Screening Issues in Pulmonary Medicine

Jacqueline Chang, MD FCCP
Chief, Division of Pulmonary/Critical Care
Scripps Clinic
La Jolla, California
Sobering facts about lung cancer

Leading cause of cancer death in men and women

Lung cancer kills more people annually than breast cancer, prostate cancer, colon cancer combined

Lifetime risk: Men 1 in 13, Women 1 in 16

 Majority of people diagnosed with lung cancer do not currently smoke

10-15% of patient diagnosed with lung cancer have never smoked

Overall 5 year survival is 15%
## Incidence, mortality, and cure rates for the major cancers

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<tbody>
<tr>
<td>Lung</td>
<td>174,470</td>
<td>162,460</td>
<td>7%</td>
</tr>
<tr>
<td>Colon</td>
<td>106,680</td>
<td>55,170</td>
<td>50%</td>
</tr>
<tr>
<td>Breast</td>
<td>214,640</td>
<td>41,430</td>
<td>80%</td>
</tr>
<tr>
<td>Prostate</td>
<td>234,460</td>
<td>27,360</td>
<td>90%</td>
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2006 Cancer Facts and Figures, American Cancer Society

Making an early diagnosis of lung cancer
Talk objectives

To understand the challenges of screening for lung cancer, we have to step back and understand the workup of the pulmonary nodule

Clinical evaluation of pulmonary nodule: Fleischner Guidelines

Use of imaging in lung cancer screening

CXR and CT scan
What is a solitary pulmonary nodule?
The answer is not always so straightforward.

SPN = rounded or oval lesion <3 cm surrounded by lung parenchyma
Small nodule seen on cross sectional view is flat in craniocaudal view, typical of a subpleural lymph node (A,B)

Polygonal density (concave margins) in right apex is 100% specific for benign etiologies usu. focal scar
Pulmonary nodules are very common

Stanford study: in a sample of 1023 patients, ages 60-69, undergoing CT for coronary calcium scoring the incidence of pulmonary nodules was 18%

The finding of a pulmonary nodule led to increased health care utilization, particularly further imaging

Chest CT was performed on 78% of participants in the 24 months after notification, compared with 2.5% in the previous 24 months.

Chest x-ray use increased from 28% to 49%. The mean number of chest CT scans per subject was 1.3 (range, 0-5).

No malignant lesions were diagnosed in the group who had pulmonary findings read.

Am J Med 2008. 121;989-996
Radiation exposure associated with diagnostic imaging
Perspective on screening for lung cancer by imaging

You’re looking for a needle in a haystack with imperfect tools that are highly subjective

How do we avoid the “missed” diagnosis?

How do we avoid “iatrogenesis maxima”

... excessive imaging and radiation exposure or unnecessary procedures?
Working up the incidentally found pulmonary nodule

Patient population of incidentally found pulmonary nodules will be different than patients being screened for lung cancer.

Since the introduction of helical and multi-detector CT in 1990’s, identification of pulmonary micronodules down to 1-2 mm has become routine.

Guidelines for Management of Small Pulmonary Nodules Detected on CT Scans: A Statement from the Fleischner Society
Radiology 2005. 237:395-400
Guidelines for Management of Small Pulmonary Nodules Detected on CT Scans: A Statement from the Fleischner Society

Pertinent review of articles about the prevalence, biologic characteristic, growth rates of small cancers

Early Lung Cancer Action Project CT (ELCAP) in 1999 enrolled 1000 asymptomatic current or ex-smokers (>10 pack years):

23% had indeterminate nodules, 2.7% were malignant
Baseline study: only 1 was <5 mm
Repeat CT: 7 new cancers. 3 were 5 mm. Rest were larger. None <= 4 mm
Other screening studies reviewed

Mayo Clinic Lung Cancer Screening Trial: 1520 patients age 50+ and 20+ pack year smoking history

69% patients had nodules (2832 nodules!), 36 lung cancers identified (2.6% participants)
Baseline: 26 cancers
Followup CT: 10 cancers
80% cancers were >8 mm. 1 was < 5 mm at initial detection

Subsequent analysis from Mayo Clinic CT screening trial estimated the likelihood of cancer based upon nodule size: 0.2% for those <3mm, 0.9% for those 4-7 mm, 18% for those 8-20 mm, 50% for those >20 mm
Review of the growth rate of tumors

