0</td>
<td>T1</td>
<td>T2</td>
<td>Total</td>
<td>T0</td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td>Total positive tests</td>
<td>7191 (100.0)</td>
<td>6901 (100.0)</td>
<td>4054 (100.0)</td>
<td>18,146 (100.0)</td>
<td>2387 (100.0)</td>
<td>1482 (100.0)</td>
<td>1174 (100.0)</td>
<td>5043 (100.0)</td>
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<tr>
<td>Lung cancer confirmed</td>
<td>270 (3.8)</td>
<td>168 (2.4)</td>
<td>211 (5.2)</td>
<td>649 (3.6)</td>
<td>136 (5.7)</td>
<td>65 (4.4)</td>
<td>78 (6.6)</td>
<td>279 (5.5)</td>
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<tr>
<td>Lung cancer not confirmed†</td>
<td>6921 (96.2)</td>
<td>6733 (97.5)</td>
<td>3843 (94.8)</td>
<td>17,497 (96.4)</td>
<td>2251 (94.3)</td>
<td>1417 (95.6)</td>
<td>1096 (93.4)</td>
<td>4764 (94.5)</td>
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</table>

NEJM Aug 2011: 365(5)
20% relative reduction in lung cancer mortality
- 247 (CT) vs 309 (x-ray) deaths
- 1\textsuperscript{st} trial to demonstrate mortality benefit

6.7% relative reduction in all-cause mortality
Stage Shift with Screening

Adapted from NEJM Aug 2011: 365(5)
Benefits and Risk

- **Benefit**
  - 20% relative reduction in lung cancer mortality

- **Risks**
  - High false positive rate
    - 25% had an abnormality on CT but 96% of those were benign
  - Increase in further non-invasive diagnostic imaging
    - More Radiation
  - Increase in invasive diagnostic procedures
    - Biopsies
    - “Unnecessary” surgeries
    - Psychological harms
    - Financial strains
NLST Study Problems

- Patient Characteristics
  - Most patients screened were younger 55-64
    - Elderly were under-represented
  - Mostly white
  - Most had higher education levels
  - More were to be former smokers
  - Adherence to screening was 95%

- Location of study was in urban, tertiary centers
  - 82% in large academic centers
Radiographic Interpretation

- Dedicated chest radiologist with specific reporting

Recommendation for follow-up

High Quality Low-dose CT scan

- ≤2 millisieverts

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**RADIATION DOSES Millisieverts (mSv)**

<table>
<thead>
<tr>
<th>10,000</th>
<th>Acute radiation poisoning - death within weeks</th>
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<tbody>
<tr>
<td>6,000</td>
<td>Typical dose received by Chernobyl nuclear plant workers who died within one month of accident</td>
</tr>
<tr>
<td>3,000</td>
<td>Survival rate approximately 50 percent</td>
</tr>
<tr>
<td>2,200</td>
<td>Reading found near tanks used to store radioactive water at Fukushima plant, Sep 3, 2013</td>
</tr>
<tr>
<td>1,000</td>
<td>Causes radiation sickness and nausea, but not death. Likely to cause fatal cancer many years later in about 5 of every 100 persons exposed</td>
</tr>
<tr>
<td>700</td>
<td>Vomiting, hair loss within 2-3 weeks</td>
</tr>
<tr>
<td>500</td>
<td>Allowable short-term dose for emergency workers taking life-saving actions</td>
</tr>
<tr>
<td>400 per hour</td>
<td>Peak radiation level recorded inside Fukushima plant four days after accident</td>
</tr>
<tr>
<td>350 per lifetime</td>
<td>Exposure level used as criterion for relocating residents after Chernobyl accident</td>
</tr>
<tr>
<td>250</td>
<td>Allowable short-term dose for workers controlling 2011 Fukushima accident</td>
</tr>
<tr>
<td>100</td>
<td>Lowest level linked to increased cancer risk</td>
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<tr>
<td>20 per year</td>
<td>Average limit for nuclear industry workers</td>
</tr>
<tr>
<td>10</td>
<td>Full-body CT scan</td>
</tr>
<tr>
<td>2.4 per year</td>
<td>Person’s typical exposure to background radiation</td>
</tr>
<tr>
<td>0.01</td>
<td>Dental x-ray</td>
</tr>
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</table>

Sources: IAEA, World Nuclear Association
NLST Study Problems

- Surgical Mortality for Lobectomy
  - NLST=1%
  - National Average=3-5%
  - Are these results replicable?
NLST- Positive Studies

- 92% of positive CT screens had a diagnostic evaluation

- 16 deaths within 60 days
  - 6 of 16 had benign pathology

- 8.4%
  - Imaging
  - Percutaneous - 1.9%
  - Transbronchial - 2.3%
  - Surgery - 4.2%

