Early Detection of Lung Cancer

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Early Detection and Screening
- Questions to be addressed -

• How to deal with CT detected nodules

• Who should be invited for CT screening

• Should CT screening for lung cancer be implemented
Low-Dose Multi-detector Computer Tomography

• > 50% of the SPN on CXR are multiple on CT

• More nodules due to smaller collimations
Baseline test performance of CT Screening

<table>
<thead>
<tr>
<th></th>
<th>Prevalence rate</th>
<th>Stage I disease</th>
<th>% Test positives</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.9% (Range 0.4-2.7)</td>
<td>85% (Range 68-96%)</td>
<td>21% (Range 5-51%)</td>
<td>96% (Range 81-100%)</td>
<td>85% (Range 68-96%)</td>
<td>6% (Range 2-15%)</td>
</tr>
</tbody>
</table>

Black WC, Cancer 2007
Test positive

Current regimens

Baseline:
• subjects with any NCN > 4 mm

Annual repeat:
• subjects with any new NCN
• Subjects with any growth of a NCN
The NELSON nodule management Strategy

• To reduce the number of test positives and the number of follow-up CT scans

• To limit the radiation exposure, costs and potential morbidity

RJ van Klaveren et al. NEJM 2009:361:2221-2230

<table>
<thead>
<tr>
<th></th>
<th>Conventional regimens</th>
<th>NELSON strategy</th>
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</thead>
<tbody>
<tr>
<td>Screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test positive</td>
<td>Median 21% (range 15-51%)</td>
<td>Baseline: 2.6%, 2nd round: 1.8%</td>
</tr>
<tr>
<td>Referral and Work-up for diagnosis</td>
<td></td>
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<tr>
<td>Cancer</td>
<td></td>
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</tbody>
</table>
The NELSON nodule management strategy

- For new nodules based on volume only

- For previously existing nodules based on growth and for growing nodules on VDT only

- Introduction of an indeterminate test result

When is a nodule Growing?

- Change is volume of at least 25% 1\textsuperscript{st} and 2\textsuperscript{nd} scan or 2\textsuperscript{nd} and 3\textsuperscript{rd} scan

- 25% threshold based on 3 zero-change datasets

- Variation in volume of individual nodules assessed between 2 low-dose CT scans (2 consecutive CT scans in same patient)
**Test result: New Nodules**

- **Determine Volume**
  - Volume < 50 mm³: Test negative
  - Volume 50-500 mm³: Test indeterminate
  - Volume > 500 mm³: Test positive

**Previously existing NCN**

- **Percentage Volume Change (PVC)**
  - PVC < 25%: No growth, test negative
  - PVC ≥ 25%: Growth

**Calculate Volume Doubling Time (VDT)**

- VDT > 600 days: Test negative
- VDT 400-600 days: Test indeterminate
- VDT < 400 days: Test positive

**Percentage Volume Change (PVC)**

\[
PVC (%) = 100 \cdot \frac{(V_2 - V_1)}{V_2}
\]

**3D: Volume Doubling Time (VDT)**

\[
VDTv \ (\text{days}) = \frac{\ln 2 \times \Delta t}{\ln \left(\frac{V_2}{V_1}\right)}
\]
Results

- N: 7,557 participants in screen arm
- Mean Age 59 ± 6 yrs
- Pack-years smoked: 42 ± 19
- Females: 16%
  - Baseline: 51% of participants ≥ 1 nodule (8,623), 98% solid
  - Second round: 21.8% of participants had new nodules (2,320) Of existing nodules 26.2% resolved
Baseline

Test negatives 7361 (97.4%)

Test positives 196 (2.6%)

19 not referred

1,77 referred

107 benign or other cancer

70 lung cancers

20 lung cancers After 2 yrs of FU

10 lung cancers Later rounds
Test results: Baseline

- Lung Cancer detection rate: 0.9% (70/7,557)
- 4 interval cancers (stage IV adenocarc)
- PPV: 35.7 (95% CI: 29.3-42.7)
- NPV: 99.9 (95% CI: 99.9-100%)

- Test negatives after 2-years of follow-up:
  - 20 lung cancers: 3 interval cancers (1st round) and 17 2nd round cancers
  - NPV 99.7 (95% CI 99.6-99.8)

2nd Round

Test negatives
7161 (98.2%)

Test positives
128 (1.8%)

- 9 not referred
  - 1 died

- 118 referred

  - 64 benign or other cancer
  - 54 lung cancers
Test results: 2\textsuperscript{nd} round

- Lung Cancer detection rate: 0.5\% (40/7.289) or 0.8\% (57/7.289)
- 2 interval cancers (stage IV SCLC and stage IV NSCLC)
- PPV: 42.2 (95\%CI: 33.9-50.9)
- NPV: 99.9 (95\% CI: 99.9-100.0\%)