Hasegawa review

Doubling time differed depending on appearance

- GGO: 813 days
- GG/with solid component: 457 days
- solid: 149 days

Doubling times was longer for cancerous nodules in nonsmokers versus smokers

Doubling time was longer for nodules not visible on CXR (smaller and lesser average opacity)

These studies support extended followup in patients with GGO or partly solid tumors perhaps even longer than 2 years
Conclusions on likelihood of cancer and nodule characteristics

Positive correlation of likelihood of cancer and nodule size

Several studies showed that <1% of small nodules (<5 mm) in patients without a history of cancer will demonstrate malignant behavior

Different natural history depending on solid nature of nodule
Risk stratification approach to patients with incidentally found pulmonary nodules

Smoking: Surgeons General’s report shows that risk was 10X greater in smokers than nonsmokers and was 15-35 X greater for heavy smokers

Other cancer risk factors:
Family history- first degree relative
Occupational exposures - asbestos, uranium, radon

Assessment of likelihood of alternative explanations:
Granulomatous Disease - residence in endemic areas
History of prior infection/ causes for scar or post inflammatory change
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>
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<tbody>
<tr>
<td>≤4</td>
<td>No follow-up needed§</td>
<td>Follow-up CT at 12 mo; if unchanged, no further follow-up‖</td>
</tr>
<tr>
<td>&gt;4–6</td>
<td>Follow-up CT at 12 mo; if unchanged, no further follow-up‖</td>
<td>Initial follow-up CT at 6–12 mo then at 18–24 mo if no change‖</td>
</tr>
<tr>
<td>&gt;6–8</td>
<td>Initial follow-up CT at 6–12 mo then at 18–24 mo if no change</td>
<td>Initial follow-up CT at 3–6 mo then at 9–12 and 24 mo if no change</td>
</tr>
<tr>
<td>&gt;8</td>
<td>Follow-up CT at around 3, 9, and 24 mo, dynamic contrast-enhanced CT, PET, and/or biopsy</td>
<td>Same as for low-risk patient</td>
</tr>
</tbody>
</table>

1 Note.—Newly detected indeterminate nodule in persons 35 years of age or older.
2 * Average of length and width.
3 † Minimal or absent history of smoking and of other known risk factors.
4 ‡ History of smoking or of other known risk factors.
5 § The risk of malignancy in this category (<1%) is substantially less than that in a baseline CT scan of an asymptomatic smoker.
6 ‖ Nonsolid (ground-glass) or partly solid nodules may require longer follow-up to exclude indolent adenocarcinoma.
Challenge of screening for lung cancer

Although rate of smoking has declined, 94 million current or former smokers remain at risk.

Randomized trials of screening CXR with or without sputum cytologic analysis has not shown to reduced lung cancer mortality.

Observational studies have shown that low dose helical CT detects more nodules and lung cancers, including early stage cancers than CXR.
Early Lung Cancer Action Project (ELCAP)

Goal: Examine the role of evolving technologies in screening for lung cancer. Specifically they began to compare CT with CXR

ELCAP initially enrolled 1000 high risk patients (>60 years age with >10 py smoking) at two NY institutions:

Screening baseline study:
CT found 27 cancers (2.7%)
CXR found 7 cancers (0.7%)
CXR missed 20 Stage I cancers
Percentage of baseline screen and interim diagnoses in ELCAP using CT and CXR as compared with baseline diagnoses in the MLP [21] and PLCO trial [22].

Henschke C. The Oncologist 2008;13:65-78
Frequency of baseline and annual repeat diagnoses of lung cancer in the ELCAP, NY-ELCAP, I-ELCAP, MLP, and mammography screening

Annual repeated round of CT identified 7 cancers: 6 (86%) were stage I
Limitations/Criticisms of ELCAP study

Not a randomized controlled trial showing improved mortality by screening with CT

Length bias: baseline study are finding ?indolent tumors with longer latent phase

Lead time bias: Because of earlier diagnosis in latent phase, apparent long survival.

Overdiagnosis: curability is over-inflated because some of these cancers would never have been life-threatening

Nondisclosure of the investigators
Two randomized trials of screening for lung cancer

National Lung Screening Trial (NLST)
Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening
NEJM 2011. 365: 395-409

Prostate,Lung,Colorectal, and Ovarian Trial (PLCO)
Screening by Chest Radiograph and Lung Cancer Mortality
PLCO Randomized Trial

**Randomization:** 154,901 participants aged 55-74 were assigned to annual screening CXR for 4 years or usual care between November 1993-July 2001.

