ESMO 2012 – CYE session

Screening & early detection of lung cancer

J. Vansteenkiste
Disclosure

J. Vansteenkiste is holder of the Amgen Chair in Supportive Cancer Care at the Leuven University (research funding)

J. Vansteenkiste is holder of the Eli-Lilly Chair in Respiratory Oncology at the Leuven University (research funding)

J. Vansteenkiste is holder of the Astra Zeneca Chair in Personalised Lung Cancer Care at the Leuven University (research funding)
Screening and early detection

- The lung cancer epidemic
- Conditions for successful screening
- Lessons from history
- Low-dose CT screening
  - Non randomised data
  - Randomised controlled trials
  - Issues for implementation
  - Conclusion-Example of recent statement
- Biomarkers
- Endoscopy
Screening and early detection > lung cancer epidemic

<table>
<thead>
<tr>
<th>Cause</th>
<th>Deaths/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>7.8 M</td>
</tr>
<tr>
<td>Smoking</td>
<td>5.0 M</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>3.9 M</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>3.8 M</td>
</tr>
<tr>
<td>Sexual transmission</td>
<td>3.0 M</td>
</tr>
<tr>
<td>Poor diet</td>
<td>2.8 M</td>
</tr>
<tr>
<td>Overweight</td>
<td>2.5 M</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>2.0 M</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.9 M</td>
</tr>
<tr>
<td>Indoor pollution</td>
<td>1.8 M</td>
</tr>
<tr>
<td>Poor sanitation</td>
<td>1.6 M</td>
</tr>
</tbody>
</table>

Screening and early detection > lung cancer epidemic

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<table>
<thead>
<tr>
<th>Lung Cancer</th>
<th>Estimated numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
</tr>
<tr>
<td>World</td>
<td>1,607,000</td>
</tr>
<tr>
<td>EU-27</td>
<td>288,000</td>
</tr>
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</table>

Screening and early detection > prevention

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Action</th>
<th>Disease</th>
<th>Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Avoid occurrence of disease <em>(population)</em></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Secondary</td>
<td>Diagnose and treat in early stage to avoid morbidity/mortality</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td><em>(selected population)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertiary</td>
<td>Reduce negative impact of existing disease <em>(patient groups)</em></td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Screening and early detection

- The lung cancer epidemic
- Conditions for successful screening
- Lessons from history
- Low-dose CT screening
  - Non randomised data
  - Randomised controlled trials
  - Issues for implementation
  - Conclusion-Example of recent statement
- Biomarkers
- Endoscopy
Screening and early detection
> principles

- **Aim of screening**
  - Diagnose in an earlier stage (**stage shift**)
  - Treat in earlier stage (**curative therapy**)
  - Avoid mortality (survival not a valid endpoint, must be reduction of disease-specific mortality)

- **Conditions**
  1. Sensitive test for detection of smaller lesions
  2. Smaller lesions ~ earlier stage
  3. Effective treatment
  4. Acceptable morbidity and cost
Screening and early detection > overdiagnosis bias
Screening and early detection

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Screening and early detection > historical RCTs

- **Historical randomised screening studies**
  - 4 large studies started in 70-ies (>37,000 patients)
  - In heavy smokers aged 45+
  - Based on
    - chest XR ± sputum cytology vs. chest XR $^{1,2,3}$
    - chest XR and sputum cytology vs. Observation only $^4$
    - variable test frequency (q4 months, q1 or q3 years)

- **Negative**: no reduction in lung cancer related mortality

1 Frost et al, Am Rev Respir Dis 130:549-554, 1984
4 Kubic et al, Cancer 57:2427-2437, 1986
Screening and early detection > chest XR in PLCO* trial

- **RCT** with 154,901 participants (ages 55-74)
  - 77,445 annual chest XR for 4 years
  - 77,456 to usual care

- **Endpoints:**
  - **Primary:** mortality from lung cancer
  - **Secondary:** lung cancer incidence, complications of diagnostic procedures, all-cause mortality
    - cumulative lung cancer incidence rates 201 vs. 192 per 100,000 person-years (RR 1.05; NS)
    - stage and histology similar between groups


* Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer screening trial
Screening and early detection > chest XR in PLCO trial

1213 (XR) vs. 1230 (OBS) lung cancer deaths (RR 0.99; NS)

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Screening and early detection
> condition 1: sensitive tool
Screening and early detection
> condition 1: sensitive tool

- Non-randomised LD-CT trials
  - Open studies in 1000-1500 in smokers aged 40+
  - CT detects smaller lesions (<1.5 cm) missed at XR
  - CT detects more cases (prevalence rate e.g. 0.8% vs. historical 0.3%)
  - Frequent stage I resectable disease
  - Better survival
  - ??? more stage shift (prevalence rate of advanced disease e.g. 0.3% vs. 0.2%)
  - ??? effect on lung cancer mortality
Screening and early detection
> non randomised LD-CT data e.g. I-ELCAP

- 31,567 asymptomatic persons at risk for lung cancer
  - LD-CT between 1993 through 2005
  - 27,456 repeated screenings (7-18 months)

- Lung cancer in 484 participants
  - 412 (85%) clinical stage I
  - estimated 10-y survival rate 88% (92% in resected cases)

- Conclusion: LD-CT can detect curable lung cancer

Screening and early detection
> non randomised LD-CT data e.g. I-ELCAP

Screening and early detection > reduced lung cancer related mortality

- **Historical comparison**
  - NY ELCAP (n=7995)
  - CARET: prevention study in similar patient group
  - correction for possible smoking cessation

- **SMR calculations**
  - 21/100,000 vs.
  - 57,4/100,000

Henschke et al, Lung Cancer 71: 328-332, 2011
Screening and early detection

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Screening and early detection

> NLST

National Cancer Institute press release
November 2010

Initial results show mortality benefit with LD-CT screening

Twenty percent fewer lung cancer deaths compared to chest XR screening

http://www.cancer.gov/newscenter/pressrelease/NLSTresultRelease
Screening and early detection

> NLST: design

- Large RCT based on previous feasibility trial (Lung Screening Study*)
  - LDCT versus XR screening
  - Primary endpoint: 90% power to detect a 21% decrease in lung cancer mortality
  - 33 participating centres
  - 53,454 eligible participants (age 55-74), ≥30 PY smoker or quit within previous 15 years
  - 3 yearly screening rounds + 3.5 years follow-up
  - All screening CT and XR standard protocol, but no standard diagnostic follow-up or diagnostic evaluation

* Gohagan et al, Lung Cancer 47: 9-15, 2005
### Screening and early detection > NLST: results

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>XR</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive result</td>
<td>24.2%</td>
<td>6.9%</td>
<td>1.13</td>
</tr>
<tr>
<td>False pos result</td>
<td>23.3%</td>
<td>6.5%</td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1060 (645/100,000 PtY)</td>
<td>941 (572/100,000 PtY)</td>
<td>1.13 [1.03;1.23]</td>
</tr>
<tr>
<td>adeno</td>
<td>36.3%</td>
<td>35.2%</td>
<td></td>
</tr>
<tr>
<td>stage I</td>
<td>50%</td>
<td>31.1%</td>
<td></td>
</tr>
<tr>
<td>stage IV</td>
<td>21.7%</td>
<td>36.1%</td>
<td></td>
</tr>
<tr>
<td>Lung cancer deaths</td>
<td>346 (247/100,000 PtY)</td>
<td>425 (309/100,000 PtY)</td>
<td>-20% [-6.8;-26.7] P=0.004</td>
</tr>
<tr>
<td>All cause deaths</td>
<td>1877</td>
<td>2000</td>
<td>-6.7% [-1.2;-13.6] P=0.02</td>
</tr>
</tbody>
</table>

Screening and early detection
> NLST: results

Incidence RR 1.13 [1.03-1.23]

Lung Cancer deaths -20% [-6.8;-26.7]
Screening and early detection > European RCTs

