CURRENT STATUS OF LUNG CANCER SCREENING IN ASIA

Pyng Lee
Associate Professor
Respiratory and Critical Care Medicine
National University Hospital
Email: pyng_lee@nuhs.edu.sg
• Nothing to disclose
Lung Cancer

- Most common cause of cancer deaths worldwide
- 1.37 million people dying annually
- More than prostate, breast and colon CA combined: 18% of all cancer deaths
- 5 year survival in USA 15% and 10% in Europe due to late diagnosis of disease
- >2/3 symptomatic patients have LN or distant metastasis at presentation
- Prognosis of lung cancer depends on stage of disease
- 5 yr survival after surgery for p-stage I is 80% if tumor <3cm
**FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2018.**

Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from the most recent observed data.
## Cancer Statistics 2018 for Lung Cancer

**American Cancer Society, Cancer Statistics; 2018**

<table>
<thead>
<tr>
<th></th>
<th>New Cases</th>
<th>Deaths (no.)</th>
<th>Cancer Deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>121,680</td>
<td>83,550</td>
<td>28</td>
</tr>
<tr>
<td>Women</td>
<td>112,350</td>
<td>70,500</td>
<td>25 (48%)</td>
</tr>
<tr>
<td>Total</td>
<td>234,030</td>
<td>154,050</td>
<td></td>
</tr>
</tbody>
</table>

234,000 new cases in 2018 - 60% will be dead within one year

**Symptomatic lung cancer** is advanced stage disease & not curable
## Cancer Statistics 2018

American Cancer Society, Cancer Statistics; 2018

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>New Cases (no.)</th>
<th>Deaths (no.)</th>
<th>1975-1977</th>
<th>2007-2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>234,030</td>
<td>154,500</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Colorectal</td>
<td>140,250</td>
<td>50,630</td>
<td>51</td>
<td>65</td>
</tr>
<tr>
<td>Breast</td>
<td>268,570</td>
<td>41,400</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>Pancreas</td>
<td>55,440</td>
<td>44,330</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Prostate</td>
<td>164,690</td>
<td>29,430</td>
<td>68</td>
<td>99</td>
</tr>
</tbody>
</table>
Incidence of lung cancer is rising in Asia. Unique characteristics related to ethnicity, genetics risk profile, prevalence of TB, access to diagnostic services, and cultural understanding of disease. TB is prevalent which means benign lung nodules require definitive diagnosis for Rx and public health implications. TB in Europe/Canada/USA <10/100,000 per year vs China 70/100,000/ year; India 171/100,000/ year; Thailand 119/100,000/ year.
Cigarette smoking primary risk factor

Singapore:
14% aged 18-64 yrs
24% men, 4% women
Malays 23%, Chinese 13%, Indians 9%
Increase in females 18-24 yrs
Cigarette smoking

WHO: 33% of all men smoke, 1.5 billion cigarettes sold/ day
China: accounts for highest smoking rate: 1 in 3 cigarettes. Men 67%, Women 4%
Europe: Men 30-40%, Women 15-30%
USA: Men 25%, Women 19%
Children: 80-100,000 start to smoke/d, 50% are in Asia.
Advising the patient to stop smoking is the single most cost-effective intervention.
- 85-90% of lung cancer occurs in smokers and former smokers
- Risk increases with no of cigarettes smoked, earlier age and longer duration of smoking
- Current smoker of 20 packyrs at 10-15X risk than never smoker
- 15 yrs after smoking cessation, risk of lung CA remains 2X c/w never smoker
Passive smoking

- Side-stream smoke unintentionally inhaled in presence of smoker
- Woman living with smoking husband has 1.2-2X risk of lung cancer c/w non-smoking woman in smoke free home
- Cigarette smoke contains more than 4000 chemicals and 400 are poisonous and 40 can cause cancer

"While you were at work I trained Jake to bite you everytime you smoke."

@The Quit Smoking Company  www.quitsmoking.com
Other causes

- **Radon exposure**: radioactive gas produced by natural decay of uranium in soils, rocks and water. Radon is present in indoor and outdoor air. Lung CA risk increases linearly with exposure. Radon in environment causes 10% of lung CA in USA, advice for houses to be tested.

- **Air pollution** from motor vehicles, factory emissions, wood/coal burning heaters: 1-2%. Particulate matter: major component of outdoor air pollution

- Chromium, nickel, arsenic
Other causes

• Asbestos and smoking increase risk by 50X
• COPD: 4-6X risk after controlling for smoking
• Genetic susceptibility: 2X risk with positive family history after controlling for smoking
  – Squamous cell CA most a/w familial clustering
  – Woman greater risk than man for equivalent smoke history
  – Difference in carcinogen metabolism, DNA repair or altered oncogene expression
• Dietary: fruit/vegetable protect
EARLY DETECTION IS THE HOLY GRAIL OF LUNG CANCER SURVIVAL
Definition of Screening
Systematic testing of individuals who are Asymptomatic with respect to Target disease. Purpose is to Prevent, Interrupt or Delay development of Advanced disease through Early Detection and Treatment

Hillman JACR 2004

Timeline of Disease

<table>
<thead>
<tr>
<th>Asymptomatic Detectable by Test</th>
<th>Symptoms or Signs</th>
<th>Death from Disease or Other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of Disease</td>
<td>Screening</td>
<td>Diagnosis</td>
</tr>
</tbody>
</table>

PRECLINICAL  CLINICAL
Ideal screening program

- **Characteristics of disease**: significant effect on quality or survival, prevalence is high enough to justify costs, effective and acceptable treatment available, asymptomatic period during which detection and treatment significantly reduce morbidity and mortality.

