Screening for Lung Cancer: Are We There Yet?

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The Epidemiology of Lung Cancer

• Tobacco is the single largest preventible cause of death
• 30% of all cancers and 80-90% of lung cancers are caused by smoking
• 20-fold higher risk of lung cancer in current smokers
• 25% increased risk for never smokers married to smokers
A Leading Killer
Causes of annual deaths in the U.S.

- Smoking: 442,000
- Alcohol: 81,000
- Motor vehicle: 41,000
- Suicide: 30,000
- Homicide: 19,000
- AIDS: 17,000
- Drug-induced: 14,000

American Cancer Society 2005
An Alarming Trend

- Lung cancers are rarely discovered until they have progressed to a late stage when they are almost untreated (16% survive 5 years)
- Surgical resection of stage 1 NSCLC offers > 50% 5-year survival
Ongoing Trials for Lung Cancer Screening CT

- Japanese
- ELCAP
- I-ELCAP
- Mayo
- NLST
- European
ADC
Phenotype vs Genotype
Small ADC (PET positive)

Follow up CT recommended but “anxious patient” chose to undergo unnecessary thoracotomy. It was a granuloma (PET positive)
Look alikes
Limitations of CT

- Relatively high false-positive rate
- Difficulty in accurately measuring the growth of small nodules (3D volumetric methods)
- A bias toward detecting adenocarcinoma (sputum analysis, bronchoscopy complementary)
- Possible inability to detect the disease before the CP in its natural history
Volumetric Measurement
Growth Assessment

Nodule ID: 1
Status: reported

Volume in mm$^3$: 167.86
X-Diameter in mm: 7.00
Y-Diameter in mm: 6.30
Z-Diameter in mm: 7.00
Min.-Diameter in mm: 5.86
Max.-Diameter in mm: 7.81
Density average in HU: 4.47
Density stddev in HU: 54.32

0.89 cm
0.70 cm
Evolving Paradigms in the Diagnosis & Treatment of Lung Cancer

• Early on CT, late in biology
• PET upstages CT stage 1 in about 20%
• Molecular signature, proteomics/tumor profile
Figure 1. Progressive theory of carcinogenesis suggesting that frequency of metastatic dissemination is related to tumor size. (Modified from Krokowski: Basic Concepts, 1964 In Kaiser, WA (ed): MR-Mammography, Berlin, Springer-Verlag, pp 3–22, 1993; with permission.)
PET/CT

Metabolic Information

• Combines functional and anatomic imaging to avoid false negatives and false positives
• FDG/PET, FLT/PET (Thymidine turnover)
• Molecular based functional imaging for diagnosis and follow-up
Screening Debate

- 31,567 screened, 484 cancers found
- 88% survival rate at least 10 yrs after diagnosis
- 3,246 screened, 144 cancers found
- No lives saved (4-yr data)
- Side effects

JAMA 2007;297:253-961
Questions

• Who to screen (about 15% lung cancer in non smokers – 28,500 people)
• Need to stratify the risk better
• Follow-up interval
• How long to follow
• Staging and treatment
Multistep Progression

- AAH (Preneoplastic) to BAC (ADC in-situ) to invasive ADC
- The earlier discovery of smaller nodules represents a challenge
- Incidentally discovered
- Familiarity with imaging features and growth patterns will assist with diagnosis and management
Recommendations for Follow-up and Management of Nodules Smaller than 8 mm Detected Incidentally at Non-screening CT

<table>
<thead>
<tr>
<th>Nodule Size (mm)*</th>
<th>Low-Risk Patient†</th>
<th>High-Risk Patient‡</th>
</tr>
</thead>
<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>

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

Radiology 2005;237:395-400
Indeterminate SPN

Clinically Biomolecular profile Screening

CT

No tumor detected Bronchoscopy? Annual S/C?

Suspicious Lung CA

> 10 mm Biopsy NSCLC
CT/PET for staging and follow-up

5 to 10 mm Follow-up CT Biopsy PET
(nonsolid often negative on PET)

< 5 mm solid or < 10 mm GGO nodule
Annual Repeat CT (watchful waiting/active surveillance)
A Decision and Cost-Effectiveness Analysis of Screening with CT

• Using a computer-simulated model, annual CT compared to no screening in a hypothetical cohort of 100,000 smokers, aged 60 years

• CT unlikely to be cost-effective without substantial reduction in mortality, high rates of adherence, lower rates of over-diagnosis & lower costs/screening

• Given uncertainty of efficacy, possibility of harm & high costs, direct-to-consumer marketing of CT is not advisable

Summary

• CT has potential for decreasing lung cancer specific mortality but not proven yet in a RCT
• Need to minimize side effects
• Need to recognize risk profiles and appropriate application for screening CT