- 6 ongoing trials - enrolled ~32,000 people
- ~150,000 person-years of FU
- In addition, UKLS trial feasibility has started (4,000, further plan up to 32,000)
- Largest study (NELSON): final results (mortality data) expected 2015-2016
### Screening and early detection > European RCTs (recruited)

<table>
<thead>
<tr>
<th>Country</th>
<th>NLST</th>
<th>NELSON</th>
<th>DLST</th>
<th>ITALUNG</th>
<th>DANTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>USA</td>
<td>NL/Belgium</td>
<td>Denmark</td>
<td>Italy</td>
<td>Italy</td>
</tr>
<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/&lt;15</td>
<td>&gt;15/&lt;10</td>
<td>≥20/&lt;10</td>
<td>≥20/&lt;10</td>
<td>≥20/&lt;10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control arm</th>
<th>XR</th>
<th>Usual care</th>
<th>Usual care</th>
<th>Usual care</th>
<th>Usual care*</th>
</tr>
</thead>
<tbody>
<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</td>
<td>1-1.2-2.5</td>
<td>1</td>
<td>1</td>
<td>1</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevalence detection</th>
<th>NR</th>
<th>0.9%</th>
<th>0.8%</th>
<th>1.5%</th>
<th>2.2%</th>
</tr>
</thead>
<tbody>
<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>

* Chest XR at baseline for controls
 ° false pos in LDCT arm at baseline
Screening and early detection

- The lung cancer epidemic
- Conditions for successful screening
- Lessons from history
- **Low-dose CT screening**
  - Non randomised data
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  - Issues for implementation
  - Conclusion-Example of recent
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- Endoscopy

1. Validity
2. Technical aspects
3. Nodule approach
4. Diagn. Workup/therapy
5. Populations at risk
6. Cost
Screening and early detection

1. validity: e.g. NLST findings

- Excellent internal validity (balanced arms, good protocol adherence, control arm with XR is fine)

- External validity
  - Specially trained radiologists in expert centres
  - Higher than expected young / highly educated / quit-smoking subjects
  - Degree of overdiagnosis at present unknown: at least 10 more years of follow-up needed
## Screening and early detection

### 1. validity: e.g. NLST findings

<table>
<thead>
<tr>
<th></th>
<th>NLST</th>
<th>US census</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male (%)</strong></td>
<td>59.0</td>
<td>58.5</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-59 (%)</td>
<td>42.8</td>
<td>35.2</td>
</tr>
<tr>
<td>60-64 (%)</td>
<td>30.6</td>
<td>29.3</td>
</tr>
<tr>
<td>65-69 (%)</td>
<td>17.8</td>
<td>20.8</td>
</tr>
<tr>
<td>70-74 (%)</td>
<td>8.8</td>
<td>14.7</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; High School</td>
<td>6.1</td>
<td>21.3</td>
</tr>
<tr>
<td>≥ College</td>
<td>31.5</td>
<td>14.4</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td>48.2</td>
<td>57.1</td>
</tr>
<tr>
<td><strong>Median pack years</strong></td>
<td>48.0</td>
<td>47.0</td>
</tr>
</tbody>
</table>

Screening and early detection
1. validity: e.g. NLST findings
Screening and early detection
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Screening and early detection
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Screening and early detection
1. validity: Mayo Clinic non-RCT modeling

TRIAL: open LD-CT trial with 5 annual screenings in 1520 patients
MODELING: \( P<0.05 \) if for 8000 patients with 6-year follow-up

