Lung Cancer Screening

nodules, cancer, mortality … and beyond

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Professor of Radiology
Lung Cancer Screening

nodules, cancer, mortality ... and beyond

before ............and after

November 2010
Screening – before Nov 2010

- impact of lung cancer
- screening CTs for lung cancer detection
- lung cancer stage at detection
- mortality ?
Lung Cancer

FREQUENT

LETHAL

- lung cancer is the leading cause of cancer death worldwide
- lung cancer kills more people annually than breast, prostate, colon, kidney and liver cancer, and melanoma combined
- more than 50 percent of new lung cancer cases will be diagnosed at a very late stage

overall 5-year survival ~ 15%
Lung Cancer

Stage IV

15% survival
Lung Cancer

Stage I

80% survival
Screening – before Nov 2010

- impact of lung cancer
- screening CTs for lung cancer detection
- lung cancer stage at detection
- mortality?
Lung Cancer Screening - Detection

high prevalence and incidence
of early stage lung cancer detected at LDCT

Lung cancer prevalence [%]

- Henschke et al, 1999
- Sone et al, 2001
- Nawa et al, 2002
- Sobue et al, 2002
- Diederich et al, 2004
- Swensen et al, 2003
- Pastorino et al, 2003
- Bastarrika et al, 2005
- Roberts et al, 2005
- Chong et al, 2005
- Novello et al, 2005
- MacRedmond et al, 2006
- I-ELCAP 2006
- Veronesi et al, 2008
- Menezes et al, 2009

Overall
early stage lung cancers [%]

Henschke et al, 1999
Sone et al, 2001
Nawa et al, 2002
Sobue et al, 2002
Diederich et al, 2004
Swensen et al, 2003
Pastorino et al, 2003
Bastarrika et al, 2005
Roberts et al, 2005
Chong et al, 2005
Novello et al, 2005
MacRedmond et al, 2006
I-ELCAP 2006
Veronesi et al, 2008
Menezes et al, 2009

Overall
screen-detected lung cancers
I-ELCAP, PMH, Toronto
(~2.3% detection rate)
Screening – before Nov 2010

- impact of lung cancer
- screening CTs for lung cancer detection
- lung cancer stage at detection
- mortality ?
Single-arm trials: survival

- International Early Lung Cancer Action Program (I-ELCAP)
  - I-ELCAP
  - 27,456
  - non-randomized
  - 10-year-survival
  - up to 92%*

survival vs. mortality

• 10-year survival up to 92%

• longer survival ≠ reduced mortality
• survival biased by
  – lead time bias
  – length time bias
  – overdiagnosis

[I-ELCAP New Eng J Med 2006]
lead time bias

Sy - Dx

no screen

death

survival

CT - Dx

screen

lead time

survival
lead time bias

no screen

Sy - Dx

death

survival

CT - Dx

screen

lead time

survival
overdiagnosis bias

no screen

death from other cause
no autopsy

screen

CT - Dx
## Randomized Trials: Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Year started</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSS</td>
<td>USA</td>
<td>CT vs CXR</td>
<td>2000</td>
<td>3318</td>
</tr>
<tr>
<td>DANTE</td>
<td>Italy</td>
<td>CT vs obs</td>
<td>2001</td>
<td>2472</td>
</tr>
<tr>
<td>NLST</td>
<td>USA</td>
<td>CT vs CXR</td>
<td>2002</td>
<td>53000</td>
</tr>
<tr>
<td>NELSON</td>
<td>NL–B</td>
<td>CT vs obs</td>
<td>2003</td>
<td>15822</td>
</tr>
<tr>
<td>DLCST</td>
<td>DK</td>
<td>CT vs obs</td>
<td>2004</td>
<td>4104</td>
</tr>
<tr>
<td>ITALUNG</td>
<td>Italy</td>
<td>CT vs obs</td>
<td>2004</td>
<td>3206</td>
</tr>
<tr>
<td>MILD</td>
<td>Italy</td>
<td>CT vs obs</td>
<td>2005</td>
<td>4479</td>
</tr>
<tr>
<td>LUSI</td>
<td>Germany</td>
<td>CT vs obs</td>
<td>2007</td>
<td>4000</td>
</tr>
</tbody>
</table>