**Endpoint:** death from all cancers, including lung cancer, through 13 years followup or Dec 31, 2009.

**Eligibility:** Because this was a screening trial for other cancers, there was no eligibility requirement concerning smoking.

**Subset analysis:** results in patients who would have been eligible for the NLST: >30 pack year smokers either currently smoking or ex-smokers quit within 15 years.
PLCO Randomized Trial - Methods

Intervention group: baseline CXR and 3 annual screening CXRs
Positive CXRs: presence of a nodule, mass, infiltrate, or other suspicious abnormality
Followup of positive exams: followup or workup was decided by the patients and their individual physicians not a protocol

Usual care group
CXR screening (cross contamination): assessed by biennial questionnaires of a sample of this group

Endpoint collection: mailed annual questionnaire, review of medical records, linkage to National Death Index, endpoint adjudication process
PLCO Randomized Trial-Results

Participants: 50.5% women, 45% never smokers, 42% former smokers, 10% current smokers

Mean followup time: 11.9 years

Adherence to screening: 86.6% baseline decreasing to 79% by year 3

Screen positivity rates; 8.9% at baseline, 7.1% at year 1, 6.6% at year 2, 7.0% at year 3

Followup or results: repeat CXR (43%), CT (20%)

Screening in usual care group: 11%
PLCO Randomized Trial- Results

Cumulative lung cancer incidence:
- intervention group - 20.1 per 100,000 person yrs
- usual care group - 19.2 per 1000,000 person yrs
- RR - 1.05 (95% CI 0.98-1.12)

Intervention group: 61% of cancers were screen detected, 39% were detected during the interval

No phase shift in cancers detected by CXR vs usual care: cancers in intervention group compared with usual care group slightly more likely to be stage I (32% vs 27%)
The absolute number of stage III and IV cancers was similar across groups
PLCO Randomized Trial - Results

Independent data and safety board ended the trial early at its meeting on October 4, 2010

Trial did not meet statistical futility criteria but board felt that further followup was unlikely to change the conclusion and the data provided an important public health message particularly in light of the concurrently published NLST results.
PLCO Randomized Trial - Results

Lung cancer mortality rates: no difference between intervention group and usual care group
RR = 0.99 (95% CI 0.87-1.22, p=0.48)

Subset analysis: participants who would have been eligible for NLST trial
No difference between two groups
RR= 0.94 (95% CI 0.81-1.10)
PLCO Trial - Conclusions

Annual CXR screening did not reduce lung cancer mortality compared with usual care

No evidence of earlier diagnosis (phase shift)

Large trial with little contamination effect: unlikely to be underpowered
PLCO Trial - Conclusions

Annual CXR screening did not reduce lung cancer mortality compared with usual care

No evidence of earlier diagnosis (phase shift)

Large trial with little contamination effect: unlikely to be underpowered
National Lung Screening Trial (NLST)
Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

Study design: Between August 2002 - April 2004
54,454 persons at risk were randomized to 3 annual screening with low dose CT or single view PA CXR

Endpoints: Cases of lung cancer and lung cancer deaths through December 2009

Persons at risk: ages 55-74 with a history of >30 pack years smoking. Former smokers had quit within 15 years
NLST trial - Methods

Radiology interpretation: radiology technologists were trained in image quality and radiologists were trained in standardized interpretation.

Defined abnormalities on CT: > 4 mm nodules, adenopathy, effusion.

Diagnostic followup of abnormalities: no specific evaluation approach, standard care determined by physicians.

Statistical analysis: sample size designed to have a 90% power to detect a 20% difference in mortality in the CT group compared with the CXR group.
NLST