- **Characteristics of test**: sensitive enough to detect disease during the asymptomatic period, specific enough to minimize false positives, acceptable to patients.

- **Characteristics of population screened**: sufficiently high disease prevalence, accessibility of follow-up medical care, willingness to comply with subsequent diagnostic tests and necessary therapy.
Growth Model of Lung Cancer

Volume doubling time
Malignant: 20-400 days
Benign: >400 days
 Likely infective: <20 days

Bach BP et al. Chest 2007
CRITICAL POINT: point in disease course before which therapy is effective
Lead-time bias: survival rates are inflated by earlier dx

If survival is measured from time of diagnosis, screening will always improve survival even if treatment is ineffective.

**AVOID LEAD TIME BIAS**
- MEASURE MORTALITY **NOT** SURVIVAL
- COUNT FROM DATE OF RANDOMIZATION NOT TIME OF DIAGNOSIS

Proportion of MDs recommending screening

**Would you recommend this screening test to your patient?**

<table>
<thead>
<tr>
<th>Data presented</th>
<th>Case 1: mortality data</th>
<th>Case 2: 5-year survival data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No screening</td>
<td>Screening</td>
</tr>
<tr>
<td></td>
<td>2 deaths per 1000</td>
<td>1.6 deaths per 1000</td>
</tr>
</tbody>
</table>

**Correct answer**
- Recommend screening because reduced mortality is valid evidence of benefit.
- Would not recommend screening because improved survival with screening is not valid evidence of benefit.

**Graph**

- Physicians Recommending Test, %
- 70% Probably yes
- 20% Definitely yes
- 95% Definitely yes
- Probable yes
LENGTH TIME BIAS: slow growing cases will be picked up

Definition: Detection of small Malignant lesions BUT DO NOT grow, spread OR cause death is Overdiagnosis
Overdiagnosis bias: Survival rates are inflated by detection of non-progressive cancer

Of the 484 participants who received a diagnosis of lung cancer, 412 (85%) had clinical stage I lung cancer. In this subgroup, the estimated 10-year survival rate regardless of treatment was 88% (95% CI, 84 to 91); as of May 2006, 39 of these 412 patients had died of lung cancer. Of these 412 participants, 375 had undergone surgical resection (284 lobectomy, 60 wedge resection, 21 segmentectomy, and 10 bilobectomy); 29 did not undergo resection but received chemotherapy, radiation, or both; and the remaining 8 did not receive treatment. Figure 2 also shows the lung-cancer–specific survival rate among the 302 participants who underwent resection within 1 month after diagnosis, among whom the estimated 10-year survival rate was 92% (95% CI, 88 to 95). All eight untreated patients died within 5 years after diagnosis.
Screening by CXR and Lung CA mortality
The Prostate, Lung, Colorectal and Ovarian Trial

• Randomized controlled trial: Oken et al JAMA 2011
  – 77,445 annual screen CXR for 3yr;
  – 77,456 to usual care
• Lung CA incidence rate 20.1/10,000 person yrs in intervention group, and 19.2/10,000 person yrs in usual care grp
• 1213 lung ca deaths in intervention grp vs 1230 lung ca deaths in usual care group

Conclusion:
• Annual screen with CXR did not reduce lung ca mortality c/f usual care
Annual Low-Dose CT Screening better than CXR for reducing lung cancer mortality (NLST)

- Annual low-dose CT reduces more lung cancer deaths than CXR among high-risk patients, according to National Lung Screening Trial.
- More than 53,000 current/former heavy smokers (age 55-74; >30 pack-years, stopped smoking <15y) without signs or symptoms of lung cancer were randomized to undergo 3 annual low-dose CT (n=26722) or CXR (n=26732) Follow-up 6.5 years, reduction of lung cancer mortality by 20% with LDCT than CXR.
- The overall screening effort meant that 320 participants had to be screened to prevent one lung cancer
NLST

• 20% relative reduction in mortality from lung cancer using low-dose CT screening 354 deaths CT vs 442 deaths CXR
  – All-cause mortality lower by 6% CT group
  – additional 1 year evaluation CT 469 deaths and CXR 552 deaths = 15% reduction

• Screening does not replace primary prevention with smoking cessation

• Impact on guideline development for lung CA screening

• Low-dose CT also identified other non-cancer abnormalities. False positivity rate was high 96% due to definition of positive screening result: non calcified nodule $>=4\text{mm}$

• Managing false positive findings without causing harm is a major challenge (eg 26 deaths from invasive procedure following positive screen)
Implication Of Stage Shift