- 91.6%
NLST Study Problems

- Who should be screened
  - “Net Benefit” may not be realized in people with lower risk of lung cancer
    - Need to weigh the greater impact of unintended harms in low risk patients
  - Need to consider co-morbidities in patients
    - As risk of lung cancer increases, so do competing causes of death (such as COPD, heart disease etc).
    - These people can have complications and less likely to get adequate treatment
Insurance Coverage Circa 2014

Covered

- Aetna
- CMS
- BlueCross BlueShield Association
- United Healthcare

Not Covered

- Kaiser Permanente
- Humana
- Priority Health
- Health Net

April 2015
# Summary of Current Guidelines

<table>
<thead>
<tr>
<th>Primary Criteria</th>
<th>• 55 – 79 years</th>
<th>• 55 – 74 years</th>
<th>• 55 – 80 years</th>
<th>• 55 – 77 years</th>
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<tbody>
<tr>
<td></td>
<td>• ≥ 30 pack-yrs</td>
<td>• ≥ 30 pack-yrs</td>
<td>• ≥ 30 pack-yrs</td>
<td>• ≥ 30 pack-yrs</td>
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<tr>
<td></td>
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<tr>
<td>Secondary Criteria</td>
<td>• Lung cancer survivor</td>
<td>• ≥ 50 years</td>
<td>• None</td>
<td>• None</td>
</tr>
<tr>
<td></td>
<td>• ≥ 50 years</td>
<td>• ≥ 20 pack-yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ≥ 20 pack-yrs</td>
<td>• At least one other risk factor (asbestos)</td>
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<tr>
<td></td>
<td>AND Added ≥5% risk of lung CA within 5 years</td>
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</table>
CMS: Additional Requirements

- Must be performed at specialized centers
  - Radiology imaging center with appropriate expertise, equipment
  - Must collect and submit data to a CMS-approved national registry

- Registries

[ACR Logo]

Quality is Our Image
APPROVED
CMS: Additional Requirements

- Initial LDCT must be ordered during a lung cancer screening counseling and shared decision making visit.

Documentation

1. Eligibility Criteria are all met and documented

2. One or more decision aids to discuss benefits, harms, follow-up diagnostic testing, over-diagnosis, false positive rate, total radiation exposure

3. Counseling on importance of adherence to annual LDCT screening, risk of screening, impact of comorbidities, willingness to undergo diagnosis and/or treatment

4. Counseling on smoking cessation (or continued abstinence), including offering additional tobacco cessation counseling services if appropriate
Cost-Effectiveness of CT Screening in the National Lung Screening Trial

- Estimated mean life-years, QALYs, costs per person, and incremental cost-effectiveness ratios (ICERs)

- Used 3 alternative strategies
  - Screening with LDCT
  - Screening with radiography
  - No screening
Results of Trial

- As compared with no screening, LDCT:
  - Cost an additional $1,631/person
  - Provided additional 0.0316 life-years/person and 0.0201 QALY/person
  - $81,000 / QALY gained
  - Caveat: “modest changes” in assumptions would greatly alter results

We estimated that screening for lung cancer with low-dose CT would cost $81,000 per QALY gained, but we also determined that modest changes in our assumptions would greatly alter this figure. The determination of whether screening outside the trial will be cost-effective will depend on how screening is implemented. (Funded by the National Cancer Institute; NLST ClinicalTrials.gov number, NCT00047385.)
What About Everyone Else?

- 90 million people who are former smokers and quit more than 15 years ago

- Individual with identifiable lung cancer risk factors other than smokers
  - Occupational exposures
  - Outdoor and indoor air pollution
  - Lung disease
Lung Cancer Risk Assessment

- What level of lung cancer risk is sufficient to justify the potential harms of screening?
  - NLST: 2-3% over 6 years
  - AATS: 5% over 5 years

- How good are we at assessing risk for lung cancer?
  - We really tend over-estimate risk

- What risk exceeds your tolerance or patient’s tolerance?
Risk assessment models have the potential to modify physician behavior by providing objective information.

- **PLCO Lung Cancer Risk Assessment Model**
  - Age, Race, BMI, COPD, Family History, Smoking Status and Duration, and several other factors
  - Predicts Probability of Lung Cancer in 6 years time.

[www.brocku.ca/cancerpredictionresearch](http://www.brocku.ca/cancerpredictionresearch)

Tammemagi, NEJM 2013; 368:728.
**Biomarker?**

<table>
<thead>
<tr>
<th>Table 1. Selected Biomarkers Associated With Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomarker Type</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Autoantibodies (EarlyCDT-Lung test)*16</td>
</tr>
<tr>
<td>Bronchial fluids C4d complement17</td>
</tr>
<tr>
<td>Serum miRNA18,19</td>
</tr>
<tr>
<td>Plasma miRNA15,19</td>
</tr>
<tr>
<td>Blood-based protein biomarkers20,21</td>
</tr>
<tr>
<td>CEA</td>
</tr>
<tr>
<td>SCC-Ag</td>
</tr>
<tr>
<td>CYFRA 21-1</td>
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<tr>
<td>NSE</td>
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</table>