<table>
<thead>
<tr>
<th>Model-predicted Outcome according to Follow-up</th>
<th>Control Arm</th>
<th>Screening Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients diagnosed with lung cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 y follow-up</td>
<td>9.2</td>
<td>22.0*</td>
</tr>
<tr>
<td>6-y follow-up</td>
<td>37.9</td>
<td>51.9†</td>
</tr>
<tr>
<td>10-y follow-up</td>
<td>64.6</td>
<td>74.1</td>
</tr>
<tr>
<td>15-y follow-up</td>
<td>97.0</td>
<td>105.5</td>
</tr>
<tr>
<td>Lifetime of cohort</td>
<td>171.4</td>
<td>179.0</td>
</tr>
<tr>
<td>Lung cancer deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5-y follow-up</td>
<td>4.2</td>
<td>4.0</td>
</tr>
<tr>
<td>6-y follow-up</td>
<td>26.5</td>
<td>19.1</td>
</tr>
<tr>
<td>10-y follow-up</td>
<td>47.8</td>
<td>36.6</td>
</tr>
<tr>
<td>15-y follow-up</td>
<td>73.5</td>
<td>62.3</td>
</tr>
<tr>
<td>Lifetime of cohort</td>
<td>131.3</td>
<td>120.8</td>
</tr>
<tr>
<td>All deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5-y follow-up</td>
<td>34.7</td>
<td>34.9</td>
</tr>
<tr>
<td>6-y follow-up</td>
<td>162.8</td>
<td>157.0</td>
</tr>
<tr>
<td>10-y follow-up</td>
<td>302.3</td>
<td>293.6</td>
</tr>
<tr>
<td>15-y follow-up</td>
<td>510.7</td>
<td>501.0</td>
</tr>
<tr>
<td>Iatrogenic deaths, 6-y follow-up</td>
<td>0.3</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Screening and early detection
2. techniques

- **Harmonization of protocols**
  - Radiological settings (rows in detector, slice thickness, image reconstruction, computer-aid, ...)
  - Optimal number of rounds / intervals

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<td>5</td>
</tr>
<tr>
<td>Interval (years)</td>
<td>1</td>
<td>1-2-2.5</td>
<td>1</td>
<td>1</td>
<td>1</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>
</tbody>
</table>
Screening and early detection of lung cancer

2. Techniques

- **Optimal number of rounds**
  - NSLT observation
    
<table>
<thead>
<tr>
<th></th>
<th>Round 1</th>
<th>Round 2</th>
<th>Round 3</th>
<th>3Y follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer detection</td>
<td>270 (3.8%)</td>
<td>168 (2.4%)</td>
<td>211 (5.2%)</td>
<td>similar</td>
</tr>
</tbody>
</table>

- **EU RCT**: prevalence detection > incidence detection
- **UKLS**: explore one single screen
Screening and early detection
3. nodule approach

- False positive screening findings may lead to a large number of additional non-invasive and invasive tests
- Efforts to reduce FP rate – use of volumetric analysis
  - Historical studies: high number of indeterminate nodules: from 23% to 51% of patients

**NLST**

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive result</td>
<td>18,146 (24.2%)</td>
<td>5043 (6.9%)</td>
</tr>
<tr>
<td>False pos result</td>
<td>17,497 (96.4%)</td>
<td>4,764 (94.5%)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>649 (3.2%)</td>
<td>279 (5.5%)</td>
</tr>
</tbody>
</table>

**EU: Nelson nodule management**

Mayo Lung Cancer Screening Project
Screening and early detection
3. nodule approach NELSON

<table>
<thead>
<tr>
<th>NODCAT baseline</th>
<th>Definition</th>
<th>Use of 3D (or 2D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Benign nodule (fat/benign calcifications) or other benign characteristics</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Any nodule, smaller than NODCAT III and no characteristics of NODCAT I</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Solid: $50 - 500, mm^3$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solid, pleural based: $5 - 10, mm, d_{\text{min}}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial solid, non-solid component: $\geq 8, mm, d_{\text{mean}}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial solid, solid component: $50 - 500, mm^3$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-solid: $\geq 8, mm, d_{\text{mean}}$</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Solid: $&gt;500, mm^3$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solid, pleural based: $&gt;10, mm, d_{\text{min}}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial solid, solid component: $&gt;500, mm^3$</td>
<td></td>
</tr>
</tbody>
</table>

Xu et al, Lung Cancer 54: 177-184, 2006
### Table 1: NELSON classification of the different non-calcified nodules according to size at baseline screening