No Screening
- 5 yr Survival < 18%
- 70% stage III & IV

LDCT Screening
- 5 yr Survival >60%
- (70% Stage I)
<table>
<thead>
<tr>
<th></th>
<th>ALCAP (22*)</th>
<th>Shinshu (23*)</th>
<th>ELCAP (24*)</th>
<th>Mayo (25*)</th>
<th>Munster (26*)</th>
<th>SMC</th>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>≥ 40</td>
<td>≥ 40</td>
<td>≥ 60</td>
<td>≥ 50</td>
<td>≥ 40</td>
<td>≥ 45</td>
</tr>
<tr>
<td>Smoking habits (pack years)</td>
<td>NL</td>
<td>NL</td>
<td>≥ 10</td>
<td>≥ 20</td>
<td>≥ 20</td>
<td>NL</td>
</tr>
<tr>
<td>CT protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tube voltage (kVp)</td>
<td>120</td>
<td>120</td>
<td>140</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Tube current (mA)</td>
<td>50</td>
<td>25-50</td>
<td>40</td>
<td>40</td>
<td>50¹</td>
<td>48-50¹</td>
</tr>
<tr>
<td>Collimation (mm)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pitch</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1.5</td>
<td>2</td>
<td>0.75-1.5</td>
</tr>
<tr>
<td>Number of Detector</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1,4,8,16</td>
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<tr>
<td>CT interval (months)</td>
<td>6</td>
<td>12</td>
<td>3, 6, 12</td>
<td>12</td>
<td>3,6,12,24</td>
<td>6, 12</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Volunteers (total)</td>
<td>1,611</td>
<td>5,483</td>
<td>1,000</td>
<td>1,520</td>
<td>817</td>
<td>6,406</td>
</tr>
<tr>
<td>Lung cancer at CT</td>
<td>32¹ (2.0)</td>
<td>60 (1.1)</td>
<td>33 (3.3)</td>
<td>38¹ (2.5)</td>
<td>12¹ (1.5)</td>
<td>23 (0.36)</td>
</tr>
<tr>
<td>SCLC</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NSCLC</td>
<td>31</td>
<td>33</td>
<td>35</td>
<td>11</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Stage IA</td>
<td>24 (77)</td>
<td>53 (93)</td>
<td>27 (82)</td>
<td>21 (60)</td>
<td>6 (55)</td>
<td>13 (62)</td>
</tr>
</tbody>
</table>

ALCAP, anti-lung cancer association project; ELCAP, early lung cancer action project; SMC, Samsung Medical Center; NL, no limitation; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer. Numbers in parenthesis are percentages.

Chong S, J Korea Med Sci, 2005
DLST, DANTE: no advantage for lung CA screening

DLST and MILD found a trend towards higher mortality in the yearly CT screening arms

<table>
<thead>
<tr>
<th>Country</th>
<th>NLST</th>
<th>NELSON</th>
<th>DLST</th>
<th>ITAL LUNG</th>
<th>DANTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of sites</td>
<td>33</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Number controls</td>
<td>26,732</td>
<td>7,907</td>
<td>2,052</td>
<td>1,593</td>
<td>1,196</td>
</tr>
<tr>
<td>Number screened</td>
<td>26,722</td>
<td>7,557</td>
<td>2,052</td>
<td>1,613</td>
<td>1,276</td>
</tr>
<tr>
<td>Age range (year)</td>
<td>55-74</td>
<td>50-75</td>
<td>50-70</td>
<td>55-69</td>
<td>60-74</td>
</tr>
<tr>
<td>Smoking history</td>
<td>≥30/15</td>
<td>&gt;15/10</td>
<td>≥20/10</td>
<td>≥20/10</td>
<td>≥20/10</td>
</tr>
<tr>
<td>Male/Female</td>
<td>M/F</td>
<td>M/F</td>
<td>M/F</td>
<td>M/F</td>
<td>M</td>
</tr>
<tr>
<td>Control arm</td>
<td>Chest X-ray</td>
<td>Usual care</td>
<td>Usual care</td>
<td>Usual care</td>
<td>Usual care</td>
</tr>
<tr>
<td>Screening rounds</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Interval (years)</td>
<td>1,2,3</td>
<td>1,2,4,6,5</td>
<td>1,2,3,4,5</td>
<td>1,2,3,4</td>
<td>1,2,3,4,5</td>
</tr>
<tr>
<td>Nodule evaluation</td>
<td>2D</td>
<td>2D,3D</td>
<td>2D,3D</td>
<td>2D</td>
<td>2D</td>
</tr>
<tr>
<td>Prevalence detection (%)</td>
<td>NR</td>
<td>0.9</td>
<td>0.8</td>
<td>1.5</td>
<td>2.19</td>
</tr>
<tr>
<td>Incidence detection (%)</td>
<td>NR</td>
<td>0.5</td>
<td>0.67</td>
<td>0.4</td>
<td>4.7</td>
</tr>
<tr>
<td>False positives (%)</td>
<td>96.4</td>
<td>1.7</td>
<td>7.9</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mortality reduction</td>
<td>20%</td>
<td>(2016)</td>
<td>(2016)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NLST: National Lung Screening Trial; NELSON: Nederlands Leuven Screening Onderzoek; DLST: Danish Lung Screening Trial

1 Smoking history expressed as total number of pack years and maximal number of quit years allowed as former smoker
2 Chest X-ray was performed at baseline in both trial arms
3 Screening Interval expressed as years from randomisation
4 False positive scans in the LDCT group at baseline
5 Lung cancer mortality reduction, either result in % relative to the control arm or the expected year of primary endpoint result

26% males
39-61% females
Nelson LDCT Screening Trial

• 157 deaths in 10 years vs 214: HR 0.74
• Mortality Reduction at 10 years:
  – 26% for males
  – 39-61% for females
• Lung Cancers Stage I detected:
  NELSON 64% (N Eng J Med)
  NLST 69%