> 90,000
Nov 4th 2010

“Lung Cancer Screening Using LDCT Reduces Deaths”
• on November 4, 2010

• the NLST reported *initial* trial results, showing 20 percent fewer lung cancer deaths among trial participants screened with low-dose helical CT (also known as spiral CT) compared to those who got screened with chest X-rays.
National Lung Screening Trial

• paper published *N Eng J Med* 2011
• 20% mortality benefit
• will change the way how lung cancer screening will be recommended
• impact on health care polices expected
Lung Cancer Screening - Sep 2011

- not paid for by OHIP
- not standard of care anywhere in the western world
- research only
  - international (USA, Europe, Japan)
  - national (Pan-Canadian, 7 sites) enrollment closed in Dec 2010
Lung Cancer Screening - Sep 2011

- not research
- not clinical

no options for
study participants
people at risk
collaborating/referring physicians

disguised screening
"emphysema, COPD, hemoptysis"
full dose contrast-enhanced CT
non-standardized follow up of nodules
Screening – beyond mortality

- nodules and false positives
- management of cancers (overdiagnosis)
- radiation exposure
- selection of individuals at risk
- the solution
Lung Cancer Screening

• nodules, nodules, nodules ….. cancer

• false positives

  nodules in the lung that turn out
  NOT to be cancer
Lung Cancer Screening - False positives

- cumulative probability of a false-positive result on low-dose CT
  - after 1 screening 21%
  - after 2 screenings 33%
- 61% of those participations with false-positive results on low-dose CT scan had to undergo additional imaging
- another 6.6% underwent invasive procedures

[Croswell et al, Ann Int Med 2010, 152, 505-12]
Screening CT results

- “negative” without nodules → annual repeat
Screening CT results

- “negative” without nodules → annual repeat
- “negative” with (small) nodules → annual repeat
Screening CT results

- “negative” without nodules
  - annual repeat

- “negative” with (small) nodules
  - annual repeat

- “positive” large nodules
  - 1 – 3 month follow up CT
    - other interventions
Lung Cancer Screening – nodules

• 5.1% - 51.4% of patients have nodules (Bepler et al, Cancer Control, 2003)

• 80-99% (!) of those are benign

• how deal with all of the nodules?
  – what is a nodule?
  – follow up of nodules
Lung Cancer Screening – nodules

– what is NOT a nodule?
Lung Cancer Screening – nodules

– what is NOT a nodule?
Lung Cancer Screening – nodules

– what is NOT a GG (ground glass) nodule?
Screening CT results

- "negative" no nodules → annual repeat
- "negative" small nodules → annual repeat
- "positive" large nodules → 1–3 month follow up CT, other interventions
positive screening CT

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELCAP <em>Lancet</em> 1999</td>
<td>any size</td>
<td>23.3</td>
</tr>
<tr>
<td>Italian SS <em>Lancet</em> 2003</td>
<td>6 mm</td>
<td>29</td>
</tr>
<tr>
<td>LSS (NCI) <em>Chest</em> 2004</td>
<td>4 mm</td>
<td>20.5</td>
</tr>
<tr>
<td>Mayo <em>Radiology</em> 2005</td>
<td>any</td>
<td>51</td>
</tr>
<tr>
<td>Toronto (n=1000) <em>Can Ass Rad J</em> 2007</td>
<td>5 mm</td>
<td>25.7</td>
</tr>
<tr>
<td>Toronto (n=3352) <em>Lung Cancer</em> 2009</td>
<td>5 mm</td>
<td>18</td>
</tr>
<tr>
<td>NLST <em>N Eng J Med</em> 2011</td>
<td>4 mm</td>
<td>27.3</td>
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Lung Cancer Screening – nodules

• how deal with all of the nodules?