<table>
<thead>
<tr>
<th>NODCAT baseline</th>
<th>Definition</th>
<th>Use of 3D (or 2D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Benign nodule (fat/benign calcifications) or other benign characteristics</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Any nodule, smaller than NODCAT III and no characteristics of NODCAT I</td>
<td>(and/or)</td>
</tr>
<tr>
<td>III</td>
<td>Solid: 50–500 mm³</td>
<td>(and/or)</td>
</tr>
<tr>
<td></td>
<td>Solid, pleural based: 5–10 mm $d_{min}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial solid, non-solid component: $\geq 8$ mm $d_{mean}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial solid, solid component: 50–500 mm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-solid: $\geq 8$ mm $d_{mean}$</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Solid: &gt;500 mm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solid, pleural based: &gt;10 mm $d_{min}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial solid, solid component: &gt;500 mm³</td>
<td></td>
</tr>
</tbody>
</table>

**Indeterminate test:**
- Repeat scan 3-4 mo

**Refer for diagnostic work-up**

**Continue as planned with next LDCT round**

---

Xu et al, Lung Cancer 54: 177-184, 2006

---

Screening and early detection

3. nodule approach NELSON
### Screening and early detection

3. nodule approach NELSON

<table>
<thead>
<tr>
<th>VDT</th>
<th>GROWCAT</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;600 days</td>
<td>A</td>
<td>Continue as planned with next LDCT round</td>
</tr>
<tr>
<td>400-600 days</td>
<td>B</td>
<td>Refer for diagnostic work-up</td>
</tr>
<tr>
<td>&lt;400 days</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

Xu et al, Lung Cancer 54: 177-184, 2006
### Table 3: NELSON follow-up protocol for non-calcified nodules at various volumes

<table>
<thead>
<tr>
<th>Volume</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>V₁</td>
<td>V₂</td>
<td>V₃</td>
<td></td>
</tr>
<tr>
<td>Percentage volume change: PVC (%) (solid nodules only)</td>
<td>100 × (V₂ − V₁)/V₂</td>
<td>100 × (V₃ − V₁)/V₁</td>
<td></td>
</tr>
<tr>
<td>Growth</td>
<td>PVC &lt; 25%: no; PVC ≥ 25%: yes</td>
<td>PVC &lt; 25%: no; PVC ≥ 25%: yes</td>
<td></td>
</tr>
</tbody>
</table>

**Select lowest VDT (either VDTᵥ or VDTₐ)**
- VDT > 600 days: GROWCAT A
- VDT 400–600 days: GROWCAT B
- VDT < 400 days or new solid component in non-solid lesion: GROWCAT C

- Annual CT year 4
- Annual CT year 3
- Refer to pulmonologist

**Annual repeat screening**
Screening and early detection
3. nodule approach NELSON

Round 1
NODCAT 2

Round 2
NODCAT 2
% vol change <25%

Round 3
NODCAT 2
% vol change >25%
GROWCAT C

Left superior lobectomy: pT1aN0 adenocarcinoma
**Screening and early detection**

3. **nodule approach NELSON**

- In 1\(^{st}\) and 2\(^{nd}\) round of screening, 2.6% and 1.8% of the participants had a positive test result.

- In 1\(^{st}\) round one, sensitivity was 94.6%, NPV 99.9%.

- In case of negative 1\(^{st}\) round, chances of finding lung cancer:
  - 1/1000 after 1 year
  - 3/1000 after 2 years

Screening and early detection
5. population at risk

- Using the NLST criteria
  - 7 million persons in the US would be screened
- There are 94 million current/former smokers
- Implementation ...
Screening and early detection > UKLS: feasibility phase

- Selection of subjects with high risk for lung cancer
  - according to validated Liverpool Lung Project risk model
- One single round of LDCT screening
  - estimated lung cancer detection rate of about 1.5%
- Nodule categorisation and follow-up according to the NELSON nodule management