ASLC WCLC Toronto 2018 Abstract PL2.05
<table>
<thead>
<tr>
<th>Guidelines by organisation</th>
<th>Date</th>
<th>Age years</th>
<th>Smoking history pack-years</th>
<th>Smoking cessation years</th>
<th>Category/level</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCN</td>
<td>Jan 2015</td>
<td>55–74</td>
<td>≥30</td>
<td>&lt;15</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥50</td>
<td>≥20 (and one additional risk factor)</td>
<td></td>
<td>2A</td>
</tr>
<tr>
<td>ALA</td>
<td>Apr 2012</td>
<td>55–74</td>
<td>≥30</td>
<td>&lt;15</td>
<td>NA</td>
</tr>
<tr>
<td>Collaborative work of ACCP/ASCO/NCCN</td>
<td>May 2012</td>
<td>55–74</td>
<td>≥30</td>
<td>&lt;15</td>
<td>2B</td>
</tr>
<tr>
<td>AATS</td>
<td>June 2012</td>
<td>55–79</td>
<td>≥30</td>
<td>Any active or former smoker</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50–79</td>
<td>≥20 and added risk ≥5% of developing lung cancer within 5 years*</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any and ≥4 years remission after bronchogenic carcinoma</td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>Jan 2013</td>
<td>55–74</td>
<td>≥30</td>
<td>&lt;15</td>
<td>NA</td>
</tr>
<tr>
<td>ACCP</td>
<td>May 2013</td>
<td>55–74</td>
<td>≥30</td>
<td>&lt;15</td>
<td>2B</td>
</tr>
<tr>
<td>USPSTF</td>
<td>July 2013</td>
<td>55–79</td>
<td>≥30</td>
<td>&lt;15</td>
<td>B</td>
</tr>
</tbody>
</table>
**Challenge #1**
Selecting the at risk group for CT to be cost effective meta analysis of 7609 cases: RR of lung ca increases w active smokers vs former smokers, Duration and Amt of smoking, cumulative pack years. Eg 30 pack years, > 55yrs, lung ca incidence of 300/100,000.

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection criteria</th>
<th>Patients screened n (follow-up)</th>
<th>Lung cancer diagnosed at initial screening (total in follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCST</td>
<td>50–70 yrs, ≥20 pack-years (0–9 years)</td>
<td>2052 (58 months)</td>
<td>0.8% [3.4%]</td>
</tr>
<tr>
<td>DANTE</td>
<td>60–74 yrs, ≥20 pack-years (0–9 years)</td>
<td>1276 (34 months)</td>
<td>2.2% [4.7%]</td>
</tr>
<tr>
<td>ITALUNG</td>
<td>55–69 yrs, ≥20 pack-years (active or former)</td>
<td>1406 (36 months)</td>
<td>1.5% [2.8%]</td>
</tr>
<tr>
<td>MILD</td>
<td>≥49 yrs, ≥20 pack-years (0–9 years)</td>
<td>1190 (120 months)</td>
<td>0.8% [2.4%]</td>
</tr>
<tr>
<td>NELSON</td>
<td>50–75 yrs, ≥15 pack-years (0–9 years)</td>
<td>7907 (60 months)</td>
<td>0.9% [2.6%]</td>
</tr>
<tr>
<td>NLST</td>
<td>55–74 yrs, ≥30 pack-years (0–15 years)</td>
<td>26722 (78 months)</td>
<td>1.1% [2.4%]</td>
</tr>
</tbody>
</table>

**CHALLENGE #2**
Overdiagnosis: detection of small lesions confirmed to be malignant but do not grow, spread or cause death. Patients die from comorbidity.

Represents potential harm: additional cost, anxiety, morbidity a/w cancer Rx.
**RISK MODELS:** to increase pretest probability and reduce over-diagnosis—Improve patient selection. Most advantageous strategy is LDCT annual screen from 55-80 yrs, smoking >30pckyrs, former smokers <15 years since quitting= 50% ca detected at stage I/II, 575 screening exam per lung ca death averted, 14% reduction in lung ca mortality, 497 lung ca deaths averted, 5250 life years gained/100,000 member cohort. Harms 67550 false pos tests, 910 bx, surgeries for benign lesions, 190 overdiagnosed ca (3.7% of all cases of lung ca)
ANY SCREENING RECOMMENDATIONS FOR NON SMOKERS?

To date no good risk models for non smokers, no convincing data to recommend screening.

BURDEN of LUNG CANCER among never smokers: 7th leading cause of cancer mortality
Significant cause of death worldwide.

Risk factors: age, environmental tobacco exposure, cooking fumes
Genetic susceptibility, Occupational and environmental exposure to carcinogens, Hormonal factors, Pre-existing lung disease such as TB, Oncogenic viruses.

NSCLC in never smokers characterised by higher proportion of females, adenocarcinoma both in early and late stages

Even though factors are known, no beneficial screening program for this group
CT screening program should achieve these objectives
1) LDCT screening and treatment will decrease lung cancer mortality
2) Benefit exceeds harm
3) Cost effective
4) Population screened must be high risk using risk models
5) Nodule management
6) Smoking Cessation Program

WHO TO SCREEN:

<table>
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<tr>
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<td>&lt;15</td>
<td>B</td>
</tr>
</tbody>
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USPSTF Recommendations:
• Lung cancer screening should be performed annually until age 80.
• Lung cancer screening should NO longer be performed if the patient has developed comorbid illness that limits life expectancy or unacceptably increases the risk of procedure-related complications.
Recent Trends in Identification of Incidental Pulmonary Nodules

- **5.2%** of all patients with IPN received a lung cancer diagnosis within 2 years of CT
  - SEER data: 28% of LC are $\leq 25 \text{mm}$
- Extrapolating this data to US adult population of 234 million in 2010
  - **1.57 million IPN per year**
  - **63,000 new lung cancer diagnosis within 2 years.**

Gould et al  AJRCCM 2015; 192:1208
Recent Trends in Identification of Incidental Pulmonary Nodules

- Percent of positive scans with IPN increased yearly from 24%-31%
  - Average of 29%: Mean age 64±14
  - 44% in never smokers
- Size: 4-5mm (24%); 6-8mm (21%)
  - 9-12mm (18%); 13-20mm (22%)
  - >20mm (15%)

Gould et al  AJRCCM 2015; 192:1208
### True and False Positive Screens

<table>
<thead>
<tr>
<th>Screen Results</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Positive</td>
<td>7,193</td>
<td>6,902</td>
<td>4,052</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>270 (4%)</td>
<td>168 (2%)</td>
<td>211 (5%)</td>
</tr>
<tr>
<td>No Lung Cancer</td>
<td>96%</td>
<td>98%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Low Dose CT
SPN: What To Do?