Gender: slight male predominance

Racial Mix: 90% Caucasian

Smoking status: 48% current smokers, 52% ex-smokers

Adherence to screening:
CT group 95%
CXR group 93%

Enrollment 08/02-04/04
Screening 08/02-09/07
Events 08/02-12/09

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low-Dose CT Group (N=26,722)</th>
<th>Radiography Group (N=26,732)</th>
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<tbody>
<tr>
<td>Age at randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55 yr†</td>
<td>2 (&lt;0.1)</td>
<td>4 (&lt;0.1)</td>
</tr>
<tr>
<td>55–59 yr</td>
<td>11,440 (42.8)</td>
<td>11,420 (42.7)</td>
</tr>
<tr>
<td>60–64 yr</td>
<td>8,170 (30.6)</td>
<td>8,198 (30.7)</td>
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<tr>
<td>65–69 yr</td>
<td>4,756 (17.8)</td>
<td>4,762 (17.8)</td>
</tr>
<tr>
<td>70–74 yr</td>
<td>2,353 (8.8)</td>
<td>2,345 (8.8)</td>
</tr>
<tr>
<td>≥75 yr†</td>
<td>1 (&lt;0.1)</td>
<td>3 (&lt;0.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15,770 (59.0)</td>
<td>15,762 (59.0)</td>
</tr>
<tr>
<td>Female</td>
<td>10,952 (41.0)</td>
<td>10,970 (41.0)</td>
</tr>
<tr>
<td>Race or ethnic group‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>24,289 (90.9)</td>
<td>24,260 (90.8)</td>
</tr>
<tr>
<td>Black</td>
<td>1,195 (4.5)</td>
<td>1,181 (4.4)</td>
</tr>
<tr>
<td>Asian</td>
<td>559 (2.1)</td>
<td>536 (2.0)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>92 (0.3)</td>
<td>98 (0.4)</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>91 (0.3)</td>
<td>102 (0.4)</td>
</tr>
<tr>
<td>Other</td>
<td>333 (1.2)</td>
<td>346 (1.3)</td>
</tr>
<tr>
<td>Data missing</td>
<td>163 (0.6)</td>
<td>209 (0.8)</td>
</tr>
<tr>
<td>Hispanic ethnic group‡</td>
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<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>479 (1.8)</td>
<td>456 (1.7)</td>
</tr>
<tr>
<td>Neither Hispanic nor Latino</td>
<td>26,079 (97.6)</td>
<td>26,039 (97.4)</td>
</tr>
<tr>
<td>Data missing</td>
<td>164 (0.6)</td>
<td>237 (0.9)</td>
</tr>
</tbody>
</table>

* CT denotes computed tomography.
† Patients in this age range were ineligible for inclusion in the screening trial but were enrolled and were included in all analyses.
‡ Race or ethnic group was self-reported.
At T0 > 90% of positive tests underwent a diagnostic evaluation: usually further imaging, invasive procedures were infrequent.
NLST - positives on screen

False positives:
CT 96.4% across 3 rounds, 24% total
CXR 94.5% across 3 rounds,
False negatives & others (dx after screening or missed screening):
CT 44 & 367
CXR 137 & 525
NLST - Lung cancer incidence

- CXR:
  - Total: 941
  - Per 100k person years: 572

- Low-Dose CT:
  - Total: 1060
  - Per 100k person years: 645

Lung Cancer Cases
Cumulative numbers of lung cancers

Cumulative numbers of deaths from lung cancer

Lung cancer deaths reduced by 20% in the CT group compared with CXR group

Number needed to screen to prevent 1 lung cancer death was 320
NLST - Conclusions

Low dose CT scanning resulted in 20% reduction in lung cancer death: proof of principle

CT scanning did result in a 3 fold higher false positive rate than CXR which were largely confirmed benign by stability on followup CT. Invasive evaluations were rare.

NEJM authors state that the findings of the study are not sufficient to serve as the basis yet for forming screening recommendations

Several other trials using low dose CT screening are underway in Europe
NLST - Limitations

Healthy volunteer effect: possible in any trial versus implementation in the community. Typically this bias results in a more favorable effect during a trial.

Current CT scanner technology is more advanced; potential greater benefit from screening but also potential higher rate of false positives.

Trial performed in medical centers recognized for expertise in radiology and treatment of cancer. Diagnosis may be lower in the community and mortality from surgical resection or treatment may be higher.
Cost-effectiveness of low dose CT screening has not been rigorously analyzed.

Cost effectiveness of CT screening should also be compared with competing interventions such as smoking cessation.

Ideal target audience: was the trial criteria too tight? Would others benefit? What is the ideal screening interval?

CT screening used in conjunction with other screening markers; molecular markers in blood, sputum, and urine.
Lung cancer screening - thoughts for primary care physicians

History Taking: importance of assessing smoking exposure and family history

CT scans in reality are frequently obtained for other reasons. Physicians need use a risk stratified approach to these findings. Look at the images yourself and know your radiologists

Screening CT programs are not ready for application yet and are not paid for as such as this point but may soon in the future

Stay tuned ...