### Screening and early detection

5. Population at risk

<table>
<thead>
<tr>
<th>Risk factor/category</th>
<th>Odds ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>(95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.00</td>
<td>Reference</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 – 20 years</td>
<td>2.16</td>
<td>(1.21 – 3.85)</td>
<td></td>
</tr>
<tr>
<td>21 – 40 years</td>
<td>4.27</td>
<td>(2.62 – 6.94)</td>
<td></td>
</tr>
<tr>
<td>41 – 60 years</td>
<td>12.27</td>
<td>(7.41 – 20.30)</td>
<td></td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>15.25</td>
<td>(5.71 – 40.65)</td>
<td></td>
</tr>
<tr>
<td>Prior diagnosis of pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>Reference</td>
<td>0.002</td>
</tr>
<tr>
<td>Yes</td>
<td>1.83</td>
<td>(1.26 – 2.64)</td>
<td></td>
</tr>
<tr>
<td>Occupational exposure to asbestos</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.89</td>
<td>(1.35 – 2.62)</td>
<td></td>
</tr>
<tr>
<td>Prior diagnosis of malignant tumour</td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.96</td>
<td>(1.22 – 3.14)</td>
<td></td>
</tr>
<tr>
<td>Family history of lung cancer</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Early-onset (&lt; 60 years)</td>
<td>2.02</td>
<td>(1.18 – 3.45)</td>
<td></td>
</tr>
<tr>
<td>Late-onset (≥ 60 years)</td>
<td>1.18</td>
<td>(0.79 – 1.76)</td>
<td></td>
</tr>
</tbody>
</table>

Screening and early detection 6. cost

- NSLT
  - ‘number needed to screen’ to prevent 1 lung cancer death
  - ‘NNS’: estimated as the reciprocal of reduction in absolute risk of death from lung cancer in one group vs. the other
  - ‘NNS’ result was 320!

- North-American modelling study
  - Incremental cost-effectiveness ratio varying between $110,000/QALY and $280,000/QALY
  - LDCT screening along with successful smoking cessation in very selected groups of patients, this could be more cost-effective ($73,000/QALY) than screening alone

Screening and early detection

- The lung cancer epidemic
- Conditions for successful screening
- Lessons from history
- **Low-dose CT screening**
  - Non randomised data
  - Randomised controlled trials
  - Issues for implementation
  - Conclusion-Example of recent statement
- Biomarkers
- Endoscopy
Screening and early detection

- LDCT first test with significant reduction in lung cancer mortality through early detection

- Issues to be addressed before implementation of LDCT
  - Target population
  - CT number of rounds and frequency
  - Optimal nodule management
  - Cost-effectiveness compared to anti-smoking actions

- 32,000 patients in 6 European RCTs
  - Final mortality data expected 2015-2016
  - Unique information on screening vs. no-screening
  - Additional data from UKLS
Screening and early detection > IASLC 2011 statement 1

- **Context and NSLT data**
  - LDCT first test with significant reduction in lung cancer mortality through early detection

- **Number of opportunities to improve further this approach**
  - Ongoing trials. Largest is Dutch-Belgian NELSON, a *population-based* trial of 20,000 smokers, which uses *refined CT* techniques, and will have *cost effectiveness* and *clinical management* data
  - IASLC encourages people to be enrolled into screening trials so that further information can be acquired as soon as possible
  - Further research needed: evolution in CT technique/protocol, surgical management, definition of risk groups with highest benefit

http://www.iaslc.org/policies/statement-on-ct-screening/
Screening and early detection > IASLC 2011 statement 2

- Implementation?
  - Crucial = multidisciplinary groups of trained specialists in all aspects of early lung cancer
  - Appropriate for heavy smokers ages 55-74 to discuss lung cancer screening information with their physicians to assist them in deciding whether to undergo spiral CT screening
  - In each country, lung cancer screening benefit, implementation costs and potential harms must be defined in a cultural context, so that national policies about implementation and quality control can be decided. Different nations will need to undertake individual health technology assessments.