- Observe
- PET for the nodule for staging
- Biopsy
- Remove

Nodule size:
- 1 mm
- 5 mm
- 10 mm
- 15 mm
- 20 mm
- 25 mm
- 30 mm
Pulmonary nodule characteristics

- Size
- Margins
- Calcification patterns
- Fat deposition
- Cavitation
- Volume doubling time
  - Malignant: 20-400 days
  - Benign: >400 days
  - Likely infective: <20 days

<table>
<thead>
<tr>
<th>Differential Diagnosis of Solitary Pulmonary Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious</strong></td>
</tr>
<tr>
<td>TB (tuberculosis)</td>
</tr>
<tr>
<td>Round pneumonia, organizing pneumonia</td>
</tr>
<tr>
<td>Lung abscess</td>
</tr>
<tr>
<td>Fungal: aspergillosis, blastomycosis, cryptococcosis,</td>
</tr>
<tr>
<td>histoplasmosis, coccidioidomycosis</td>
</tr>
<tr>
<td>Parasitic: amebiasis, echinococcosis, Dirofilaria immitis</td>
</tr>
<tr>
<td>(dog heartworm)</td>
</tr>
<tr>
<td>Mumps</td>
</tr>
<tr>
<td>Nocardia</td>
</tr>
<tr>
<td>Atypical mycobacteria</td>
</tr>
<tr>
<td><em>Pneumocystis jiroveci</em></td>
</tr>
<tr>
<td>Septic embolus</td>
</tr>
</tbody>
</table>

**Neoplastic**

- Benign
  - Hamartoma
  - Chondroma
  - Fibroma
  - Lipoma
  - Neural tumor (Schwannoma, neurofibroma)
  - Sclerosing hemangioma
  - Plasma cell granuloma
  - Endometriosis

- Malignant
  - Lung cancer
  - Primary pulmonary carcinoma
  - Solitary metastasis
  - Teratoma
  - Leiomyoma

**Vascular**

- Arteriovenous malformation
- Pulmonary infarct
- Pulmonary artery aneurysm
- Pulmonary venous varix

- Hematoma

**Congenital**

- Bronchogenic cyst
- Lung sequestration
- Bronchial atresia with mucus impaction

**Inflammatory**

- Rheumatoid arthritis
- Granulomatous with polyangiitis (Wegener)
- Microscopic polyangiitis
- Sarcoidosis

**Lymphatic**

- Intrapulmonary or subpleural lymph node

**Lymphoma**

**Outside lung fields**

- Skin nodule
- Nipple shadows
- Rib fracture
- Pleural thickening, mass or fluid (pseudotumor [ie, loculated fluid])

**Miscellaneous**

- Rounded atelectasis
- Lipoid pneumonia
- Amyloidosis
- Mucoidal impaction (mucocoele)
- Infected bulla
- Pulmonary scar
### Table 3—Margin Characteristics of SPNs

<table>
<thead>
<tr>
<th>Margin</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth</td>
<td>Suggests a benign lesion. However, may be malignant in up to one-third of cases.</td>
</tr>
<tr>
<td>Lobulated</td>
<td>Suggests uneven growth; a PPV of 80% for malignancy. Up to 25% of benign lesions, such as hamartomas, can have lobulated margins.</td>
</tr>
<tr>
<td>Spiculated</td>
<td>A spiculated margin (the so-called corona radiata sign) is highly predictive of malignancy, with a PPV of 88% to 94%. A few exceptions of benign SPNs that could have spiculated margins include lipid pneumonia, focal atelectasis, tuberculosis, and progressive massive fibrosis.</td>
</tr>
<tr>
<td>Ragged</td>
<td>Suggests growth pattern along the alveolar wall; lepidic pattern of adenocarcinoma.</td>
</tr>
<tr>
<td>Tentacle or</td>
<td>Seen in fibrosis, alveolar infiltration, and collapsed alveoli.</td>
</tr>
<tr>
<td>polygonal</td>
<td></td>
</tr>
<tr>
<td>Halo</td>
<td>SPN surrounded by a “halo” of ground glass attenuation, also called the “CT halo sign.” Seen in aspergillosis, Kaposi sarcoma, granulomatosis with polyangiitis (Wegener), and metastatic angiosarcoma. Adenocarcinoma in situ (previously known as bronchoalveolar carcinoma) can also produce a halo, due to its lepidic growth.</td>
</tr>
<tr>
<td>Notches</td>
<td>SPN with notches or concavity in the margin is seen in some SPNs with tumor growth. These notches are frequently found in adenocarcinomas with overt invasion and are associated with poor prognosis.</td>
</tr>
<tr>
<td>Pattern of Calcification</td>
<td>Etiology</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Laminated and concentric</td>
<td>Usually benign</td>
</tr>
<tr>
<td>Dense central core</td>
<td>Usually benign</td>
</tr>
<tr>
<td>Diffuse and solid</td>
<td>Usually benign</td>
</tr>
<tr>
<td>Popcorn</td>
<td>Hamartoma</td>
</tr>
<tr>
<td>Punctate</td>
<td>Malignant lesions: scar carcinoma, typical and atypical carcinoids, large-cell neuroendocrine carcinoma and metastasis from colon, ovary, breast, thyroid, and osteogenic tumors.</td>
</tr>
<tr>
<td>Eccentric</td>
<td>Due to necrosis within the malignant nodule or engulfment of adjacent granuloma</td>
</tr>
</tbody>
</table>
• Attenuation of -40 to -120 Hounsfield units suggest fat deposition
  – Harmatoma
  – Lipoid pneumonia, Pulm mets from RCC, lipoidsarcoma