Additional diagnostic investigations

<table>
<thead>
<tr>
<th></th>
<th>NELSON</th>
<th>PLuSS</th>
<th>Cosmos</th>
<th>Toronto</th>
<th>LSS</th>
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</thead>
<tbody>
<tr>
<td>1\textsuperscript{st} Round</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recall CT</td>
<td>19%</td>
<td>23%</td>
<td>9%</td>
<td>19%</td>
<td>21%</td>
</tr>
<tr>
<td>FNA</td>
<td>1%</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Inv Procedures</td>
<td>1%</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>2\textsuperscript{nd} Round</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Recall CT</td>
<td>4%</td>
<td>41%</td>
<td>3%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>FNA</td>
<td>0%</td>
<td>NA</td>
<td>NA</td>
<td>1%</td>
<td>NA</td>
</tr>
<tr>
<td>Inv Procedures</td>
<td>1%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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Interpretation (1)

What is the probability of a false negative baseline test result:

- After 3 months: none lung cancer
- After 1 year: 1:1000 subjects LC
- After 2 years: 3:1000 subjects LC

Interpretation (2)

- Data applicable only for heavy current and former smokers between 50-75 yrs of age
- Optimal VDT thresholds to be determined
- Validation in independent cohort is needed before being clinical directive.
Questions

• Is the still a role for the “known risk factors for malignancy” as identified for SPN’s?

• How should we deal with NCN’s if someone has more than 1 NCN?

• How long should a solid NCN be followed?

• What is the optimal follow-up recommendation for non-solid NCN (GGO)

Is the still a role for the “known risk factors for malignancy” as identified for SPN’s?

• 4 Lung cancer risk models
  • Liverpool Lung Project (LLP)
  • MD Anderson (M Spitz)
  • Peter Bach
  • NELSON

• Age, smoking history, asbestos, COPD, family history, dust exposure, BMI
Improvements of LC risk models

- Adding DNA repair capacity: no improvement in sensitivity
- 15q25.1 locus
- CHRNA3 and CHRNA5 nicotine dependence genes; direct relation with carcinogenesis
- 5p15.33 locus 2 genes, telomerase reverse transcriptase gene

Is there still a role for the “classical risk factors for malignancy”
What to do if > 1 NCN?

• Test outcome is determined by the largest nodule or the fastest growing nodule

• Each NCN has its own history and needs to be followed

• Cancer risk is not dependent on the number of NCN’s detected

How long should we follow-up solid NCN’s?

If the baseline test is negative the probability that after

• 1 year of follow-up this person has lung cancer is 1:1000
• 2 years of follow-up this person has lung cancer is 3: 1000
How long should we follow-up solid NCN’s?

- Will the probability of cancer further rise after 2-years of follow-up?
- Yet unknown
- Probably yes, especially for very slowly growing lesions (VDT>600 days)
- Overdiagnosed cases?

Test results: Baseline

<table>
<thead>
<tr>
<th>1st Screening round</th>
<th>Final diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>Size</td>
</tr>
<tr>
<td>1 50-500</td>
<td>&lt;400</td>
</tr>
<tr>
<td>2 50-500</td>
<td>&lt;400</td>
</tr>
<tr>
<td>3 &gt;500</td>
<td>NA</td>
</tr>
<tr>
<td>4 50-500</td>
<td>&lt;400</td>
</tr>
<tr>
<td>5 50-500</td>
<td>400-600</td>
</tr>
<tr>
<td>6 &gt;500</td>
<td>NA</td>
</tr>
<tr>
<td>7 &gt;500</td>
<td>NA</td>
</tr>
<tr>
<td>8 50-500</td>
<td>&lt;400</td>
</tr>
<tr>
<td>9 25 mm</td>
<td>NA</td>
</tr>
<tr>
<td>10 &gt;500</td>
<td>NA</td>
</tr>
</tbody>
</table>
Modelling

• Use available data from observational studies

• Bach Model, validated: JAMA 2007

• Lung Cancer Policy Model: Radiology 2008 (comprehensive microsimulation model, validation ?)

Combined Results for the Studies of Lung Cancer Screening With Computed Tomography

Limitations JAMA study

- Control arm = prediction model, not real life
- Control arm observed stage distributions adjusted for age/gender but not for smoking status (not in SEER)
- Small size of 3,246 subjects with 10,738 person-years of follow-up
- Could have missed a mortality reduction as large as 30%

LCPM

- Models both screen and control arm
- Models true disease (stage /growth rates)
- Models benign nodules/resections
- Incorporates competing mortality risks
- Incorporates smoking history/smoking cessation
- 500,000 simulated pts per arm; normalised to 1520 participants
- Data Mayo Clinic CT screening trial were used to feed the model: screen AND control arm
Red: 5 annual screening examinations, n=1520 p=NS; n= 8,000 p<0.05
Green: 10 annual screenings

<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>0.0</td>
</tr>
<tr>
<td>6-y follow-up</td>
<td>-28%</td>
<td>26.5</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>-15%</td>
<td>62.3</td>
</tr>
<tr>
<td>Lifetime of cohort</td>
<td>-8%</td>
<td>-14%</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>-4%</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>-2%</td>
<td>-3%</td>
</tr>
<tr>
<td>All deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5-y follow-up</td>
<td>0.3</td>
<td>0.5</td>
</tr>
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