- IASLC continues to advocate for effective tobacco control, and integrated public health messages for both tobacco control and lung cancer early detection

http://www.iaslc.org/policies/statement-on-ct-screening/
Screening and early detection

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- Endoscopy
Screening and early detection > biomarkers

- Ideal early detection biomarker
  - permits large-scale screening
  - applicable on easily accessible specimens through non-invasive procedures
  - easy and reproducible quantification
  - high sensitivity and specificity
  - low cost
Screening and early detection > biomarkers

- Stratify high-risk populations for screening studies
  - early detection biomarker in e.g. blood sample
  - improve definition of populations at risk
  - thereby making LDCT screening cost-effective

- Help in the DD of screen-detected nodules

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive result</td>
<td>18,146 (24.2%)</td>
<td>5043 (6.9%)</td>
</tr>
<tr>
<td>False pos result</td>
<td>17,497 (96.4%)</td>
<td>4,764 (94.5%)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>649 (3.2%)</td>
<td>279 (5.5%)</td>
</tr>
</tbody>
</table>

- Help to define which nodules are the indolent ones
Screening and early detection > biomarkers

Very large number of early detection biomarker studies

- **Targets**
  - DNA, promoter hypermethylation, microsatellite instability, loss of heterozygosity (LOH), chromosomal aneusomy
  - messenger RNA (mRNA), microRNA (miRNA)
  - tumour-associated antibodies, antigens, proteomic profiles
  - volatile organic compounds

- **Specimens**
  - bronchial biopsies or lavage
  - induced sputum
  - buccal/nasal swabs
  - plasma, serum, circulating tumour cells
  - exhaled breath
Screening and early detection
> biomarkers

- Many with high sensitivity and specificity (up to 100%) in feasibility studies
- None recommended as tests for screening
  - lack of validation
  - unsure if appropriate for risk individuals or very early stages
- Best candidates
  - miRNAs
    - high tissue specificity and incredible stability -> easily detectable and quantifiable in body fluids
    - promising in work-up of LDCT detected nodules
  - VOCs in exhaled breath
    - non-invasive and repeatable
    - moderate accuracy to distinguish lung cancer from controls

Shen et al, BMC Cancer 11: 374, 2011
Dragonieri et al, Lung Cancer 64: 166-170, 2009
Screening and early detection

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  - Issues for implementation
  - Examples of recent statements
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- Endoscopy
Central endobronchial pre-invasive/early invasive lesions

- not detected by spiral CT
- standard white light videobronchoscopy (WLB), complemented autofluorescence bronchoscopy (AFB)
  - pooled relative sensitivity of AFB + WLB versus WLB was 2.04 (95% CI 1.72-2.42)
  - specificity only 65%: quite some ‘false-positive’ lesions that need extra biopsies
Screening and early detection > endoscopy: investigations

- **Primary screening**
  - patients at risk for early intra-epithelial pre-invasive or early invasive lesions

- **Secondary screening**
  - search for other synchronous lesions in patients with radiologically visible lung cancer
  - search for metachronous pulmonary lesions during follow-up of patients with a curatively treated lung or H&N cancer

- **Surveillance**
  - follow-up of patients known with central pre-invasive lesions
Screening and early detection > endoscopy: investigations

<table>
<thead>
<tr>
<th>Pre-invasive lesion</th>
<th>Regression</th>
<th>Persistence</th>
<th>Progression to CIS/INV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metaplasia</td>
<td>37-42%</td>
<td>29%</td>
<td>0-9%</td>
</tr>
<tr>
<td>Mild/moderate dysplasia</td>
<td>64%</td>
<td>22%</td>
<td>0-11%</td>
</tr>
<tr>
<td>Severe dysplasia</td>
<td>52-63%</td>
<td>16%</td>
<td>11-56%</td>
</tr>
<tr>
<td>Carcinoma in situ (CIS)</td>
<td>12%</td>
<td>70%</td>
<td>21-67%</td>
</tr>
</tbody>
</table>

Dooms et al, Eur Respir Rev 19: 229-236, 2010
Thank you for your kind attention

Leuven, Gothic Town Hall (1448)