• Cavitation
  – Most common neoplastic cause is SCC
  – Cavity wall thickness <5mm suggests benign etiology,
    irregular thicker walls >15mm can suggest malignancy
Nodule Guidelines

Recommendation 4.1

- In every patient with a solid, indeterminate nodule, > 8mm, estimate the pretest probability of malignancy quantitatively or qualitatively using a validated model or clinical judgement. Grade 2C

  Gould et al., ACCP guideline Chest 2013

Independent predictors of malignancy

- Older age (OR 1.04 for each year)
- Current or former smoking (OR 2.2)
- Hx of cancer > 5 years (OR 3.8)
- Nodule diameter (OR 1.14 for each mm)
- Spiculation (OR 2.8)
- Upper-lobe location (OR 2.2)

ACCP Guideline

Likelihood categorized into three groups:
• < 5%, 5%-65% and > 65%
• Suggest: < 10% and 85-90%

Recommendation #4.2
• In a patient with a solid indeterminate, > 8 mm nodule and low-to-moderate probability of malignancy (5 to 65%), perform functional imaging, preferably with PET.

Grade 2C

Gould et al., ACCP guideline Chest 2013
Management of IPN by Community Pulmonologists

• 377 patients with IPNs 8-20mm diameter
  – Prevalence of malignancy: 25%
  – Surveillance alone: 175 (46%)
  – PET performed in 141 (37%)
  – PET false positive in 39%
• 77 pts had surgery: 27 (35%) Benign Dz
• Surgical resection 17%, 21%,17% in the low, intermediate and high risk groups

Tanner et al Chest 2015: 148:1405
Timeliness of Care: Lung Cancer

Progression of Tumor Stage with delay of >60 days vs <60 days

30% progressed (20/67): >60 days
22% progressed (23/107): < 60 days

P=0.278

Maiga AW et al Ann Thor Surg 2017; 104:1791-7
The BTS guideline suggests standardisation of the terminology applied to pulmonary nodules, classifying them as solid and subsolid nodule (SSN), and further dividing the subsolid category into part-solid nodule (PSN) and pure ground glass nodules (pGGN).
Evaluation of Pulmonary Nodules
Clinical Practice Consensus Guidelines for Asia
Chunxue Bai, MD, PhD, FCCP; Chang-Min Choi, MD, PhD; Chung Ming Chu, MD, FCCP; James Chung-man Ho, MD, FCCP; Ali Zamir Khan, MD, PhD; Jang-Ming Lee, MD, PhD; Sawang Saenghirunvattana, MD, PhD; and Anthony Yim, MD, PhD

Indeterminate nodule on chest radiography

Review prior imaging tests (1.1)

Nodule is stable?

Yes

Discuss annual low-dose CT surveillance with patient based on clinical judgment and patient preference (1.2)

No

Perform high-resolution chest CT scan (1.3)

Solid or subsolid malignant features?

Solid

Nodule > 8 mm in diameter

Figure 3

Nodule ≤ 8 mm in diameter

Figure 4

Subsolid

See Figure 5

Solid nodule > 8 mm in diameter

Refer to center with appropriate diagnostic equipment and expertise (2.1)

Determine clinical (pretest) probability of malignancy (2.2)

Low (< 5%)

Serial CT surveillance (2.3, 2.4)

Negative or mild

Moderate (5-60%)

PET scan hypermetabolic? (2.5)

Intense

Clear growth?

Yes

Surgical biopsy (2.8)

Suspicious

No

Surgical resection

Nonsurgical biopsy (2.7)

Positive

Positive
Solid nodule ≤ 8 mm in diameter

Determine clinical (pretest) probability of malignancy

- Low (< 5%) (3.1)
  - Characterize nodule size
    - ≤ 4 mm
    - > 4 to ≤ 6 mm
    - > 6 to ≤ 8 mm
      - Patient discussion
      - CT scan at 12 mo
      - CT scan at 6-12 and 18-24 mo
      - 12 months
      - CT scan at 6-12 and 18-24 mo
      - CT scan at 3, 6, and 12 mo

- Moderate to high (> 5%) (3.2)
  - Characterize nodule size
    - ≤ 4 mm
    - > 4 to ≤ 6 mm
    - > 6 to ≤ 8 mm

Annual CT surveillance after discussion with patient based on clinical judgment/patient preference

Subsolid nodule

Determine if nonsolid (pure ground glass) or part-solid (> 50% ground glass) and diameter

- Nonsolid
  - ≤ 5 mm (4.1)
  - > 5 mm (4.2)
    - Discuss role of continued surveillance with patient
    - Consider ongoing annual CT surveillance after discussion with patient

- Part-solid
  - ≤ 8 mm (5.1)
  - > 8 mm (5.2)
    - Repeat CT scan at 3 mo and consider antimicrobial therapy
    - Nonsurgical ± surgical biopsy (consider PET scanning for staging before biopsy)
Solid non-calcified nodule(s) on CT

Clear features of benign disease* or nodule <5mm diameter (or <8mm volume) or patient unfit for any treatment?

Yes

Discharge

No

Assess risk of lung cancer according to surveillance algorithm

Previous imaging?

Yes

Nodule <8mm diameter or <300mm$^3$ volume?