  – follow up of nodules
Lung Cancer Screening – nodules

- follow up of nodules
- I-ELCAP flowchart
Lung Cancer Screening – nodules

- follow up of nodules
- Fleischner criteria *MacMahon Radiology 2005*

<table>
<thead>
<tr>
<th>Nodule Size (mm)*</th>
<th>Low-Risk Patient†</th>
<th>High-Risk Patient‡</th>
</tr>
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<tr>
<td>≤4</td>
<td>No follow-up needed§</td>
<td>Follow-up CT at 12 mo; if unchanged, no further follow-up‖</td>
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<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>
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<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>
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Lung Cancer Screening – nodules

- follow up of nodules
- Fleischner criteria

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<tr>
<td>$&gt;6–8$</td>
<td>Initial follow-up CT at 6–12 mo then</td>
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* Diameter of any nodule
† Definitions differ by risk
§ Follow-up not required
‖ If unchanged, no further follow-up
Lung Cancer Screening – nodules

- follow up of nodules
- Fleischner criteria

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Lung Cancer Screening – nodules

• how deal with all of the nodules?
  – follow up of nodules
  – protocol
  – size + growth
nodule follow up

• solid lesions < ~ 5 mm
  – “negative”, no follow up

→ annual repeat
nodule follow up

• solid lesions $< \sim 5$ mm
  – no follow-up

• solid lesions 5 – 10 mm
  – surveillance of growth
  – doubling time $30 – 360 = \text{malignant}$
doubling time 72 days
combined small cell-large cell neuroendocrine carcinoma
mucinous adenocarcinoma

3 months
nodule follow up

- solid lesions < ~ 5 mm
  - no follow up
- solid lesions 5 – 10 mm
  - surveillance of growth

- non-solid lesions
  - risk of malignancy relates to size and growth of solid component
same size, higher density

adenocarcinoma

3 months
measurement?

adenocarcinoma
false positives

- NELSON study
- protocol keyed to
  - size of solid nodules at first observation
  - 3D volume doubling times in follow-up scans
  - location and morphology
- rate of false-positive diagnoses 7.9%
- relatively low rate of false-positive screen results compared with previous studies on lung cancer screening

ECR 2009 / Pedersen et al, J Thorac Oncol 2009
Screening – positive baseline

Menezes, Roberts Lung Cancer 2009
false positives

• 4782 participants
• simple algorithm based on size and growth
  – 130 biopsies (2.7%) recommended
  – 20 biopsies (0.4%) for benign lesions

nodule follow up

• solid lesions < ~ 5 mm  
  – no follow-up

• solid lesions 5 – 10 (15?) mm  
  – surveillance of growth

• solid lesions > 10 (15?) mm  
  – immediate bx?
example: screen-detected nodule
baseline

3 months follow up
bx planning CT
Screening – beyond mortality

- nodules and false positives
- management of cancers (overdiagnosis)
- radiation exposure
- selection of individuals at risk
- the solution
overdiagnosis bias

no screen

death from other cause
no Dx autopsy

screen

CT - Dx
overdiagnosis bias

- diagnosis of "disease" that will never cause symptoms or death during a patient's lifetime
- diagnosis is correct, but irrelevant
- treatment causes harm

- early, unexpected death of other cause
  - co-morbidities in smokers
- indolent disease
overdiagnosis bias?

• untreated T1 lung cancers
  – 13% 8-year survival compared to 71% following surgery
    [Henschke Lung Cancer 2003]
  – median overall survival 9 months compared to 69 months following surgery
    [Raz Cheset 2007]

• unselected, all histologies
overdiagnosis bias

- indolent disease

- small subgroup: bronchioalveolar ca
  - malignant cells
  - non-invasive growth
    - CT: GGO, slow or no growth
    - lepidic growth
      growth along preexisting alveolar structure
overdiagnosis bias?
- non-solid (ground glass)
  - biopsy shows malignant cells
  - not palpable @ surgery
  - non-invasive on pathology
lepidic growth

overdiagnosis bias?
overdiagnosis bias

- indolent disease
- small subgroup
  - non-invasive growth
    - GGO
    - lepidic growth, growth along preexisting alveolar structures
  - slow growing
overdiagnosis bias?