Abbreviations: CEA, carcinoembryonic antigen; CYFRA 21-1, cytokeratin 19 fragment; NSE, neuron-specific enolase; SCC-Ag, squamous cell carcinoma antigen. *EarlyCDT-Lung test; Oncimmune, Nottingham, United Kingdom.
**Pulmonary Nodules: NCCN**

**EVALUATION OF SCREENING FINDINGS**

- **≤6 mm**
  - LDCT in 3 mo

- **6–8 mm**
  - LDCT in 3 mo
  - Consider PET/CT
  - Low suspicion of lung cancer
  - Solid or part-solid nodule

- **>8 mm**
  - Solid endobronchial nodule
  - LDCT in 1 mo (Immediately after vigorous coughing)
  - If no resolution
    - Bronchoscopy

**FOLLOW-UP OF SCREENING FINDINGS**

- **Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment**

- **Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment**

- **If no increase in size, LDCT in 6 mo**

- **If increase in size**
  - Surgical excision (see below)

- **Biopsy**
  - Cancer confirmed

- **No cancer**
  - Annual LDCT for 2 years (category 1) and suggest annual LDCT until patient is no longer a candidate for definitive treatment

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1. All screening and follow-up CT scans should be performed at low dose (100–120 kVp and 40–80 mAs or less), unless evaluating mediastinal abnormalities or lymph nodes, where standard-dose CT with IV contrast might be appropriate. (See LCS-A). There should be a systematic process for appropriate follow-up.

2. Without benign pattern of calcification, fat in nodule as in hamartoma, or features suggesting inflammatory etiology. When multiple nodules are present and occult infection or inflammation is a possibility, an added option is a course of a broad-spectrum antibiotic with anaerobic coverage, followed by LDCT 1–2 months later.

3. If new nodule at annual or follow-up LDCT, see LCS-6. New nodule is defined as ≥3 mm in mean diameter.

4. There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.

5. Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter.

6. PET has a low sensitivity for nodules with less than 8 mm of solid component and for small nodules near the diaphragm. PET/CT is only one consideration of multiple criteria for determining whether a nodule has a high risk of being lung cancer. If a patient has granulomatous disease, PET/CT is less specific.

7. Criteria for suspicion of malignancy: hypermetabolism higher than the background of surrounding lung parenchyma, regardless of absolute SUV.

8. For nodules <15 mm: increase in mean diameter ≥2 mm in any nodule or in the solid portion of a part-solid nodule compared to baseline scan. For nodules ≥15 mm: increase in mean diameter of ≥15% compared to baseline scan.

9. Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer. (see LCS-6)


11. If biopsy is non-diagnostic and a strong suspicion for cancer persists, suggest repeat biopsy or surgical excision or short-interval follow-up (3 months).

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## Lung-RADS for Pulmonary Nodules

<table>
<thead>
<tr>
<th>Category Descriptor</th>
<th>Category Descriptor</th>
<th>Primary Category</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete</td>
<td>-</td>
<td>0</td>
<td>Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed</td>
</tr>
<tr>
<td>Negative</td>
<td>No nodules and definitely benign nodules</td>
<td>1</td>
<td>Continue annual screening with LDCT in 12 months</td>
</tr>
<tr>
<td>Benign Appearance or Behavior</td>
<td>Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth</td>
<td>2</td>
<td>6 month LDCT</td>
</tr>
<tr>
<td>Probably benign</td>
<td>Probably benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer</td>
<td>3</td>
<td>3 month LDCT; PET/CT may be used when there is a ( \geq 8 \text{ mm} ) solid component</td>
</tr>
<tr>
<td>Suspicious</td>
<td>Findings for which additional diagnostic testing and/or tissue sampling is recommended</td>
<td>4A</td>
<td>chest CT with or without contrast, PET/CT and/or tissue sampling depending on the probability of malignancy and comorbidities. PET/CT may be used when there is a ( \geq 8 \text{ mm} ) solid component.</td>
</tr>
<tr>
<td>Significant - other</td>
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<tr>
<td>Prior Lung Cancer</td>
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Tobacco Cessation Counseling with Screening

- Decreases risk of lung cancer and other smoking-related conditions
- Increases cost effectiveness of lung cancer screening
- It is the right thing to do
- Required by CMS for reimbursement
Lung Cancer Screening

- Need to Consider
  - Assessment of baseline risk
  - Getting the screening test
  - Time interval between test
  - Judicious management of nodules
    - Lung-Rads Model
  - Availability of effective treatment
  - Compliance
  - Risk Modification
Lung Cancer Screening

- Attracts people with greater anxiety and fear
- High rate of finding inconsequential nodules
- Thoughtful evaluation and management is key
- Program structure is important
  - Standardized Reading/Nodule assessment
  - Quality control
  - Multidisciplinary team
- Shared decision making
- Many details are still unclear
Thank You!!!