Yes

Assess risk using Brock model

≥10% risk of malignancy

PET-CT with risk assessment using Herder model (provided size is greater than local PET-CT threshold)

>70% risk of malignancy

Consider excision or non-surgical treatment (+/-image-guided biopsy)

10-70% risk of malignancy

<10% risk of malignancy

CT surveillance (Figure 3)

No

Assess risk using Brock model

<10% risk of malignancy

No

PET-CT with risk assessment using Herder model (provided size is greater than local PET-CT threshold)

>70% risk of malignancy

Consider excision or non-surgical treatment (+/-image-guided biopsy)

10-70% risk of malignancy

<10% risk of malignancy

CT surveillance (Figure 3)
Brock model shows the highest accuracy for predicting malignancy, and has recently been validated in UK population where AUC was 0.90.6

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Brock OR (95% CI)</th>
<th>Herder OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (0.99 to 1.07)</td>
<td>1.04 (1.01 to 1.07)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.82 (1.12 to 2.97)</td>
<td>N/A</td>
</tr>
<tr>
<td>Family history</td>
<td>1.34 (0.83 to 2.17)</td>
<td>N/A</td>
</tr>
<tr>
<td>Emphysema</td>
<td>1.34 (0.78 to 2.33)</td>
<td>N/A</td>
</tr>
<tr>
<td>Nodule size</td>
<td>Non-linear</td>
<td>1.14 (1.09 to 1.19)</td>
</tr>
<tr>
<td>pGGN</td>
<td>0.88 (0.48 to 1.62)</td>
<td>N/A</td>
</tr>
<tr>
<td>PSN</td>
<td>1.46 (0.74 to 2.88)</td>
<td>N/A</td>
</tr>
<tr>
<td>Upper lobe</td>
<td>1.93 (1.14 to 3.27)</td>
<td>2.19 (1.27 to 3.79)</td>
</tr>
<tr>
<td>Nodule count</td>
<td>0.92 (0.85 to 1.00)</td>
<td>N/A</td>
</tr>
<tr>
<td>Spiculation</td>
<td>2.17 (1.16 to 4.05)</td>
<td>N/A</td>
</tr>
<tr>
<td>Smoker</td>
<td>N/A</td>
<td>2.21 (1.17 to 4.16)</td>
</tr>
<tr>
<td>Cancer ≥5 years ago</td>
<td>N/A</td>
<td>3.8 (1.39 to 10.5)</td>
</tr>
<tr>
<td>PET findings</td>
<td>N/A</td>
<td>Increased AUC of Mayo model from 0.79 to 0.92</td>
</tr>
</tbody>
</table>

*From Mayo model.
AUC, area under the curve; pGGN, pure ground glass nodules; PSN, part-solid nodules.
Semiautomated volumetry is preferred method of nodule assessment and volume doubling time (VDT). Improved accuracy compared with manual calliper measurement of nodule diameter. Volumetry is able to detect nodule growth at a rate consistent with malignancy at 3-month interval scan allowing prompt intervention.
Sub-solid nodule(s) on CT

Yes

Nodule <5mm, patient unfit for any treatment or stable over 4 years?

No

Repeat thin section CT at 3 months

Yes

Previous imaging?

No

Assess interval change. If stable over less than 4 years, assess risk of malignancy as below.

Resolved

Assess risk of malignancy (Brock model\(^f\)/morphology\(^s\)), patient fitness and patient preference.

Stable

Low risk of malignancy (approximately <10%)\n
Discharge

Thin section CT at 1, 2, 4 years from baseline

High risk of malignancy (approximately >10%) or concerning morphology\(^s\) - discuss options with patient

Growth/ altered morphology\(^*\)

Image-guided biopsy

Favour resection/ non-surgical treatment

---

\* Change in mass/new solid component

\(f\) Brock model may underestimate risk of malignancy in SSN that persist at 3 months

\(s\) Size of the solid component in PSN, pleural indentation and bubble-like appearance
Pulmonary Nodules

CT guided transthoracic needle aspiration:
• sensitivity 90%; specificity 97% for malignant disease
• meta-analysis of 48 studies: sensitivity 86%, specificity 99%
• 50% yield for PN 0.5-0.7cm; PN >1.5cm 73.5% more likely to give diagnostic specimen vs 51.4% for PN ≤ 1.5cm
• Distance from pleura <60% yield when path >4cm
• Pneumothorax 15% in 15865 pts of which 6.6% required chest tube, bleeding 1% of which 18% required blood transfusion
• Risk of pthorax increases with depth, size of lesion, gauge of bx needle, emphysema, increased no of pleural passes, acuity of angle of needle entry

Transbronchial lung biopsy via fluoroscopy

<table>
<thead>
<tr>
<th>Contraindications to percutaneous TTNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding diathesis</td>
</tr>
<tr>
<td>Contralateral pneumonectomy or pneumothorax</td>
</tr>
<tr>
<td>Severe emphysematous disease or large bullae in biopsy path</td>
</tr>
<tr>
<td>Intractable cough</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Patients unable to cooperate with procedure</td>
</tr>
</tbody>
</table>
  • Unable to hold breath consistently |
  • Inability to lie in required position |
  • Unable to give informed consent |
  • Unable to follow directions |
| FEV<sub>1</sub> less than 0.8 L       |
Improve yield: EBUS-guided TBBX SPN

- 150 patients with single lesion
- Size: 10->30 mm
- Overall yield 77%, malignant 81%, benign 69%
- Higher in >30mm (92%) c/f ≤30mm 69-77%.
- Nodules ≤10mm, yield= 76%
- Highest for RML (14/14), and lowest in LUL (6/15=40%)
- Probe within 87% of SPN