3 months

no growth

biopsy: malignant cells

surgical resection

1.1 cm bronchioloalveolar carcinoma, no invasion
July 2007
March 2008
July 2008

growth rate > 380 days
Slow growing BAC

2009  2010  2011
overdiagnosis bias

- indolent disease

- small subgroup
  - non-invasive growth
    - GGO
    - lepidic growth, growth along preexisting alveolar structures
  - slow growing
  - cured with resection
  - often multiple
multifocal adeno ca / BAC
multifocal adeno ca / BAC

2004  
2006  
2009  
2011
Multifocal BAC

2005
Multifocal BAC

2009

2010

2011
overdiagnosis bias

- indolent disease

- selection
  - imaging (CT, PET)
  - growth analysis
  - biomarker (genetic markers)
multifocal BAC

multiple GGOs, most suspicious RUL was biopsied: adeno-ca
no treatment, had semiannual follow up CTs
Screening – beyond mortality

- nodules and false positives
- management of cancers (overdiagnosis)
- radiation exposure
- selection of individuals at risk
- the solution
Lung Cancer Screening – Method

- low-dose
- 40-60 mA
- 120 kV
- 1 mm – 1.25 mm
Lung Cancer Screening – Method
Lung Cancer Screening – Method
Lung Cancer Screening

Low Dose Chest CT Values from NLST

- F. Larke et al at RSNA 2008 (SSG18-09)
- data from 96 CT scanners at NLST sites, 2003-2007
- mean CTDI_{vol}: 3.4 mGy, S.D.: 1.7 mGy
- assumed typical scan length of 35 cm
- mean Effective Dose: 2.0 mSv, S.D.: 1.0 mSv
  - Min/Max: 0.5 – 7.0 mSv
- for comparison:
  - standard chest CT: 8 - 9 mSv
  - screening chest radiograph: 0.08 – 0.12 mSv
  - transatlantic flight: 0.25 mSv
  - mammography: 0.7 mSv
Screening – how long?

- detectable risk factor or disease marker
  - smoking and ex-smoking population

10 year mortality for lung cancer by smoking status

- Smoker-life long
- Nonsmokers
- Smokers-quit aged 50 yo
- Smokers-quit aged 60 yo
- Smokers-quit aged 70 yo

courtesy N Young, NZ
Screening – how long?

- risk to die from lung cancer ➔ 55 years – 75/80 years

10 year mortality for lung cancer by smoking status

- Smoker-life long
- Nonsmokers
- Smokers-quit aged 50 yo
- Smokers-quit aged 60 yo
- Smokers-quit aged 70 yo

Deaths/100 men vs Age (years)
Screening – how often?

baseline 50 - 55 years
annual / biennial until 75 - 80 years
Lung Cancer Screening

baseline 50 - 55 years
annual / biennial until 75 - 80 years

proposal
• baseline + 1 annual
• if no change - biennial
Screening – beyond mortality

- nodules and false positives
- management of cancers (overdiagnosis)
- radiation exposure
- selection of individuals at risk
- the solution
Lung Cancer Screening – Whom?

NOT everybody

limit advertisements and promotion

“Demand a CAT Scan” advertising campaign
Lung Cancer Screening – Whom?

risk factors: age (>50 – 55 years)
smoking (10-30 pack-years)

- large smoking population
- large ex-smoking population
  lung cancer risk decreases only very slowly
  (as opposed to cardiovascular risk)
During the past 11 years 1999-2009, CTUMS has reported a decline in the overall current smoking rate among Canadians aged 15 years and older from 25% in 1999 to 18% in 2009.