Kurimoto et al. Chest 2004
Electromagnetic Navigation Bronchoscopy
ENB combined with EBUS

<table>
<thead>
<tr>
<th></th>
<th>EBUS n (%)</th>
<th>ENB n (%)</th>
<th>EBUS and ENB n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall diagnostic yield</td>
<td>27/39 (69)</td>
<td>23/39 (59)</td>
<td>35/40 (88)</td>
<td>0.02†</td>
</tr>
<tr>
<td>Yield by lesion size:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 20 mm</td>
<td>7/9 (78)</td>
<td>3/4 (75)</td>
<td>9/10 (90)</td>
<td>0.02†</td>
</tr>
<tr>
<td>20 - 30mm</td>
<td>16/23 (70)</td>
<td>11/22 (50)</td>
<td>21/24 (88)</td>
<td>P=0.99</td>
</tr>
<tr>
<td>&gt; 30 mm</td>
<td>4/7 (57)</td>
<td>9/13 (69)</td>
<td>5/6 (83)</td>
<td></td>
</tr>
<tr>
<td>Yield by lobar location:</td>
<td></td>
<td></td>
<td></td>
<td>0.01†</td>
</tr>
<tr>
<td>Bilateral upper lobes</td>
<td>16/27 (59)</td>
<td>17/22 (77)</td>
<td>17/20 (85)</td>
<td></td>
</tr>
<tr>
<td>Right middle lobe</td>
<td>3/3 (100)</td>
<td>2/3 (67)</td>
<td>2/2 (100)</td>
<td>P=0.99</td>
</tr>
<tr>
<td>Bilateral lower lobes</td>
<td>8/9 (89)</td>
<td>4/11 (29)</td>
<td>16/18 (89)</td>
<td></td>
</tr>
<tr>
<td>Yield for malignant disease:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>23/32 (72)</td>
<td>16/29 (55)</td>
<td>28/31 (90)</td>
<td>0.009†</td>
</tr>
<tr>
<td>Specificity</td>
<td>7/7 (100)</td>
<td>10/10 (100)</td>
<td>9/9 (100)</td>
<td>----</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>23/23 (100)</td>
<td>16/16 (100)</td>
<td>28/28 (100)</td>
<td>----</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>7/16 (44)</td>
<td>10/23 (44)</td>
<td>9/12 (75)</td>
<td>0.16</td>
</tr>
<tr>
<td>Yield for benign disease:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>4/7 (57)</td>
<td>7/10 (70)</td>
<td>7/9 (78)</td>
<td>0.79</td>
</tr>
<tr>
<td>Specificity</td>
<td>32/32 (100)</td>
<td>29/29 (100)</td>
<td>31/31 (100)</td>
<td>----</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>4/4 (100)</td>
<td>7/7 (100)</td>
<td>7/7 (100)</td>
<td>----</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>32/35 (91)</td>
<td>29/32 (91)</td>
<td>31/33 (94)</td>
<td>0.90</td>
</tr>
<tr>
<td>Pneumothorax rate</td>
<td>2/39 (5)</td>
<td>2/39 (5)</td>
<td>3/40 (8)</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Virtual Bronchoscopic Navigation

• Virtual path to the lesion is generated through application of 3D display techniques of the airways from uploaded CT.
• **VBN with CT guided Ultrathin bronchoscopy:** diagnostic yield 81.6%
• **VBN with Xray fluoroscopy:** overall yield 62.5% (35% < 10mm; 61% 10-20mm, 95% >20mm)
• **VBN with EBUS-GS:** prospective randomized trial VBN assisted R-EBUS-GS yield 80% for SPN <3cm, 13% higher than non VBN assisted
• 49 year old Chinese Male, Ex-smoker of 30 pack year
• Has been followed up GOLD 4 COPD, not on LTOT. On Seretide, Tiotropium and Ventolin
• LUL nodule to be evaluated before referral for Lung transplant
Tolerated procedure
EBUS radial fluoroscopic guided biopsy, no pthorax
Histology: adenocarcinoma
T3 involvement of pleura, N0Mo
Palliative RT
56/Ch/female non-smoker
cough, hemoptysis, fever.
GP referred to Medical Oncology.
CT: cavitating nodules, tree in bud, RML consolidation, sputum:AFB/TB molecular neg.
Bronchoscopy, aspirate RML, TBLB of RLL cavitatory nodule via navigational bronchoscopy, radial EBUS.
Histo: caseous necrosis, ZN stain +AFB
Culture of lung tissue: M Kansasi, Rx: rifampicin, isoniazid, ethambutol
Screening with CT, Exhaled Breath

Lung Cancer Nodule

Central Airway Cancer

Surgery, Bronchoscopic therapy
Molecular-based individualized Rx
RECOMMENDATIONS:
Treatment options for nodules depend on the fitness of the individual for surgery. **Lobectomy** is the treatment of choice or **anatomical segmentectomy** where preservation of functioning lung is important. If wedge resection is performed, this should be followed by frozen section and definitive anatomical resection.

Sublobar resection is recommended for pGGN, insufficient evidence for SPN. Nodule localisation techniques are recommended prior to surgery for smaller nodules.

Where fitness levels preclude surgery, stereotactic ablative radiotherapy or radiofrequency ablation is recommended, even where biopsy is not possible, provided the probability of malignancy is high. Patient Discussion about risk, harms of investigation and options for surveillance, biopsy or treatment.

Semiautomated volumetry to evaluate nodules at baseline and to calculate VDT. PET-CT scans reporting according to four-point ordinal scale so that the Herder model can be employed in risk prediction.

A local, dedicated nodule service may be the best way to manage people with nodules (and implement the guideline).
Thank you!