The population aged 15 years and older increased by about 3.1 million Canadians, the number of current smokers has decreased by 1.3 million, former smokers increased by 1.3 million and never smokers increased by 3.4 million.

ever smokers: 44%
people at risk

• Ontario: population > 13 million
  – 6.5 M male, 6.7 M female
people at risk

- Ontario: population > 13 million
- 18% *current* smokers ~ 2.3 million
- 44% *ever* smokers ~ 5.7 million
TORONTO, April 20 /CNW/

“Ontario's doctors released their latest report on the status of tobacco in the province and most surprisingly, it revealed that there are more smokers today than in the mid-1960s. There are some 2.3 million smokers in Ontario right now compared to 2.1 million people back then.”
## Ontario - demographics

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4 years</td>
<td>671,250</td>
<td>343,340</td>
<td>327,910</td>
</tr>
<tr>
<td>5–9 years</td>
<td>772,650</td>
<td>396,385</td>
<td>376,265</td>
</tr>
<tr>
<td>10–14 years</td>
<td>788,845</td>
<td>404,970</td>
<td>383,880</td>
</tr>
<tr>
<td>15–24 years</td>
<td>1,487,835</td>
<td>754,565</td>
<td>733,270</td>
</tr>
<tr>
<td>25–34 years</td>
<td>1,558,495</td>
<td>760,695</td>
<td>797,800</td>
</tr>
<tr>
<td>35–44 years</td>
<td>1,959,520</td>
<td>963,840</td>
<td>995,680</td>
</tr>
<tr>
<td>45–54 years</td>
<td>1,635,280</td>
<td>801,540</td>
<td>833,735</td>
</tr>
<tr>
<td>55–64 years</td>
<td>1,064,000</td>
<td>520,570</td>
<td>543,430</td>
</tr>
<tr>
<td>65–74 years</td>
<td>818,170</td>
<td>383,625</td>
<td>434,540</td>
</tr>
<tr>
<td>75–84 years</td>
<td>503,930</td>
<td>202,270</td>
<td>301,665</td>
</tr>
<tr>
<td>85 years and over</td>
<td>150,075</td>
<td>45,260</td>
<td>104,810</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>11,410,045</strong></td>
<td><strong>5,577,055</strong></td>
<td><strong>5,832,990</strong></td>
</tr>
</tbody>
</table>
people at risk

- Ontario: population > 13 million

- Ontario: population 55-75 years old ~ 2 million

- 18% current smokers 360,000
- 44% ever smokers 880,000
people at risk

- Ontario: population ~ 2 million
  - 55-75 years old

- 18% current smokers 360,000
- 44% ever smokers 880,000

screening compliance 25% - to be screened:

- current smokers 90,000
- ever smokers 220,000
people at risk - cancers

- 18% *current* smokers 360,000
- 44% *ever* smokers 880,000

Cancer prevalence: 1.5%

- *current* smokers 5,400 lung cancers
  Stage 1 (75%)
- *ever* smokers 13,200 lung cancers
  9,900 Stage 1
Lung Cancer Screening – Whom?

- better selection of “at risk” population

  - multifactorial risk assessment
    - smoking, family history, spirometry, BMI, education
    - Pan-Canadian Lung Cancer Screening Study
  
  - sputum analysis
  
  - blood analysis (biomarkers)
Screening – beyond mortality

- nodules and false positives
- management of cancers (overdiagnosis)
- radiation exposure
- selection of individuals at risk
- the solution
Lung Cancer Screening – network

- family practice / respirology, etc.
- risk assessment
- smoking counselling

medical imaging
- low-dose nodule detection
- nodule follow up biopsies

thoracic surgery oncology
- immediate surgery
- minimal invasive (VATS) resection
- local treatments

“Screening is a process, not a procedure”
Screening – mortality and beyond

- impact of lung cancer
- screening CTs for lung cancer detection
- lung cancer stage at detection
- mortality
- nodules and false positives
- overdiagnosis
- radiation exposure
- selection of individuals at risk
- screening network